

Penile Granuloma as a Rare Complication of Intravesical Bacillus Calmette Guerin Therapy

İntravezikal Bacillus Calmette-Guérin Tedavisinin Nadir Bir Komplikasyonu Olarak Penil Granülom

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ABSTRACT Intravesical Bacillus Calmette-Guérin (BCG) therapy is a common treatment for high-risk non-muscle-invasive bladder cancer and is generally well-tolerated. While common side effects include cystitis, hematuria, and low-grade fever, penile cutaneous granulomas are exceptionally rare, with only 14 cases reported in the literature. This case presents a rare complication of BCG therapy. A 71-year-old male diagnosed with T1 high-grade urothelial carcinoma underwent intravesical BCG therapy. During treatment, the patient experienced mild fever, joint pain, and cystitis. Therapy was halted due to elevated c-reactive protein and liver enzymes. Examination revealed painless, nodular lesions on the glans penis and penile shaft, and biopsy confirmed granulomatous tuberculosis. Treatment with quinolones and non-steroidal anti-inflammatory drugs resolved the lesions within 14 days without scarring. This case emphasizes the importance of recognizing rare BCG-related complications and highlights quinolone therapy as a successful treatment for penile granulomas.

Keywords: Bacillus Calmette-Guérin vaccine; administration vesicale; granulomas; tuberculosis male genital

ÖZET İntravezikal Bacillus Calmette-Guérin (BCG) tedavisi, yüksek riskli kas tabakası invazyonu olmayan mesane kanseri için yaygın olarak kullanılmakta ve çoğu hasta tarafından iyi tolere edilmektedir. Yaygın yan etkiler arasında sistit, hematüri ve düşük dereceli ateş bulunurken, penil cilt granülomları son derece nadirdir. Literatürde yalnızca 14 vaka bildirilmiştir. Bu vaka, penil granülomları intravezikal BCG tedavisinin nadir bir komplikasyonu olarak ele almaktadır. 71 yaşındaki erkek hastaya, T1 yüksek dereceli ürotelyal karsinom tanısı konmuş ve intravezikal BCG tedavisi başlatılmıştır. Tedavi sırasında hastada hafif ateş, eklem ağrısı ve sistit semptomları gelişmiş, tedavi c-reaktif protein ve karaciğer enzimlerinde yükselme nedeniyle durdurulmuştur. Fizik muayenede, glans penis ve penil shaftta ağrısız, nodüler lezyonlar gözlenmiş ve biyopsi granülatöz tüberküloz tanısını doğrulamıştır. Lezyonlar, kinolon ve non-steroidal antiinflatuar ilaçlar tedavisiyle 14 gün içinde iyileşmiş ve iz bırakmamıştır. Bu vaka, BCG tedavisinin nadir komplikasyonlarına dikkat çekmekte ve kinolon tedavisinin etkinliğini vurgulamaktadır.

Anahtar Kelimeler: Bacillus Calmette-Guérin aşısı; mesane içine ilaç verme; granülom; erkek genital tüberküloz

Bladder cancer is among the most common malignancies worldwide, ranking 7th in men globally. In Türkiye, the standardized incidence rates are 21.1 per 100,000 men and 2.9 per 100,000 women. While bladder cancer is the 6th most diagnosed cancer in

Türkiye, it ranks 11th in cancer-related mortality. Approximately 75% of cases are non-muscle invasive bladder cancer (NMIBC), which generally has a better prognosis and longer survival times compared to invasive bladder cancer.¹

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The treatment of high-risk NMIBC often includes intravesical *Bacillus Calmette-Guérin* (BCG) immunotherapy, a well-established modality that utilizes the antitumor properties of attenuated *Mycobacterium bovis*. This therapy triggers an immune response in the bladder, which helps destroy malignant cells and prevent disease progression.² While most patients tolerate BCG therapy well, common side effects include cystitis, hematuria, low-grade fever, malaise, and nausea.³ Severe complications are rare, with penile granuloma being an exceptionally uncommon manifestation, documented in only 14 cases in the literature.^{4,5}

In this case report, we present a rare instance of penile granuloma following intravesical BCG therapy, emphasizing the importance of recognizing and managing such atypical complications.

CASE REPORT

STATEMENT OF ETHICS

The study was conducted in accordance with the principles of the Declaration of Helsinki and written informed consent form has received from the patient.

A 71-year-old male presented with gross hematuria caused by a 3 cm solitary bladder tumor. The patient underwent transurethral resection, and histopathology revealed T1 high-grade urothelial carcinoma. Intravesical BCG therapy was initiated.

After the 1st 2 instillations, the patient developed mild fever, joint pain, and symptoms of cystitis lasting 3-4 days. These were managed with non-steroidal anti-inflammatory drugs (NSAIDs) and empirical quinolone antibiotics after a 1-week interruption of therapy. Similar symptoms recurred after the 3rd instillation. Despite sterile urine cultures, therapy was suspended due to elevated CRP levels and liver enzymes. After a 15-day pause, the 4th instillation was administered at 1-3 of the previous dose. However, treatment was discontinued entirely following a further rise in liver enzymes.

Upon physical examination, multiple painless, mobile, and nodular lesions were observed under the skin of the glans penis and penile shaft. Biopsies were obtained for further evaluation (Figure 1).

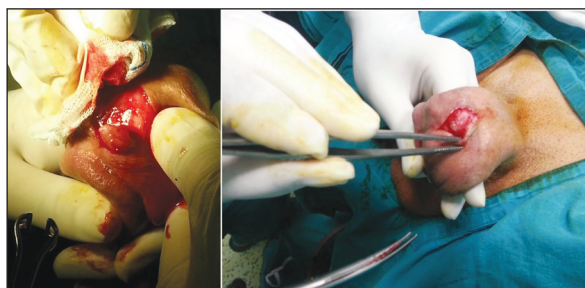


FIGURE 1: Presentation of penile granuloma lesions on glans penis.

The histopathological examination of the penile biopsy revealed granuloma structures composed of epithelioid histiocytes with occasional central necrosis (Figure 2).

The patient was treated with quinolones and NSAIDs, leading to the complete resolution of the lesions without scar formation within 14 days (Figure 3). Histopathological analysis confirmed granulomatous tuberculosis. At the 1st 3 cystoscopic evaluations

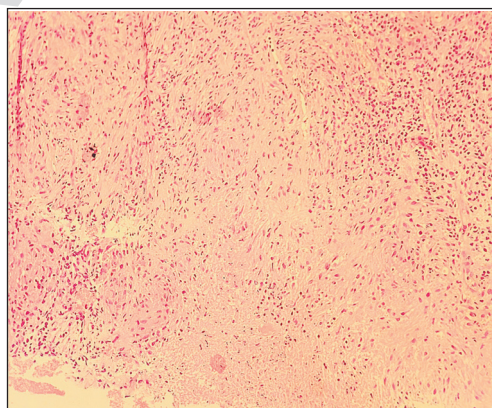


FIGURE 2: Granuloma structures composed of epithelioid histiocytes with occasional central necrosis (caseation) (Hematoxylin&Eosin, x200)



FIGURE 3: Complete resolution of penile granuloma lesions.

conducted at three-month intervals, no tumor recurrence was observed.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

DISCUSSION

The side effects of intravesical BCG therapy arise due to the live bacilli.⁶ Serious systemic side effects occur in 10-15% of cases, often via hematogenous dissemination, and typically require anti-tuberculosis medication. Cutaneous manifestations of BCG therapy are exceedingly rare.⁴ In 54% of reported cases, inguinal lymphadenopathy is observed, often accompanied by balanitis, fever, and flu-like symptoms, though these occur in only 14% of balanitis cases.^{7,8} Concerning localized reactions, granulomatous inflammation of the mucosal glans is an uncommon occurrence, with only a few cases documented in the literature.⁹

In the reported case from the literature, treatment was achieved using cryotherapy with liquid nitrogen.¹⁰ In contrast, our case demonstrated complete resolution with medical therapy alone.

In our case, no inguinal lymphadenopathy was detected. Instead, fever, joint pain, and cystitis symptoms were the predominant findings.^{5,11} There is no standard treatment protocol for BCG-related balanitis.¹² While isoniazid has been the primary treatment in previously reported cases, we opted for quinolone

therapy, which successfully resolved the lesions completely without any residual scarring.⁵

Penile cutaneous granulomas secondary to intravesical BCG therapy are an extremely rare but manageable complication. Quinolone therapy offers an effective alternative to traditional anti-tuberculosis regimens in select cases. This case highlights the importance of recognizing and appropriately managing this rare complication to ensure patient recovery without lasting sequelae.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Muammer Aydın; **Design:** Arif Özkan; **Control/Supervision:** Muammer Aydın; **Data Collection and/or Processing:** Buğra Çetin; **Analysis and/or Interpretation:** Nusret Can Çile-siz; **Literature Review:** Buğra Çetin; **Writing the Article:** Buğra Çetin; **Critical Review:** Muammer Aydın; **References and Fundings:** Buğra Çetin; **Materials:** Arif Özkan.

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