



Case report

Case report: *Mycobacterium bovis* orchitis post intravesical Bacillus Calmette Guerin

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ABSTRACT

Bacillus Calmette-Guérin (BCG) therapy is a common adjunctive therapy for superficial bladder carcinoma but there has been noted to be complications from this treatment ranging from general disseminated infections to osteomuscular involvement. We report a case regarding a 63 year old gentleman who presented with right testicular swelling and pain and later found to have evidence consistent with *Mycobacterium bovis* orchitis. We also detail a literature review regarding genitourinary infections secondary to BCG therapy and discussion regarding current testing modalities.

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Introduction

Bacillus Calmette-Guérin (BCG) therapy is being more widely used as an adjunctive therapy for the treatment of superficial bladder carcinoma. Administration of intravesical BCG, a live attenuated strain of *Mycobacterium bovis* triggers long lasting local immune activation with different effector mechanisms that include increased expression of interferons and NK cells activity [1]. Although some complications involving different organs are being reported, the diagnosis of infectious complications associated with BCG therapy including epididymo-orchitis still remains a challenge due to the lack of definitive diagnostic criteria and microbiological identification as well as in differentiating BCG orchitis from tuberculous orchitis in a timely manner. Here we report a case of late-onset BCG orchitis most likely a consequence of previous BCG therapy and a review of previous cases reported in the literature.

Presentation of case

A 63-year-old man was initially evaluated by Urology for right testicular swelling and pain for 3 months. As part of the workup, he underwent an ultrasound of the scrotum which showed 0.1 × 0.3

× 0.1 cm irregular hyperechoic focus with no shadowing or internal vascularity in the superior pole of the right testicle (Figs. 1 and 2). Due to the concern for malignancy, the patient underwent an orchiectomy. Histopathology revealed acute and chronic necrotizing granulomatous changes. Upon further questioning, the patient denied any fevers, night sweats, weight loss or urinary symptoms. He did not have a history of BCG vaccination or prior history of tuberculosis infection. He did not report any contacts with tuberculosis and had never traveled outside the United States. He was not a healthcare worker, nor had he been in contact with incarcerated people. The only prominent finding in his past medical history was that he previously underwent a transurethral resection of a bladder tumor diagnosed 2 years prior. He had undergone transurethral resection of the bladder tumor (TUR-Bt) and received intravesical instillation with BCG 6 courses. CT head, chest and abdomen-pelvis were done and were unremarkable. *Mycobacterium tuberculosis* complex PCR of the sample was positive.

The patient was started on rifampicin, isoniazid, pyrazinamide and ethambutol and the sample was sent to the Texas Department of State Health Services for further identification. Spoligotyping of isolate combined with the VNTR-MIRU pattern (see below) was consistent with the *Mycobacterium bovis*-BCG strain. Sensitivity of this strain also later returned resistant to pyrazinamide. With these results, pyrazinamide was stopped but he continued on rifampin, isoniazid and ethambutol. The patient's condition gradually improved and has remained stable and asymptomatic to date.

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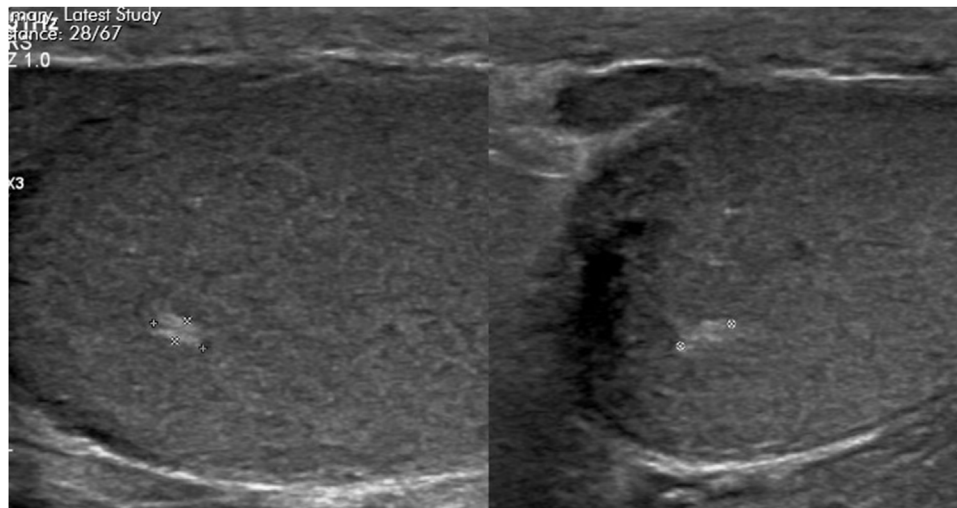


Fig. 1. Ultrasound of scrotal contents showing 0.1 × 0.3 × 0.1 cm irregular hyperechoic focus in the superior pole of the right testicle.

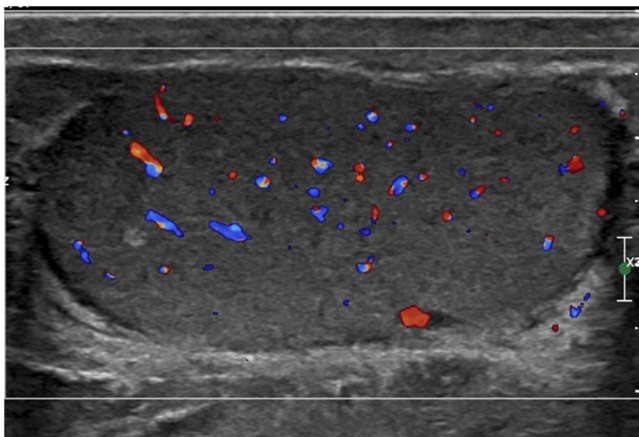


Fig. 2. Ultrasound of scrotal contents showing no shadowing or internal vascularity of irregular hyperechoic focus in the superior pole of the right testicle.

Discussion

In a large retrospective analysis published in 1989, the rate of epididymitis was 0.4% (10) of 2602 patients with superficial bladder cancer treated with BCG [2]. A more recent retrospective study including 282 patients identified three most common presentations of BCG infection in this population of patients: disseminated (34.4%), genitourinary (23.4%), and osteomuscular (19.9%) infections; of those 282 patients, 10 (3.5%) were diagnosed with epididymo-orchitis [3]. A Cochrane review including six trials of intravesical BCG with 585 patients reported epididymitis in 6% of patients with the most common adverse effects being cystitis (67%), hematuria (23%), fever (25%) and urinary frequency (71%) [4].

The *Mycobacterium tuberculosis* complex consists of seven species. In order to differentiate *M. tuberculosis* from *M. bovis*, biochemical tests have classically been used. For example, *M. tuberculosis* is positive for both nitrate reduction and niacin accumulation while *M. bovis* is negative [5]. In addition, *M. bovis* is inherently resistant to pyrazinamide and susceptibility testing will support confirmation of the species [6]. Presently, the Texas Department of State Health Services performs genotyping to

discriminate *M. tuberculosis* and *M. bovis*-BCG. In this case, differentiation of the isolate was necessary to determine whether the biopsy from the patient that grew the isolate identified as “*Mycobacterium tuberculosis* complex” was indeed the species used to treat the carcinoma. Many bacteria, including mycobacterial species, contain repeated DNA sequences known as variable number of tandem repeats or VNTR. One type of VNTR called MIRU, or mycobacterial interspersed repetitive units, can be used to differentiate *Mycobacterium* species. To further confirm species identification, spoligotyping, or spacer oligonucleotide typing, has been employed. This test is a hybridization assay that detects variability in the direct repeat region in the DNA of *Mycobacteria*. The direct repeat region consists of multiple copies of a conserved sequence and is separated by multiple unique spacer elements. A banding pattern produced by the assay is converted to a code, which can then be compared to the various *Mycobacteria* to provide identification. Spoligotyping of the isolate combined with the VNTR-MIRU pattern obtained is consistent with the *M. bovis*-BCG strain.

Conclusion

BCG orchitis is a potential complication of BCG therapy. BCG must be considered as the cause of infection in patients that received BCG therapy even if administered years prior. Microbiological confirmation can be sought by molecular methods such as genotyping to distinguish BCG from other agents in the *Mycobacterium tuberculosis* complex since the treatment.

Author statement

The following outlines the authors' individual contributions:
 Mohammed Samannodi MD - Conceptualization; Data curation; Formal analysis
 Aasith Villavicencio MD - Writing – original draft
 Andrew Zhao MD - Writing – review & editing
 Violeta Chavez PhD - Investigation; Methodology; Resources
 Charles D. Ericsson MD - Supervision; Validation

Conflict of interest statement

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