Case Report

Granulomatous Epididymo-Orchitis, A Rare Complication of Bacillus Calmette-Guerin Immunotherapy for Bladder Cancer: A Case Report

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Granulomatous epididymo-orchitis (GEO) is a rare disease characterized by granulomatous inflammation due to etiologies such as infection with mycobacteria. A well-known mycobacterial infection, Mycobacterium tuberculosis (M. tb) which causes tuberculosis (TB), can disseminate from the lungs to infect other organs. However, a mycobacterial infection in the genitourinary system without clinical evidence of TB is unusual. A 79-year-old man with nonmuscle invasive papillary urothelial carcinoma (PUC) was treated with chemotherapy and Bacillus Calmette-Guerin (BCG) immunotherapy, a live-attenuated strain of Mycobacterium bovis (M. bovis). One year later, he developed an epididymal cyst on the left testicle and an enlarged left epididymis. A simple left orchiectomy was performed. Microscopic examination showed granulomas within the testicular and epididymal parenchyma. Ziehl-Neelsen (AFB) stain revealed scattered acid-fast bacilli. The positive AFB stain raised the possibility of TB infection. However, the patient had no clinical evidence of latent or active TB, family history of TB, or TB treatment in the past. Here, we present a rare case of GEO, not caused by TB, but by BCG, a live-attenuated strain of M. bovis.
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INTRODUCTION

GEO is caused by many different etiologies, one of which is infection with mycobacteria. An example of a well-known mycobacterial infection is TB, which is caused by *M. tb*, and can present as pulmonary or extrapulmonary TB due to dissemination. Pulmonary TB is the most common form, but dissemination can occur due to worsening pulmonary infection or reactivation of a latent focus with subsequent spread.[1] The most common site for extrapulmonary TB is the lymph nodes, so genital TB, especially testicular TB, is rare.[1] However, the patient had no clinical evidence of TB, so a mycobacterial infection of the testicle is unusual, and another possible source was investigated.

It was found that the patient had a history of nonmuscle invasive PUC treated with intravesical BCG immunotherapy. BCG was first developed as a vaccine for TB, but beyond this use, it is also the mainstay of treatment for patients with nonmuscle invasive bladder cancer.[2] BCG is infused into the bladder through a urethral catheter after a transurethral resection of bladder tumor (TURBT) and is given once a week for 6 weeks.[3] A rare complication of this form of immunotherapy is GEO due to retrograde spread of the mycobacteria from the urinary tract.[4]

CASE PRESENTATION

A 79-year-old male presented to the emergency department with left-sided flank pain and hematuria that began in the morning. Computed tomography scans of the abdomen and pelvis, with and without intravenous contrast, showed an 18-millimeter hyperdense nodule in the right posterior bladder lumen. Once the patient's symptoms improved, he was discharged home and recommended to follow up with urology.

Cystoscopy revealed a mildly trabeculated bladder with a papillary urothelial tumor located lateral to the right ureteral orifice measuring 3 centimeters (cm). A TURBT was performed, and the patient was diagnosed with low-grade nonmuscle invasive PUC. The patient was treated with chemotherapy and BCG immunotherapy for 6 weeks, and followed up with regular cystoscopies, all of which showed no recurrence of the bladder tumor.

About a year later, the patient complained of pain and discomfort in his left scrotum over the course of several months. A scrotal ultrasound revealed an epididymal cyst on

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the left testicle. A Doppler ultrasound revealed an enlarged and mildly hyperemic left epididymis. A follow-up testicular ultrasound a month later revealed an increasing size of the epididymis with a fluid collection presumed to be a small abscess. The abscess was drained, but the patient continued to have pain and discomfort. The patient followed up with another testicular ultrasound about a month later which showed a diffusely and substantially enlarged epididymis. The clinicians speculated at this stage that the patient's bladder cancer treatment, surgery, or clinical course had resulted in a testicular complication. A simple left orchiectomy was performed.

Gross examination of the resulting specimen included a left testicle with attached spermatic cord, in total weighing 67 grams and measuring 10.2 x 4.6 x 3.7 cm. The testicle was bisected to reveal an epididymis measuring 5.8 x 3.4 x 1.8 cm containing white-yellow purulent material. The testicular parenchyma appeared grossly unremarkable, and the tunica albuginea was smooth, white, and 0.2 cm thick.

Noncaseating granulomas within the testicular parenchyma (**Figure 1**) and caseating granulomas within the epididymal parenchyma (**Figure 2**) were seen on microscopic examination of the processed tissue. AFB stain revealed scattered acid-fast bacilli (**Figure 3**) which were identified to be the cause of the patient's clinical presentation. Based on these findings, the diagnosis of GEO due to a mycobacterial infection was made. The diagnosis was relayed to the patient's clinical providers who started the patient on 6 months of rifampin, isoniazid, pyrazinamide, and ethambutol. After 4 months of treatment, subsequent cultures and testing for mycobacteria were negative.

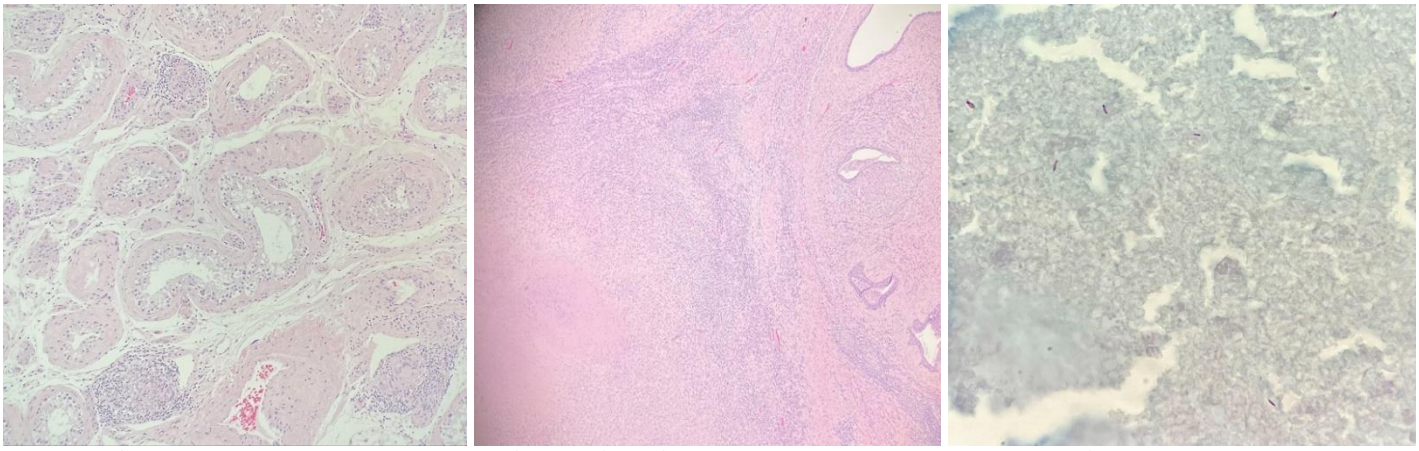

Figure 1 (Left). Hematoxylin and eosin stain (100 x magnification) of the left testicle showing noncaseating granulomatous inflammation.
Figure 2 (Middle). Hematoxylin and eosin stain (40 x magnification) of the left epididymis showing caseating granulomatous inflammation.
Figure 3 (Right). AFB stain (1000 x magnification) showing scattered acid-fast bacilli.

DISCUSSION

Granulomatous processes occur due to infectious or noninfectious etiologies. Infectious etiologies include mycobacteria and many kinds of bacterial, fungal, or viral infections, while noninfectious etiologies include sarcoidosis, trauma, and immune reaction.[5] Infectious causes are associated with caseating granulomas which are characterized by a central region of necrosis leading to the formation of a core of cell debris.[6] Noninfectious causes are associated with noncaseating granulomas which are characterized by the collection of epithelioid histiocytes and giant cells with minimal peripheral chronic inflammation.[7]

Histologically, mycobacterial infections are classically associated with the formation of caseating granulomas, wherein the central region of the granuloma has undergone necrotic cell death leading to the formation of a core of cell debris.[6] The presence of granulomas that destroy the structure of the testis or the epididymis, necrosing tubules, or interstitium is characteristic of this type of infection.[6] Mycobacteria are acid-fast bacilli and will appear red against a blue background on AFB stain.[8] The patient in this case was confirmed to have scattered acid-fast bacilli, so a mycobacterial infection was established, and the patient was treated with the corresponding medications.

Another source of the infection was investigated due to the patient having no clinical indication of TB. BCG immunotherapy is given after TURBT for patients with nonmuscle invasive bladder cancer, such as the patient in this case.[3] It is infused into the bladder through a urethral catheter on a maintenance schedule consisting of weekly instillations for 6 weeks.[9] This results in a local immune response that leads to an increase in T helper 1 urinary cytokines and predicts an improved outcome for bladder cancer patients.[3] Unfortunately, side effects can occur. The most common side effects are dysuria, urinary frequency, and hematuria.[4] In more rare cases, retrograde spread of live-attenuated *M. bovis* and associated granulomatous inflammation to involve the remainder of the

genitourinary tract can occur.[1] In this case, the patient had retrograde spread of *M. bovis* into the left epididymis to result in GEO.

The onset of GEO from BCG is very wide and ranges from 2 weeks to 17 years.[9] This patient presented with GEO about 1 year and 5 months after BCG instillation. Although he experienced symptoms for months and received multiple ultrasounds with abscess drainage, the correct diagnosis was not established until an orchiectomy was performed. While the diagnosis of GEO has mostly been made by microscopic examination following surgery, methods for diagnosing before surgery should be considered to avoid unnecessary orchiectomy. Awareness of its sonographic appearance may help narrow the diagnosis, and once a testicular malignancy or torsion are ruled out, a fine needle aspiration (FNA) can be performed. The acquired sample can reveal granulomas and necrosis which can then be stained with AFB to show acid-fast bacilli. FNA is minimally invasive and in situations of clinical uncertainty, as can occur with GEO due to its rarity, it may be effective in confirming a diagnosis and guiding treatment before an orchiectomy.[10] However, in cases where conservative treatment is ineffective, orchiectomy can then be considered necessary.

CONCLUSION

Because granulomas were seen in the testis and epididymis of this patient, and mycobacteria were identified on AFB stain, the diagnosis of GEO due to a mycobacterial infection was made. This patient, however, did not have clinical evidence of TB, so *M. tb* could not have been the source. Considering this patient had a history of nonmuscle invasive PUC treated with TURBT, chemotherapy, and BCG immunotherapy, we conclude that the source of the infection was from the live-attenuated strain of *M. bovis.* Review of the literature suggests that GEO is rare as its own entity caused by many different etiologies, but it is rarer when it results as a side effect of BCG immunotherapy. Histopathological assessment is the primary method of diagnosing GEO, but methods of diagnosing before surgery should be considered. Conservative treatment should be the first choice of treatment. Awareness of this rare complication can lead to the correct diagnosis, avoiding unnecessary orchiectomy.

CONFLICT OF INTEREST DISCLOSURES
None.

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