Urology Case Reports 54 (2024) 102694

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Necrotizing granulomatous epididymo-orchitis post intravesical BCG administration after brachytherapy for prostate cancer

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ARTICLE INFO

Keywords:
Necrotizing
Granulomatous
Granuloma
Epididymo-orchitis
Brachytherapy
Prostate cancer
Intravesical
BCG

ABSTRACT

Urothelial carcinoma of the bladder remains a challenging disease to treat. Intravesical instillation of BCG has demonstrated tremendous efficacy in preventing recurrence. BCG related necrotizing granulomatous epididymo-orchitis is rare and has not been previously linked to brachytherapy for adenocarcinoma of the prostate. We hypothesize that prior brachytherapy has a deleterious effect on the verumontanum that can result in retrograde transmission of BCG particles leading to granulomatous epididymo-orchitis. This is the first case report of necrotizing granulomatous epididymo-orchitis related to BCG in a patient status post brachytherapy for adenocarcinoma of the prostate.

1. Introduction

Urothelial carcinoma of the urinary bladder (UCUB) remains a major public health concern in the United States with an estimated 82290 new cases and 16710 deaths from UCUB in 2023.[1] At presentation, the majority of UCUB are non-muscle invasive. The treatment of superficial UCUB includes complete transurethral resection of tumor when possible and intravesical instillation of therapeutic agents, such as bacillus Calmette-Guerin (BCG) vaccine.

BCG is the most effective agent to prevent recurrence and progression for high grade, non-muscle invasive UCUB. Although effective in reducing tumor burden, BCG therapy is associated with a multitude of adverse local and systemic effects, which include life-threatening conditions such as BCG-related septicemia.[2,3] Moreover, granulomatous disease has been reported in regional lymph nodes, bones, liver, lung, spleen, kidneys, prostate, testes & epididymis following BCG therapy.[3] In this report, we describe the first case of BCG-related necrotizing granulomatous epididymo-orchitis (NGEO) following transurethral resection of a bladder tumor in a patient with a history of brachytherapy.

2. Case presentation

A 74 year-old Caucasian male presented for evaluation of painless gross hematuria, hematospermia, and right testicular tenderness. His urologic history was significant for adenocarcinoma of the prostate (Gleason 3 + 4) successfully treated with brachytherapy treatment two years prior at an outside institution. He was diagnosed with gross hematuria and right epididymo-orchitis. The latter was treated with ciprofloxacin for 14 days, which resulted in resolution of symptoms. Workup for gross hematuria showed on CT urogram a 4 cm bladder wall mass. Transurethral resection of the bladder tumor revealed a high-grade papillary urothelial carcinoma with superficial lamina propria invasion.

Four weeks postoperatively, the decision was made to initiate BCG therapy. At the fourth instillation visit, the patient complained of severe left testicular pain. A diagnosis of epididymo-orchitis was made and therapy consisted of a single dose of intramuscular gentamicin, followed by 14 days of ciprofloxacin. Upon return, physical examination demonstrated a firm testicular mass that was no longer tender; ultrasound findings confirmed a septated, heterogeneous, suspicious appearing lesion concerning for a primary testicular neoplasm [Fig. 1].

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https://doi.org/10.1016/j.eucr.2024.102694
Received 31 January 2024; Received in revised form 18 February 2024; Accepted 27 February 2024
Available online 10 March 2024

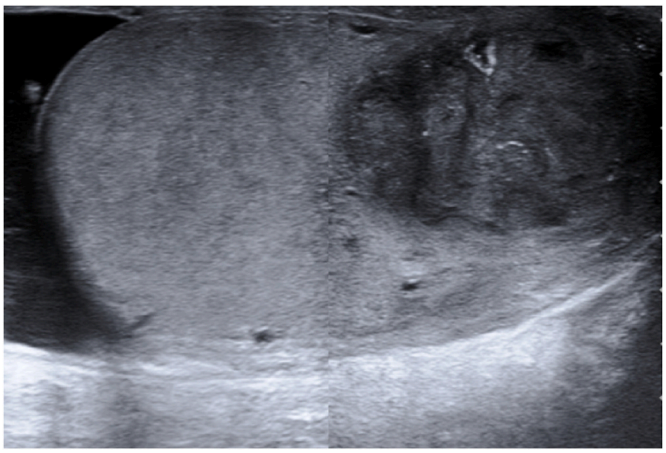

Fig. 1. Ultrasound imaging of the left testicle demonstrating heterogeneity concerning for a primary testicular neoplasm.

Tumor markers including α-fetoprotein, lactate dehydrogenase and β-human chorionic gonadotropin levels were within normal limits. Liver function tests, as well as an abdominal CT scan were unremarkable. Following informed consent, the patient underwent a radical inguinal orchiectomy.

Within the specimen, a 2.5 × 2.4 × 1.4cm yellow soft necrotic mass was found in the inferior pole without extension into the tunica albugenia [Fig. 2]. Mycobacterium immunostain was positive for granular material in these necrotic areas. There was no invasion of the vas deferens, arteries or veins with negative margins. GMS and PAS special stains were negative for fungi, while Ziehl-Neelsen stains were negative for acid-fast bacilli. Granular staining with mycobacterium suggested post-BCG granulomas. Final pathologic diagnosis was NGEO with no evidence of malignancy [Fig. 3]. Based on these findings, the patient was further treated with a 6-month course of isoniazid and rifampin.

3. Discussion

This is the first case report of NGEO following intravesical BCG administration in a patient with a history of brachytherapy. For clinicians, it is important to be aware of these sequelae following brachytherapy along with the theoretical pathophysiological mechanism. Furthermore, it is difficult to distinguish NGEO from primary testicular neoplasia and not possible to do so with radiologic or laboratory values alone.

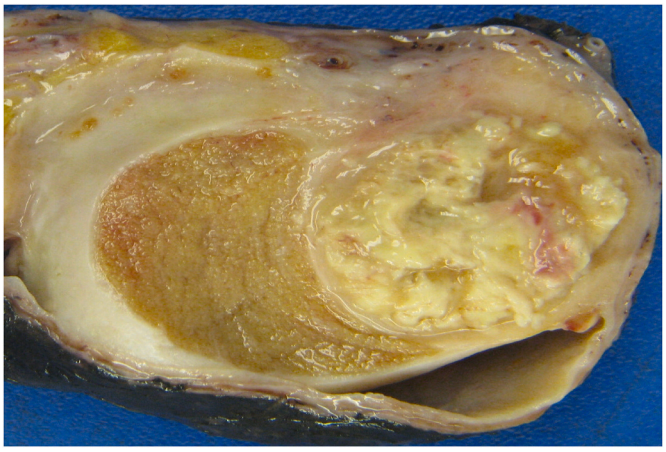

Fig. 2. The yellow soft inferior pole necrotic mass without extension into the tunica albugenia. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

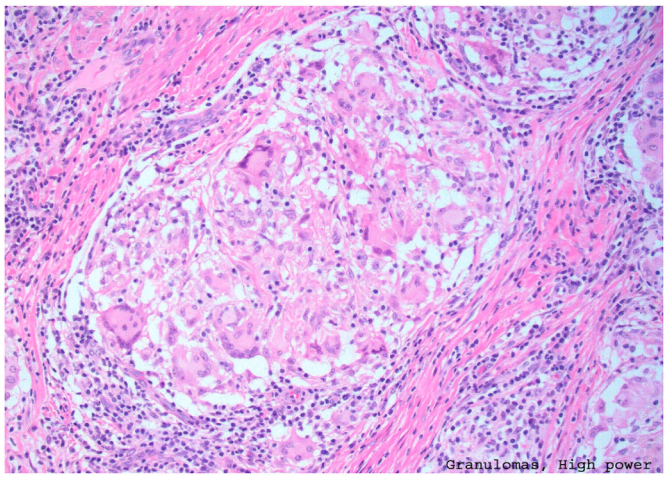

Fig. 3. Granuloma. Staining technique: Hematoxylin & eosin; magnification: 100x

The suspected etiology of BCG-related granulomatous disease has been linked to prior prostate surgery including transurethral resection of the prostate and suprapubic prostatectomy.[4] Additional causes include: vasectomy, transurethral resection of bladder tumor, and infectious causes (tuberculosis, rickettsia, brucellosis. Sarcoidosis, fungal infection.)[2,3] Genitourinary-related granulomatous disease may also be a result of testicular trauma. Nonetheless, the etiology of granulomatous epididymo-orchitis is primarily infectious. These lesions develop as a late systemic manifestation of tuberculosis, brucellosis, syphilis, sarcoidosis, fungal, rickettsial and parasitic infections.

NGEO following intravesical immunotherapy with BCG is an uncommon phenomenon. Lamm et al. reported on the incidence of complications in a large multi-institutional study and showed that BCG epididymo-orchitis is a rare event.[3] These investigators reported an estimated incidence at 0.4%, while manufacturers of BCG have reported incidence rates to be as low as 0.02%.[5] The most common site for abscess formation is the epididymis following intravesical BCG instillation; in most cases, the treatment is orchiectomy.[5] Scrotal involvement has been postulated to stem from systemic immune reactions and direct dissemination of BCG to the scrotum. Granulomatous epididymo-orchitis is a common condition in tuberculosis patients. The suspected mechanism is hematogenous spread with preceding involvement of other genitourinary organs.[4]

Various pathophysiological processes have been proposed to explain granulomatous testicular disease. TURP has been suspected to cause retrograde dissemination of infective particles into the vasa seeding the epididymis.[2,5] Pathologic examination has revealed granulomatous involvement of the wall of the proximal vas and epididymal tubules suggesting a retrograde transmission in such individuals. Catheter drainage may have been helpful in this scenario, as particles would not have been introduced to the verumontanum or vasa, which are susceptible to reflux.[4]

Brachytherapy or internal radiotherapy has been used for treatment of breast, cervical, skin and prostate cancer. Strategic placement of short-range radioisotopes allows radiation to be directed at tumors from close proximity. Ionizing radiation escapes a protective capsule, which remains stationary and does not dissolve. We hypothesize that the energy emitted from brachytherapy had an deleterious effect on the verumontanum rendering the vasa susceptible to retrograde dissemination of BCG particles. This is consistent with a previously theorized mechanism status post TURP.[4] Retrograde seeding of the epididymis can result in epididymo-orchitis, and necrotizing granulomatous infection is a known complication of this condition that was confirmed on final pathology. While logical, this does remain speculative as there are well documented cases of BCG orchitis in the absence of previous

brachytherapy and thus we can not truly define how it may have contributed in this patient.

4. Conclusion

To the best of our knowledge, this is the first report of NGEO following BCG administration in a patient status post both TURBT for high-grade urothelial carcinoma and brachytherapy treatment for prostate cancer. This information can prove useful to clinicians and reported cases warrant consideration of this condition during investigation of testicular mass/primary testicular neoplasm in a patient receiving BCG therapy.

CRediT authorship contribution statement

Jay K. Jhaveri: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Aaron Dahmen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Alon Lazarovich:** Writing – review & editing, Data curation. **David Nusbaum:** Writing – review & editing, Writing – original draft. **Quoc-Dien Trinh:** Writing – review & editing, Writing – original draft. **Nilesh Gupta:** Writing – review & editing, Writing – original draft, Visualization. **Piyush K. Agarwal:** Writing – review & editing, Writing – original draft, Conceptualization.

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