Caseating Granulomas on the Glans Penis as a Complication of Bacille Calmette-Guérin Intravesical Therapy

Christopher G. French, MD, Liam Hickey, David G. Bell, MD, FRCSC

Dalhousie University, Halifax, Nova Scotia

Intravesical instillation of bacille Calmette-Guérin (BCG) in patients with superficial bladder cancer or with carcinoma in situ of the bladder is a frequently used therapeutic option. As with other cancer therapies, BCG instillation has its share of side effects and complications. This case report highlights an uncommon complication. [Rev Urol. *2001;3(1):36-39, 61*]

Key words: Bacille Calmette-Guérin vaccine • Complications • Penis

Bacille Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis,* is an effective treatment for patients with superficial bladder cancer and bladder carcinoma in situ (CIS). Side effects of this treatment are not rare and usually result from the local and systemic inflammatory effects of the attenuated tubercle bacillus. Rare systemic infections with *M bovis* have been known to occur, however, in the prostate, blood, liver, kidneys, and lungs of patients undergoing treatment with intravesical BCG.[1]

We report the case of a man who developed papulonecrotic tuberculids on his glans penis as a complication of intravesical BCG immunotherapy for transitional cell carcinoma of the bladder.

Case Report

A 67-year-old man underwent transurethral resection for multiple (4), small (less than 1 cm), noninvasive grade 1/3 papillary transitional cell carcinoma of the bladder. Resection was followed immediately by a single dose of intravesical doxorubicin to avoid tumor seeding. (Single-dose mitomycin-C has been shown to have similar efficacy, but it is more expensive and can produce undesirable local dermatitis, which has limited its use in our patient population.) Despite therapy with doxorubicin, multiple recurrences were discovered during the follow-up cystoscopic examination at 3 months; these were managed by complete transurethral resection and fulguration. Because these superficial bladder tumors recurred quickly and continued to be multifocal, we recommended that a 6-week course of intravesical BCG be started 4 weeks after the second transurethral resection.

The patient resided in a small community, which was a 2-hour drive from our institution; therefore, the BCG treatments were carried out by his family physician, who was experienced with intravesical instillation. The patient's fifth treatment

with intravesical BCG involved a problematic catheterization. There was difficulty in passing the catheter at the posterior urethra. The catheter subsequently passed easily when the patient took some deep breaths, suggesting that the difficulty was at the external sphincter. There was no spillage of BCG noted. Seven days later, the patient presented to his family physician with multiple, painless, 5-mm papules on the penis; painful induration of the ventral glans (Figure); and complaints of nausea, fever, malaise, frequency, and urgency. Mild improvement of the penile lesions was noted following initial treatment with trimethoprim-sulfamethoxazole and a topical fungicide.

The sixth treatment with BCG was withheld on suspicion of *M bovis* infection, and the patient began therapy with 300 mg of isoniazid and 600 mg of rifampin once daily. Ten days after starting this antituberculous chemotherapy, biopsy specimens were obtained from several papules and were sent for histologic and microbiologic examination. Cystoscopy revealed an erythematous distal urethra and generalized erythema of the bladder mucosa, without any evidence of tumor. The histology report of the penile papules described "granulomas with focal central necrosis consistent with BCG-related granulomatous response." Ziehl-Neelsen stain did not reveal any acid-fast bacilli, and periodic acid–Schiff stain showed no fungi. After 8 weeks of therapy, culture of urine and tissue from the biopsy sites and bladder mucosa were negative. The patient tolerated the chemotherapy well, and monthly testing during isoniazid therapy revealed no elevation in liver enzyme levels.

After 3 months, the patient's systemic symptoms resolved and there was marked improvement of the penile lesions. At this point, isoniazid and rifampin were discontinued. When he was seen 1 year after discontinuation of antituberculous chemotherapy, he had not had any recurrence of systemic symptoms, penile lesions, or bladder cancer.

Main Points

- Bacille Calmette-Guérin (BCG) immunotherapy can be used to manage superficial bladder cancer and urothelial carcinoma in situ.
- BCG cannot be instilled immediately following surgery for tumor removal.
- Granulomatous reactions to BCG instillation are common in the bladder and prostate but are usually not associated with systemic symptoms.
- Infection of the penis by *Mycobacterium bovis* is rare.
- Traumatic catheterization and BCG spillage may be risk factors for penile infection with *M bovis*.

Comments

BCG intravesical immunotherapy is indicated in the management of residual superficial bladder cancer and urothelial CIS and for prophylaxis of multiple and/or early recurrent bladder tumors.[2] Intravesical chemotherapy concurrent with initial resection of bladder tumors, while not widely accepted, has been shown to increase the time to recurrence and may decrease tumor implantation.[3] BCG cannot be instilled immediately after surgery because of the high rate of systemic complications. Even when there are no contraindications to BCG, side effects are common. These consist primarily of local irritative voiding symptoms in the majority of patients. Low-grade fever, arthralgias, and mild constitutional symptoms develop in many patients; these symptoms are usually alleviated by acetaminophen. Sepsis syndrome is an uncommon complication. In a mild form, sepsis syndrome can be managed symptomatically, but hemodynamic instability develops in some patients, and some deaths have occurred. Thus, when patients become severely ill, antituberculous therapy is indicated and further BCG treatments should be withheld.

Granulomatous reactions to BCG occur commonly in the bladder and prostate of patients treated, but these are not usually associated with systemic symptoms. If the attenuated mycobacteria gain access to the bloodstream, disseminated infections can occur anywhere in the body.[1]

There are numerous cases in the literature citing a primary or secondary infection of the penis with *Mycobacterium tuberculosis*,[4] but infection of the penis by *M bovis* is rare. There is only 1 other case in the literature of an *M bovis* infection of the penis as a complication of intravesical BCG therapy.[5] In that case,

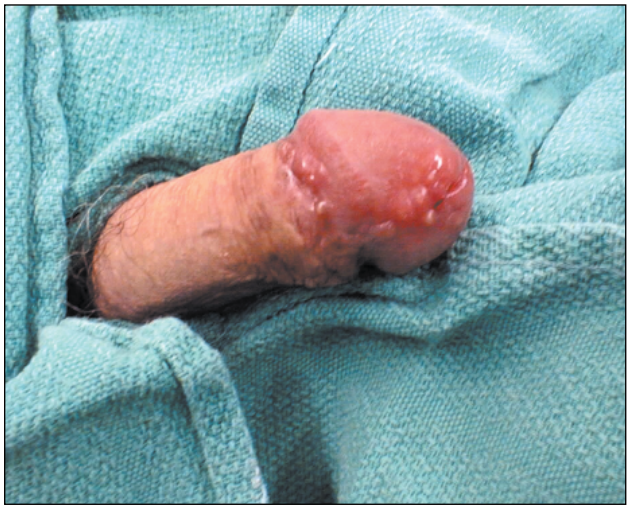

Figure. *Penis showing erythematous ventral glans and multiple periurethral and subcoronal papules with a pale center.*

the 16th instillation of BCG was complicated by a difficult catheterization, and BCG was spilled over the penis. In that patient, systemic symptoms developed and biopsy specimens of penile papules grew *M bovis* on culture. The patient was treated successfully with 6 months of isoniazid and rifampin.

Our case likely represents a local infection of *M bovis* involving the glans penis. It is possible that the difficulty in passage of the catheter through the posterior urethra may have contributed to the infection, but the papules were on the coronal surface of the glans. This suggests that BCG came in direct contact with the involved area either by inadvertent spillage or from voided urine. Although cultures were negative, antituberculous therapy was started before biopsy. The development of moderate systemic symptoms and multiple penile papules (histologically showing caseating granulomas) after BCG immunotherapy suggests *M bovis* infection. Traumatic catheterization or BCG spillage appears to be a risk factor for this rare complication. ■

References

1. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol.* 1992;147:596-600.
2. Intravesical chemotherapy and immunotherapy for bladder cancer and carcinoma-in-situ. *CUA Guidelines. Canadian Urological Association Membership Booklet.* 1999-2000:127-129.
3. Van der Meijden AP, Kurth KH, Oosterlinck W, Debruyne FM. Intravesical therapy with Adriamycin and 4-epirubicin for superficial bladder cancer: the experience of the EORTC GU Group. *Cancer Chemother Pharmacol.* 1992;30(suppl):S95-S98.
4. Agarwalla B, Mohanty GP, Sahu LK, Rath RC. Tuberculosis of the penis: report of 2 cases. *J Urol.* 1980;124:927.
5. Ribera M, Bielsa J, Manterola JM, et al. *Mycobacterium bovis*-BCG infection of the glans penis: a complication of intravesical administration of bacillus Calmette-Guérin. *Br J Dermatol.* 1995; 132:309-310.