

## CASO CLÍNICO



# Granulomas of the penis - A rare complication of intravesical therapy with Bacillus Calmette-Guerin \*

## Granulomas do pênis - uma complicação rara da terapia intravesical com Bacilo Calmette-Guérin

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**Abstract:** Immunotherapy with Bacillus Calmette-Guérin is widely used for treatment and prophylaxis of superficial urothelial cancer. Complications associated with Bacillus Calmette-Guérin treatment are common. The authors describe a case of granulomatous inflammation of the penis associated with intravesical Bacillus Calmette-Guérin therapy, presenting with multiple erythematous and painless nodules located on the glans. A review of the literature is also performed. Granulomatous balanoposthitis is a rare complication of Bacillus Calmette-Guérin immunotherapy, with heterogeneous clinical presentation, which can make the diagnosis difficult. Its clinical recognition is essential for early start of therapy with antitubercular agents and interruption of Bacillus Calmette-Guérin.

**Keywords:** Administration, intravesical; Antitubercular Agents; Inflammation; Mycobacterium bovis; Penis

**Resumo:** A imunoterapia com o Bacilo Calmette-Guérin é amplamente usada no tratamento e profilaxia da neoplasia urotelial superficial. As complicações associadas ao tratamento são comuns. Os autores relatam um caso de inflamação granulomatosa do pênis, associada à terapia intravesical com Bacilo Calmette-Guérin, com múltiplos nódulos eritematosos indolores localizados na glândula. É também efetuada uma revisão da literatura. A balanopostite granulomatosa é uma complicação rara associada à imunoterapia com Bacilo Calmette-Guérin, com uma apresentação clinicamente heterogênea que pode dificultar o diagnóstico. O seu reconhecimento clínico é essencial para o início precoce de tuberculostáticos e interrupção de Bacilo Calmette-Guérin.

**Palavras-chave:** Administração intravesical; Antituberculosos; Inflamação; Mycobacterium bovis; Pênis

### INTRODUCTION

Intravesical therapy with Bacillus-Calmette-Guerin (BCG) is indicated in the treatment and prophylaxis of recurrent high-grade superficial carcinoma and/or *in situ* bladder carcinoma. The benefits of this therapy were first demonstrated in 1976, and it has been more and more widely used since then in the therapeutic approach to this pathology.<sup>1</sup> At present, immunotherapy with BCG is considered a first-line therapeutic option for patients with high-grade super-

ficial urothelial carcinoma and/or *in situ* bladder carcinoma.<sup>2</sup> The most frequently utilized treatment scheme is that recommended by the Southwest Oncology Group (SWOG).<sup>3</sup> This scheme consists in a first induction cycle with weekly intravesical instillation for 6 consecutive weeks, followed by consolidation cycles with 3 weekly instillations, on months 3, 6, 12 and every 6 months afterward until 3 years of treatment are completed. The complications associated

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with BCG intravesical therapy may be specific or unspecific. The latter are related to urethral catheterization prior to BCG instillation. The specific complications are related to the BCG and may be classified as local or systemic.<sup>4,5</sup> Cystitis associated with dysuria (80%) and hematuria (40%) is the most common local side effect. Less frequently, other local-regional complications may arise, such as granulomatous prostatitis, epididymitis, ureter obstruction and involvement of renal parenchyma. Low fever (lower than 38.5°C) accompanied by myalgias, shivering and asthenia, is the most frequent systemic side effect, appearing in 30.5% of cases. It represents a response to BCG hypersensitivity, usually lasting for less than 48 hours, with symptomatic treatment. More severe systemic complications are rare and include the specific involvement of organs and/or systems (pulmonary, hepatic, skeletal, muscular) as well as infection disseminated by BCG, requiring early treatment with tuberculostatic agents.<sup>5,6</sup>

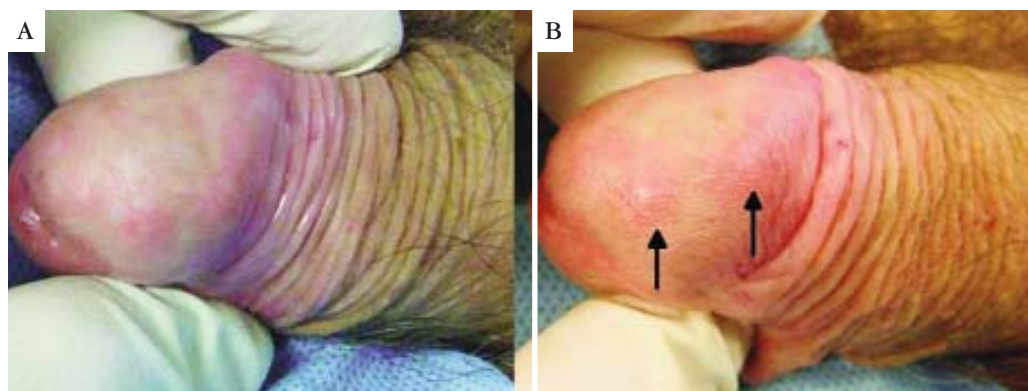
#### CASE REPORT

Sixty-five year old Caucasian male patient, with multiple erythematous nodules located on the glans penis, 3 months after onset. The patient had been diagnosed as having high-grade superficial urothelial carcinoma (T1G3) about one year before, when he was subjected to transurethral bladder resection (RTU-V) and referred to begin BCG intravesical therapy that would last for three years (SWOG scheme). Contraindications to the treatment, particularly the presence of active tuberculosis and infection by the human immunodeficiency virus (HIV), were excluded. One year after BCG immunotherapy was started, while in treatment consolidation phase, the patient mentioned low fever (lower than 38°C), myalgias and asthenia. These symptoms appeared after a traumatic urethral catheterization associated with the first of 3 weekly BCG instillations, when spillage on skin surface occurred. He denied dysuria, hematuria or pyuria complaints. He also denied presence of signs or symptoms related to other organs or systems. The administration of antipyretics and anti-inflammatories resulted in progressive improvement of the clinical picture, with no need to discontinue the treatment with BCG. Two weeks after the end of the consolidation cycle mentioned above, the patient mentioned the onset of multiple painless nodules located on the glans penis. In face of the persistence of nodular lesions, he was referred to the Dermatology Department. Upon observation, the patient had multiple erythematous nodules located on the glans penis, with erythematous color, firm on palpation and with dimensions varying between 5 and 6 mm at the wider diameter (Figure 1). No inguinal lymphadenopathies were

detected. The objective examination revealed no other significant alterations. Taking into consideration the clinical context, a diagnostic hypothesis of skin tuberculosis was generated. The complementary exams carried out showed a discreet increase of transaminases (AST 42 U/L, ALT 50 U/L), gama-GT (101 U/L), alkaline phosphatase (124 U/L) and C-reactive protein (0.6 mg/dl). The hemogram, renal functional and sedimentation speed were normal. Viral infections (HIV, hepatitis A, B and C) and syphilis were excluded. Urinalysis was normal and urine test for mycobacteria was negative. The tuberculin test was slightly positive (6 mm induration). A penis ultrasound was also carried out, showing hypoechogenic nodular images with 3 nodules on glans (4, 5 and 6 mm diameter) and 2 nodules on posterior medial third of the penis (4 and 5 mm in diameter). The thorax X-ray and abdominal echography did not reveal any relevant alterations. Skin biopsy showed a granulomatous inflammation with epithelioid histiocytes (granuloma) and giant cells, surrounded by lymphocytes and plasmacytes (Figure 2). Detection of acid-alcohol resistant bacilli (AARB) and culture were negative. After diagnosis of granulomatous balanitis associated with BCG immunotherapy, a tuberculostatic therapy was started with isoniazid 300mg/day, rifampicin 600 mg/day and ethambutol 1200 mg/day. An excellent clinical response was observed, with complete regression of lesions one month after treatment was begun. Isoniazid and rifampicin were maintained for 6 months and ethambutol was suspended after 2 months. No relapses were observed during the 9-month follow-up. BCG immunotherapy was interrupted after the diagnosis of penis granulomas. The patient is currently under clinical vigilance and periodic cystoscopy, without detection of any clinical and/or histological relapse of the vesical tumor.

#### DISCUSSION

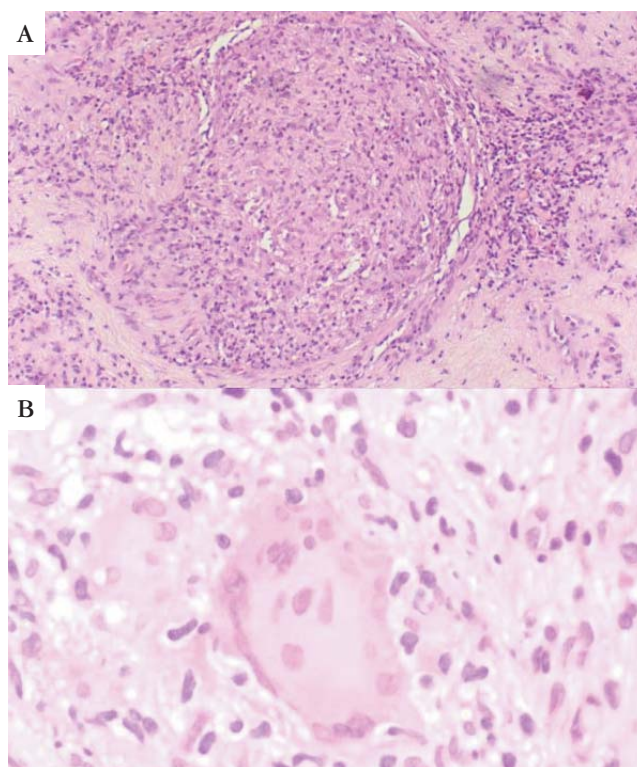
In the last 30 years, intravesical therapy with BCG has played a central role in the therapeutic approach to bladder neoplasia. The mechanism of action that would explain its antitumoral activity is not completely understood; however, it seems to be related to nonspecific stimulation of the local immune system. After the intravesical instillation, the bacillus is internalized by the vesical epithelial cells, triggering an intense immunologic cell response with liberation of several cytokines (predominantly type Th1) and formation of a granulomatous inflammatory infiltrate in the bladder mucosa. The immunological response leads to the activation of cytotoxic cell mechanisms, permitting selective destruction of tumoral cells.<sup>2,7</sup> BCG is an attenuated variety of *Mycobacterium bovis* (*M. Bovis*); however, the bacillus remains viable and in



**FIGURE 1: A.** Erythematous nodules on glans penis. **B.** Detail of nodular lesions, marked by arrows

some circumstances its hematogenic dissemination may occur. In view of this, intravesical therapy with BCG is contraindicated for patients with active tuberculosis, immunodeficiency and untreatable urinary infections. It should also be avoided in the first two weeks following TUBR (transurethral bladder resection) and in patients with persistent hematuria and/or traumatic urethral catheterization.<sup>4,5</sup> The most frequently observed genitourinary complication is granulomatous prostatitis. More rarely, the inflammatory process may involve the epididymis, the testicle and

the renal parenchyma.<sup>5</sup> Granulomatous inflammation of the penis associated with BCG intravesical therapy is a rare complication. In medical literature, only 11 cases are described (Chart I). The clinical manifestations are heterogeneous and of variable severity, including penis edema, papules of yellowish color, ulcers and abscesses. The presence of inguinal lymphadenopathies is frequent.<sup>8-14</sup> In the case described above, only erythematous and asymptomatic nodules were observed on the glans penis, which could easily go undetected in a clinical examination. In our patient, there was a temporal association with BCG immunotherapy and particularly with a traumatic instillation. However, the time interval between BCG immunotherapy and the onset of skin lesions has been variable, occurring both immediately after the instillation or 1 year after the end of treatment.<sup>8-10</sup> The mechanism of infection seems to be related to a history of traumatic urethral catheterization prior to BCG instillation with direct penis inoculation; however, this risk factor is not always identified.<sup>8,9,11,13</sup> Histologically, tuberculoid granulomas with giant cells are observed. Caseous necrosis may be absent.<sup>11</sup> In our case, detection of AARB and culture were negative. The difficult identification of *M. bovis* by traditional methods (Ziehl-Neelsen stain and culture) has been described in literature<sup>8,9,12,13</sup>. This problem may be overcome by the utilization of polymerase chain reaction (PCR), a method that has been shown to be more effective and more specific in BCG detection.<sup>15</sup> The rarity of this local-regional complication makes treatment definition more difficult. In every previously published case, the skin lesions were found to undergo resolution after tuberculostatic therapy was started. Nevertheless, as is shown in Chart I, the duration of the treatment has varied, as well as the number of antitubercular agents used.<sup>8-14</sup> The treatment scheme recommended for other genitourinary complications with local-regional granulomatous inflammation consists of isoniazid and rifampicine for 3 to 6



**FIGURE 2: A.** Granuloma of epithelioid histiocytes surrounded by lymphocytes and plasmacytes (hematoxylin-eosin 100x). **B.** In a bigger photo enlargement, multinucleated giant cells (hematoxylin-eosin 400x)



**CHART I:** Review of granulomatous balanitis cases associated with intravesical BCG therapy

Author	Clinic symptoms	Traumatic catheterization	AARB	Culture	Treatment	Duration (months)
Erol <sup>14</sup> (1995)	Edema, ulcers, crusts	NS	Pos	ND	RE	3
Ribera (1995)	Papules	Yes	Neg	Pos	HRE	9
Baniel (1996)	Edema, erythema, ulcer	No	NS	NS	H	3
	Edema, ulcer	No	NS	NS	HR	3
Latini <sup>11</sup> (2000)	Erythema, abcess	No	Neg	Pos	HE	6
French <sup>12</sup> (2001)	Papules	Yes	Neg	Neg	HR	3
Hattori <sup>10</sup> (2006)	Papules, edema	Yes	Neg	ND	H	12
Kureshi <sup>8</sup> (2006)	Papules, nodules, ulcer	No	Neg	Neg	HRE	3
Yates (2007)	Edema, ulcer	No	Neg	Neg	HREZ	6
Yoshida <sup>13</sup> (2008)	Papules	No	Pos	Neg	HR	6
Hillyer <sup>9</sup> (2009)	Papules, ulcer	No	Neg	Neg	HRE	NS

Neg: Negative; Pos: Positive; ND: Not done; NS: Not specified; H: Isoniazid; R: Rifampicin; E: Ethambutol; Z: Pyrazinamide

months and interruption of BCG therapy. The association of ethambutol is usually reserved for situations with hepatic, pulmonary, renal and skeletal involvement.<sup>5</sup> The granulomatous inflammation of the penis associated with BCG immunotherapy is a rare complication, little known among dermatologists. Its clinical

recognition is essential for the early start of tuberculo-statics and interruption of BCG treatment. The diagnosis should be made in the presence of penis lesions in patients previously subjected to intravesical BCG therapy. □

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