

Primary tuberculosis of glans penis after intravesical Bacillus Calmette Guerin immunotherapy

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ABSTRACT

A 55-year-old male with carcinoma *in situ* of urinary bladder was treated with weekly intravesical injections of Bacillus Calmette Guerin (BCG) vaccine. Three days after the sixth injection, he developed low grade fever and multiple grouped punched out, 2–3 mm ulcers around meatus and corona glandis. In addition, multiple, firm, indurated, nontender papules and few deeper nodules were present on the proximal part of glans penis, along with bilateral enlarged, matted and nontender inguinal lymph nodes. There was no history suggestive of sexually transmitted diseases and high risk behavior. Chest X-ray was within normal limits, and Mantoux, Venereal Disease Research Laboratory (VDRL) and HIV antibody tests were negative. The biopsy from the penile ulcer revealed epithelioid cell granuloma with Langhans giant cells. Fine needle aspiration cytology from the lymph node also revealed epithelioid cell granuloma and acid fast bacilli on Ziehl Neelsen's stain. The tissue biopsy grew *Mycobacterium tuberculosis*. The BCG immunotherapy was stopped and patient was treated with four drug antitubercular therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide in standard daily doses along with pyridoxine. The edema resolved and the ulcers started healing within 2 weeks, and at 6 weeks after starting antitubercular therapy almost complete healing occurred. To the best of our knowledge, we describe the first case of an Indian patient with BCG induced primary tuberculosis of penis after immunotherapy for carcinoma urinary bladder and review the previously described cases to increase awareness of this condition in dermatologists and venereologists.

Key words: Balanitis, Bacillus Calmette Guerin immunotherapy, carcinoma bladder, penile ulceration

INTRODUCTION

Bacillus Calmette Guerin (BCG) is a live attenuated strain of *Mycobacterium bovis*, and is used for the treatment of superficial and *in situ* carcinoma of urinary bladder, residual bladder tumor left after surgical resection and prophylaxis of multiple and/or recurrent bladder tumors.^[1] Primary infection of glans penis is an extremely rare complication of this therapy and we report here one such case.^[2-13]

CASE REPORT

A 55-year-old man who was diagnosed with carcinoma *in situ* of urinary bladder and treated with weekly intravesical injections of BCG vaccine (80 mg) was referred to our venereology clinic for redness, pain and ulceration of glans penis. Symptoms were noted 3 days after the sixth sitting of BCG instillation. This last sitting of intravesical therapy was associated with difficulty in insertion of the catheter and traumatic bleeding. There was no past history of tuberculosis. On examination, he had multiple grouped punched out ulcers of size 2–3 mm in the peri-meatal location. Similar discrete ulcers were present on corona glandis [Figures 1 and 2]. Multiple, firm, indurated, nontender papules and few deeper nodules on the proximal part of glans penis were also present. The whole of penis including the glans was edematous. Bilateral inguinal lymph nodes were enlarged, with size

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Figure 1: Bacillus Calmette Guerin induced balanitis: Multiple ulcers of size 2–3 mm in the peri-meatal location



Figure 2: Bacillus Calmette Guerin induced balanitis: Multiple ulcers spreading from meatus along the posterior surface of glans penis to corona glandis

varying from 3 to 5 cm, matted and nontender. There was no fluctuation. No other lymph nodes in the body were enlarged. There was no history of premarital or extramarital sexual exposure. There was no history of genital ulceration in the past. He had low grade fever and malaise at the time of presentation but there was no history of weight loss or chronic cough. Chest X-ray was within normal limits, and Mantoux was 8 mm at 48 hours. Tzanck smear for multinucleated giant cells as well as Venereal Disease Research Laboratory (VDRL) and HIV antibody tests were negative. Culture for herpes simplex virus was not done.

The biopsy from the penile ulcer revealed epithelioid cell granuloma with Langhans giant cells

[Figure 3a and b]. Fine needle aspiration cytology (FNAC) from the lymph node also revealed epithelioid cell granuloma [Figure 3c] and acid fast bacilli (AFB) on Ziehl Neelsen’s stain [Figure 3d]. The tissue biopsy subjected for mycobacterial culture had grown *Mycobacterium tuberculosis*; however, the polymerase chain reaction (PCR) for *M. tuberculosis* and *M. bovis* was negative.

The BCG immunotherapy was withheld and we initiated therapy with isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 800 mg/day, pyrazinamide 1500 mg/day, and pyridoxine 20 mg/day. The edema resolved and the ulcers healed when the patient was evaluated 2 weeks after starting antitubercular therapy. There was almost complete re-epithelization after 6 weeks of antitubercular therapy [Figure 4].

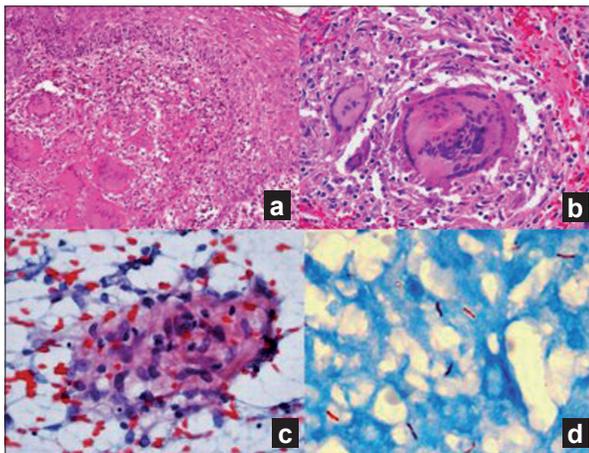


Figure 3: (a) Section showing epithelioid cell granuloma with Langhans giant cells (H and E, ×200); (b) Section showing epithelioid cell granuloma with Langhans giant cells (H and E, ×400); (c) FNAC from inguinal lymph nodes showing epithelioid cell granuloma (Giemsa, ×40); (d) FNAC from inguinal lymph nodes showing AFB (Ziehl Neelsen, ×1000)



Figure 4: Healing Bacillus Calmette Guerin induced balanitis: Post antitubercular treatment at 6 weeks

DISCUSSION

BCG is a live, attenuated organism used to provide protective immunity against tuberculosis. It is administered intradermally in children, and it limits the primary infection to subclinical proportions and also appears to protect against disseminated tuberculosis. It is also used to confer immunity against *Mycobacterium leprae*, either alone or in combination with killed *M. leprae*. Intravesical instillation of BCG is a widely accepted immunotherapeutic modality of superficial and *in situ* transitional cell carcinoma of urinary bladder. BCG immunotherapy has also been described for the treatment of malignant melanoma. Since it is a live attenuated vaccine; it should not be administered to patients with immunocompromised status.

A large number of local and generalized reactions have been reported after BCG vaccination. Nonspecific reactions include urticaria, erythema multiforme, generalized maculopapular or purpuric eruption, extensive and protracted ulceration. Specific reactions include lupus vulgaris, lichen scrofulosorum, papulonecrotic tuberculid, development of basal cell carcinomas and disseminated cutaneous granulomas.^[12] Distant cutaneous granulomas have been reported after BCG immunotherapy for malignant melanoma.^[11]

BCG intravesical therapy may cause minor reactions like cystitis, hematuria, low-grade fever, malaise and nausea. Major side effects include fever >39.5°C, granulomatous pneumonitis, hepatitis, bladder contracture, renal abscess and fatal sepsis.^[12]

Occurrence of balanitis and penile ulcers is a rare complication of intravesical instillation of BCG. It was first described by Kohona *et al.* in 1992 in a 63-year-old man. However, the culture of the tissue grew *M. tuberculosis*. So, they concluded that their case represents primary tuberculosis of glans penis.^[2] Thereafter, it has been described in 11 more patients so far. The clinical features of these patients are summarized in Tables 1 and 2. The patients developed these complaints after 3–16 sittings of BCG intravesical instillation. Most of the patients had associated inguinal lymphadenopathy, and biopsy from the ulcer revealed granulomatous inflammation. It should be noted that in addition to multiple ulcers on the glans, most of the patients had indurated plaques, deep-seated papules, nodules, nodules coalescing to form cords rendering a granulomatous clinical appearance to the genital lesions. French *et al.* have concluded that their patient had papulonecrotic tuberculids induced by BCG, whereas other workers have described their cases as granulomatous balanitis or balanoposthitis or meatal ulceration.

The draining inguinal lymph nodes were usually enlarged bilaterally or unilaterally. In our case, they were matted together. The occurrence of these lesions within days to weeks after the therapy provides evidence that BCG *M. bovis* is the pathogenetic agent. It seems that traumatic catheterization predisposes to the development of primary infection and consequently balanitis.

Of all these cases, one case demonstrated the growth of *M. tuberculosis*,^[2] while two cases demonstrated the

Table 1: Profile of patients with Bacillus Calmette Guerin-induced granulomatous balanoposthitis

Ref no.	Age (years)	Sittings	Duration after last sitting	Difficulty in catheterization	L.N. inv	Biopsy	AFB demonstration	Treatment [#]	Time of response
2	63	—	—	—	Pos	G, N	Pos [†]	RH, 6	6 months
3	52	6	15 days	—	Pos	—	Pos	RHE, 3	Quick
4	29	16	2 days	Present	Pos	G, N	Pos*	RHE, 9	2 months
5	60	3	1 week	Absent	Pos	—	—	H, 3	6 weeks
5	67	4	—	Absent	Pos	—	—	RH, 3	weeks
6	65	6	2 weeks	Absent	—	G	Pos*	HE, 6	6 months
7	67	5	1 week	Present	—	G, N	Neg	RH, 3	3 months
8	58	7	—	Present	Neg	G, N	Neg	H, 12	1 week
9	69	6	1 month	Absent	Pos	G, U, N	Neg	HRE, 3	6 weeks
10	75	10	—	Absent	Pos	G, N	Pos	HR, 6	—
11	77	7	1 week	Absent	—	G	—	2 drugs, 12	12 months
11	61	6	1 week	Present	—	G, N	Pos	3 drugs	—
P	55	6	3 days	Present	Pos	G, N	Pos	HRZE, 6	2 weeks

[†]Positive on culture, negative on smear (*M. tuberculosis* isolated), [#]Duration of treatment in months, *Positive on culture, negative on smear (*M. bovis* isolated),

L.N: Lymph nodes, Pos: positive, Neg: negative, G: granuloma, U: ulceration, N: necrosis, R: rifampicin, H: isoniazid, E: ethambutol, Z: pyrazinamide, P: Present case

Table 2: Morphology of Bacillus Calmette Guerin-induced granulomatous balanoposthitis

Ref no.	Morphology of the lesions	Systemic symptoms
1	Infiltrated red plaque with deep-seated yellow papules on glans penis around the urethral meatus	Not mentioned
2	Necrotic crusts covering whole glans, purulent exudate on ulcerated base	Not mentioned
3	Infiltrated red plaque, 2–3 mm deep-seated yellow papules on glans penis including urethral meatus	Not mentioned
4	Meatal ulcer, penile edema, local pain	Not mentioned
4	Meatal ulcer, penile edema	Not mentioned
5	Diffuse distal penile erythema, coronal abscess, subcoronal, meatal induration, cord of nodules	Absent
6	Multiple painless 5-mm papules on the penis, painful induration of ventral glans	Nausea, fever, malaise, frequency, urgency
7	Multiple painless firm papules on glans and edema of foreskin	Low grade fever
8	1 × 0.6 cm ulcer punched out, an adjacent indurated patch, papules, nodules	Not mentioned
9	Infiltrated red plaque that contained small deep-seated white-yellow papules involving the glans penis and urethral meatus	Not mentioned
P	Penile edema, multiple punched out peri-meatal 2–3 mm ulcers, firm indurated papules and nodules on glans	Low grade fever, malaise

P: Present case

growth of BCG *M. bovis* on tissue culture.^[4,6] In our patient, the tissue culture grew *M. tuberculosis*, so we conclude that he had primary tuberculosis of glans penis after intravesical instillation of BCG, as described before by Yoshida *et al.*^[10] The plausible explanation for this could be that either traumatic BCG inoculation predisposes to tubercular infection or BCG undergoes some mutational changes to acquire *M. tuberculosis* like characteristics. The PCR for *M. tuberculosis* was negative and it was found to be of low specificity and sensitivity in cutaneous tuberculosis in another study carried out at our institute.^[14] It also emphasizes the fact that BCG-induced granulomatous balanoposthitis should be given four drug regimen to prevent systemic dissemination.

To the best of our knowledge, we describe the first Indian patient with this entity and re-emphasize that the dermatologists and venereologists be aware of this entity for accurate diagnosis and adequate treatment as BCG immunotherapy is a widely used and efficacious treatment modality for superficial and *in situ* carcinoma of urinary bladder.

The risk of BCG balanitis or very rarely primary tuberculosis of glans does not warrant the withdrawal of modality in carcinoma urinary bladder, but the BCG immunotherapy has to be stopped and antitubercular therapy initiated as soon as possible. Careful and atraumatic intravesical BCG instillation can reduce the risk of its complications.

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