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Case Report

Testicular tuberculosis: An uncommon complication after treatment of urothelial carcinoma [☆]

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ABSTRACT

Tuberculous epididymo-orchitis is an uncommon complication after intravesical bacilli Calmette-Guerin therapy for nonmuscle invasive bladder cancer. Spread of granulomatous disease through the genitourinary tract specifically to the testes occurs in 0.4% of treated patients. The following case presents a 77-year-old man who underwent intravesical therapy after transurethral resection of bladder tumor and developed testicular discomfort and a palpable mass 2 years after initiation of therapy. After wide range of serum and urine analyses, repeated testicular ultrasonography, and an unsuccessful course of antibiotics, the patient elected to undergo orchiectomy and was confirmed to have tuberculous epididymo-orchitis. Diagnosis based on imaging and laboratory serum and urine analysis may be elusive and therefore review of this entity and associated sonographic findings is discussed.

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Introduction

The earliest microbiological confirmation of tuberculosis (TB) dates back to the Neolithic Period approximately 9000 years ago [1]. TB is known as the great mimicker and can evade diagnosis due to clinical and radiologic overlap with several disease processes. TB reached epidemic proportions in the 18th and 19th centuries. In 1882, Robert Koch isolated the tubercular bacillus. Nearly a century later, a Canadian urologist used bacille Calmette-Guerin (BCG) to treat recurrent noninvasive bladder cancer via weekly intravesical instillation for 6 weeks [2]. Intravesical BCG was approved by the Food and

Drug Administration in 1990 for the treatment of carcinoma in situ of the bladder and is currently also approved for stage TaT1 tumors at high risk for recurrence [3]. Adjuvant treatment with BCG is currently the most effective strategy in nonmuscle invasive bladder cancer after transurethral resection [4]. Intravesical BCG is effective in prophylaxis against both recurrence and progression of intermediate or high-risk non-muscle invasive bladder cancer.

A standard dose of BCG is administered by diluting a powdered vial of BCG vaccine. After a urethral catheter is placed, the urinary bladder is drained and the BCG solution is infused into the bladder where it remains for 1-2 hours. The solution is drained through the catheter prior to catheter

[☆] "I give consent to be included as the subject of a case report". - R.K.

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Fig. 1a – Urogram phase CT performed on initial presentation for hematuria outlines an eccentric tissue mass at the base of the bladder suspicious for neoplasm. There is no lymphadenopathy in the pelvis.

removal. Infusion is performed once weekly for 4-6 weeks and may commence 2-4 weeks after resection. Subsequent maintenance therapy may be given once per week for 3 weeks 3, 6, and 12 months after initial treatment and can be extended for up to 3 years. Clinical surveillance takes place by cystoscopy and urine cytology every 3-6 months for four years then once yearly. Imaging surveillance with computed tomography (CT) is often performed on a yearly basis.

Case report

A 77-year-old male with history of benign prostatic hyperplasia and urothelial carcinoma of the bladder presented with testicular discomfort and a palpable mass two years after intravesical BCG therapy. The patient initially presented with hematuria in 2017 and underwent CT (Fig. 1a) and post-CT abdominal radiograph in excretory phase (Fig. 1b) which demonstrated a soft tissue mass in the bladder suspicious for urothelial carcinoma. This was confirmed visually during cystoscopy at which time the patient underwent excision of the mass and transurethral resection of the bladder tumor. Pathology revealed noninvasive high grade papillary urothelial carcinoma, stage Ta. Therefore, the patient was determined to be a candidate for BCG therapy and was successfully treated with subsequent intravesical BCG instillation for 6 weeks followed by maintenance BCG instillation for 1 year.

Two years after initiation of intravesical BCG therapy, the patient complained of mild left testicular pain and a palpable mass. Testicular ultrasound demonstrated multiple vague hypoechoic lesions in the left epididymis (Fig. 2a) and testicle (Figs. 2b-d) and fluid within the scrotal sac containing septations consistent in appearance with a complex hydrocele (Figs. 2a-d). The left testicle was mildly hyperemic compared to the right (Figs. 2e-f) suggestive of underlying infectious process. Urinalysis revealed small leukocyte esterase and urine culture was negative. The patient was treated with routine antibiotic therapy for epididymo-orchitis without significant improvement.



Fig. 1b – Frontal abdominal radiograph obtained on initial presentation after intravenous contrast administration demonstrates filling defect at the base of the bladder. Trabeculation in the bladder wall is identified due to longstanding history of benign prostatic hyperplasia and bladder outlet obstruction.

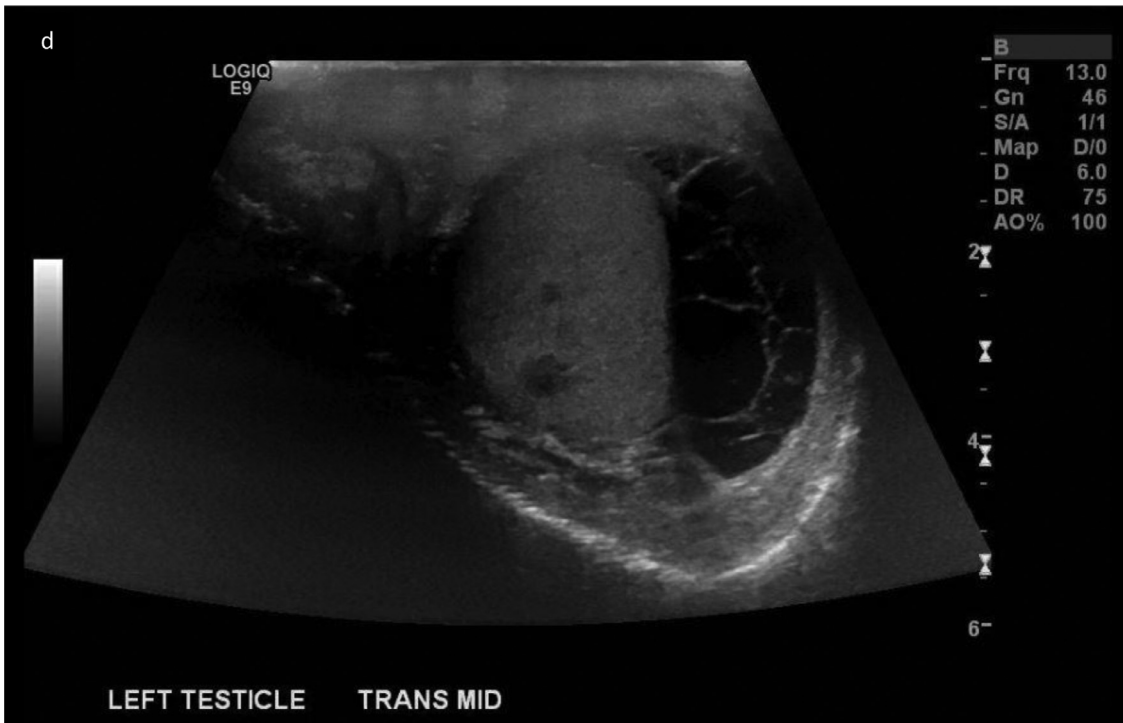
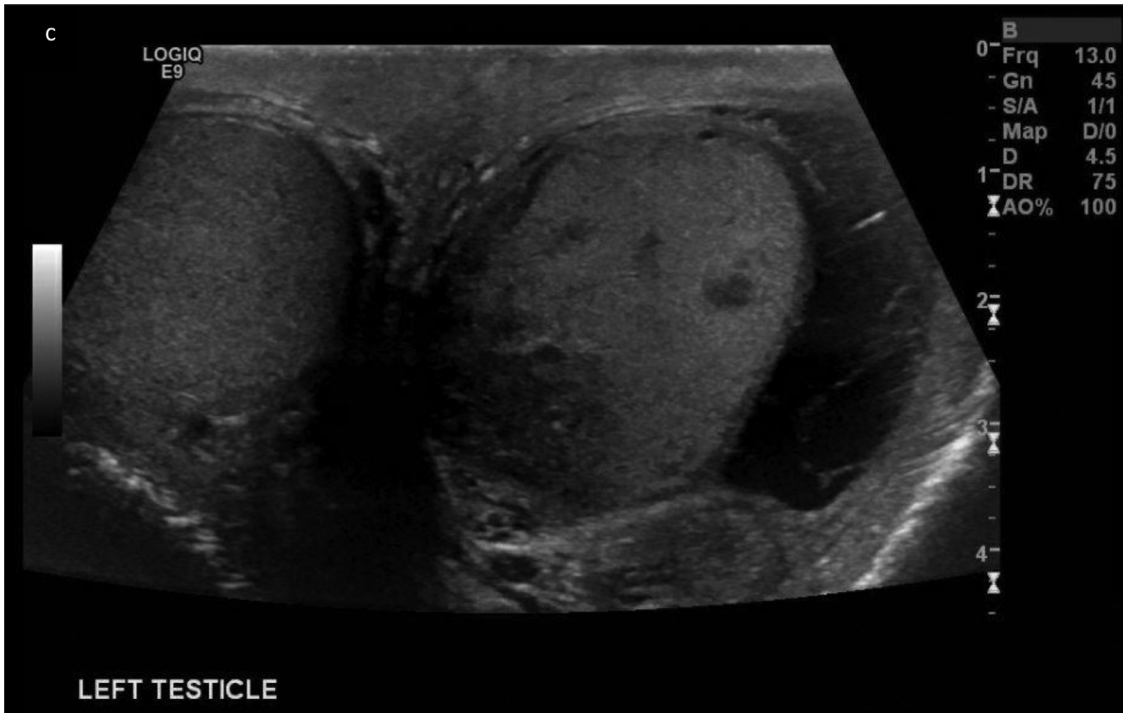
Follow-up sonographic imaging after antibiotic therapy demonstrated interval resolution of complex hydrocele but increase in size and number of hypoechoic testicular lesions (Figs. 3b-c). Patient's urinalysis was again noted to be positive for leukocyte esterase and urine culture was again negative. Discussion between urology and radiology regarding the patient's history and imaging findings led to a differential diagnosis including sequelae of chronic infection such as testicular TB in light of prior intravesical BCG treatment. Serology was within normal limits including alpha fetoprotein at 2.0 ng/mL, b-HCG at 1.0 mIU/mL, and lactate dehydrogenase at 162 U/L.

Discussion with the patient regarding treatment options led to the decision to undergo orchiectomy. Pathology from radical orchiectomy revealed necrotizing and non-necrotizing granulomatous inflammation involving the testis, epididymis, and rete testis, with rare acid-fast bacilli forming a 4.5-cm dominant mass consistent with tuberculous epididymo-orchitis. Staining for acid fast bacilli revealed rare acid-fast bacilli (Figs. 4a-4c).

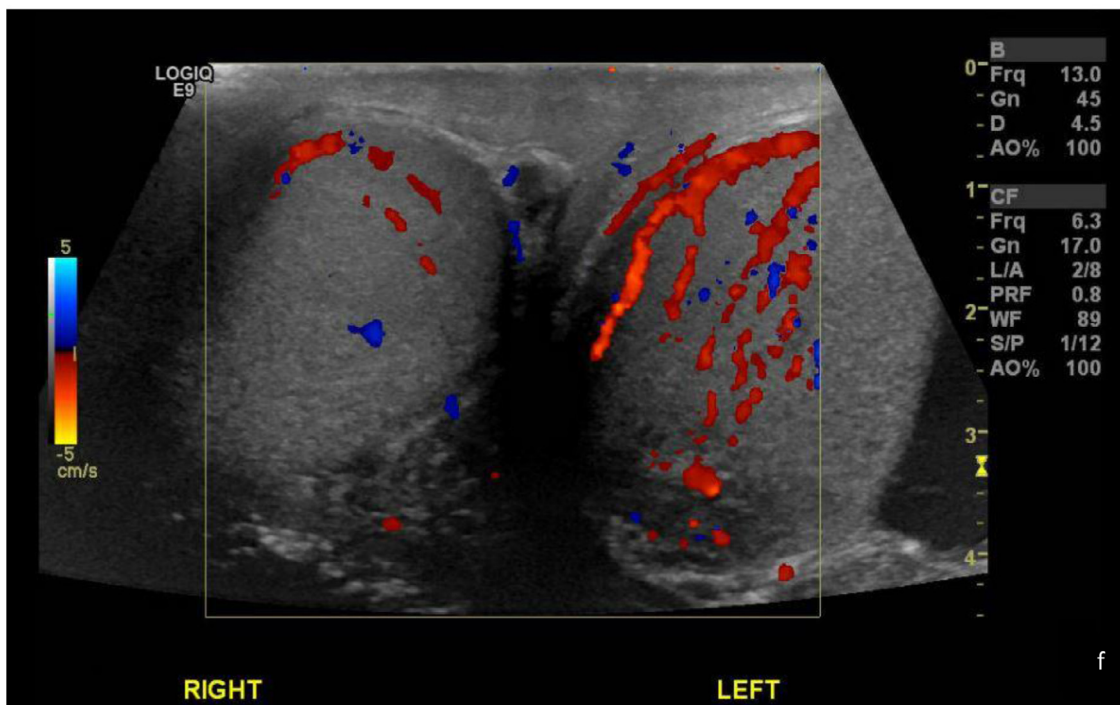
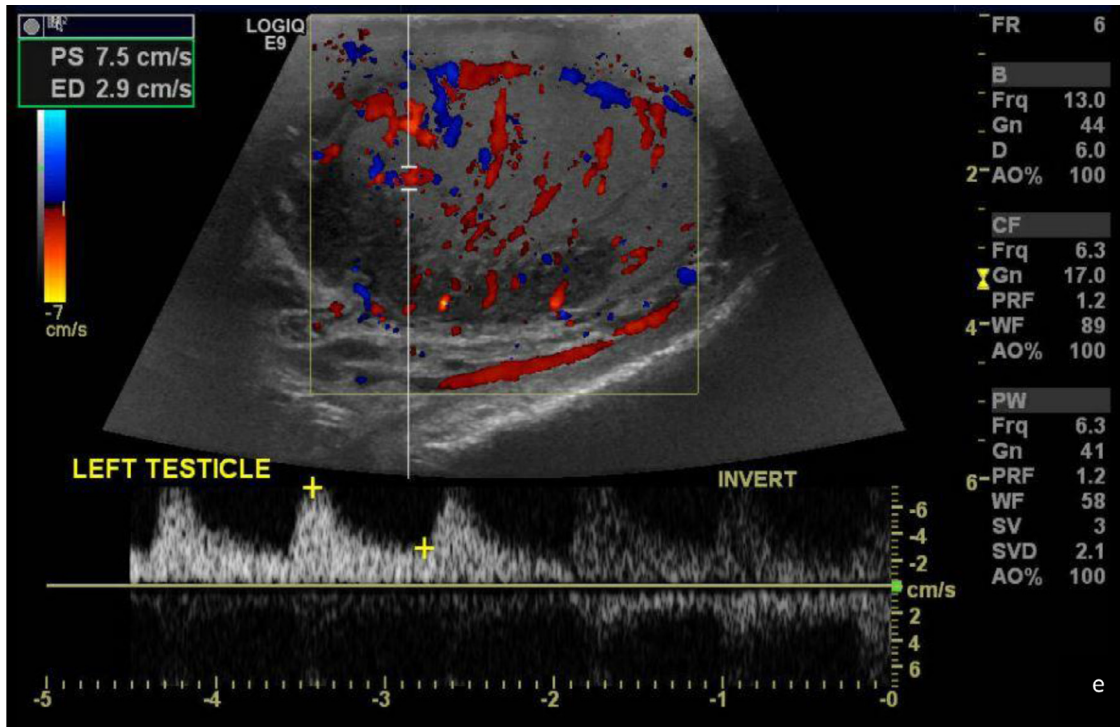
Subsequent surveillance cystoscopy and biopsy of the bladder tumor scar showed predominantly denuded urothelial mucosa with mild chronic inflammation and reactive changes consistent with successful treatment of the tumor. Follow-up urinalysis was negative for leukocyte esterase suggesting successful treatment of testicular TB.



Figures 2 – Two years after TURBT and subsequent initiation intravesical BCG therapy, the patient presented with testicular pain and palpable abnormality. Sonographic image of the left testicle shows hypoechoic areas within the testicular parenchyma and a complex hydrocele (a-d). There is asymmetric hyperemia of the left testicle (e-f).



Figures 2 - Continued



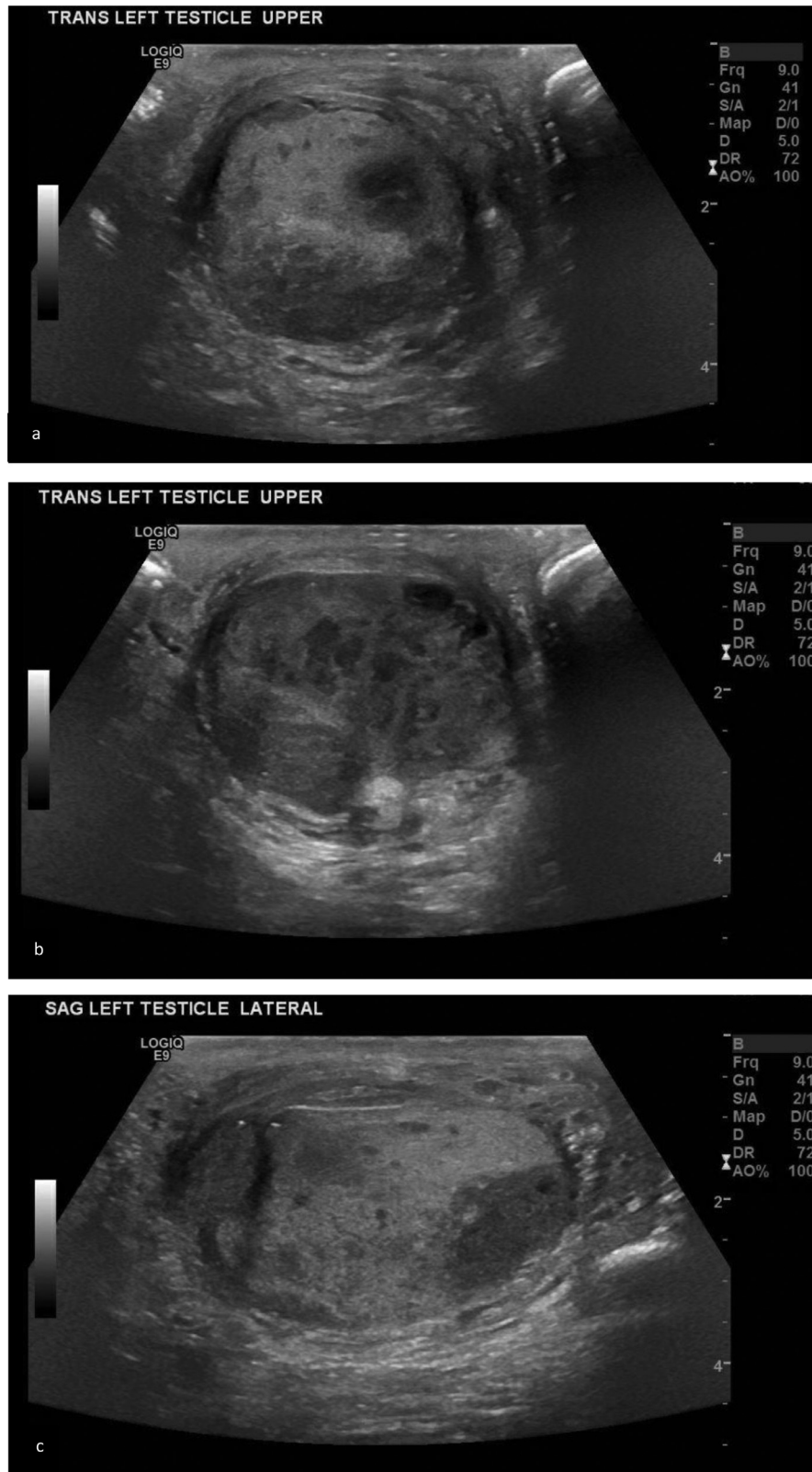
Figures 2 - Continued

Discussion

TB involving the genitourinary tract is most commonly seen after primary pulmonary TB. The kidneys, ureters, and bladder are commonly affected up to 15% of the time in the setting of extrapulmonary TB. Urinary tract TB may also occur in isolation and comprises 25% of cases of genitourinary TB. Spread

of TB to the testicle and epididymis is thought to occur via retrograde spread of tubercular bacilli from the affected urinary tract into the prostate via reflux, followed by canalicular spread to the seminal vesicle, ductus deferens, and epididymis [5]. Disseminated spread may occur due to poor healing after transurethral resection of bladder tumor.

Intravesical BCG therapy is not without risk as it uses an active but weakened strain of bovine TB bacillus, *Mycobacterium*



Figures 3 – (a-c) Follow-up sonography 4 weeks later after antibiotic therapy shows resolution of complex hydrocele but increasing size and number of hypoechoic lesions in the left testicle. Possibility of testicular tuberculosis was raised after initial failed antibiotic therapy.

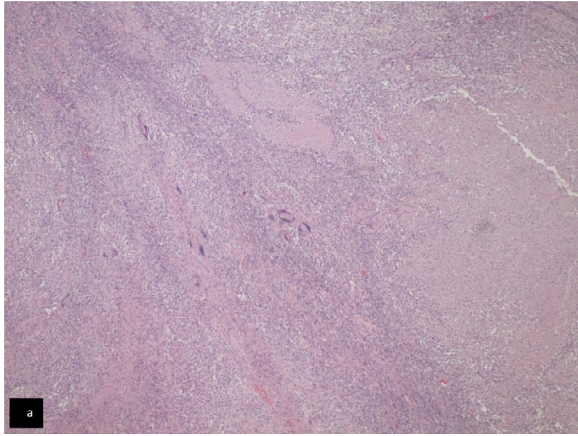


Fig. 4a – Low power photomicrograph of orchietomy specimen demonstrates areas of granulomatous and nongranulomatous inflammatory change and displacement of testicular parenchyma.

bovis. Most common side effects are related to inflammatory response within the bladder leading to chemical cystitis

including dysuria, frequency, and hematuria. Direct contact of the BCG solution may lead to anterograde or retrograde spread of *M. bovis* and associated granulomatous inflammation to involve to the remainder of the genitourinary tract including the penis, epididymis, testis, prostate, and kidney [6]. In this case, spread of live attenuated *M. bovis* from the prostatic urethra through the vas deferens and ductus deferens into the epididymis and testes and caused epididymal and testicular TB. Prostatitis and associated elevation of prostate-specific antigen levels is common after intravesical BCG therapy and may occur with an incidence of up to 10%. Tuberculous epididymo-orchitis is relatively uncommon and occurs in approximately 0.4% of patients [6]. Pyelonephritis and renal abscess are also less common at 0.3%. Systemic complications also occur infrequently at a rate of approximately 3% and include military TB, mycotic aneurysms, granulomatous hepatitis, tuberculous spondylitis, and BCG-related sepsis [6,7].

Sonographic findings of testicular TB include diffuse enlargement of the testicle, heterogeneous or homogeneous hypoechoic echotexture, and hypoechoic nodules [8–10]. Tuberculous epididymitis is similar in appearance with diffuse enlargement and hypoechoic areas of heterogeneity. Tuberculous orchitis usually is the result of contiguous extension from tuberculous epididymitis [8–10]. Extension of TB to the

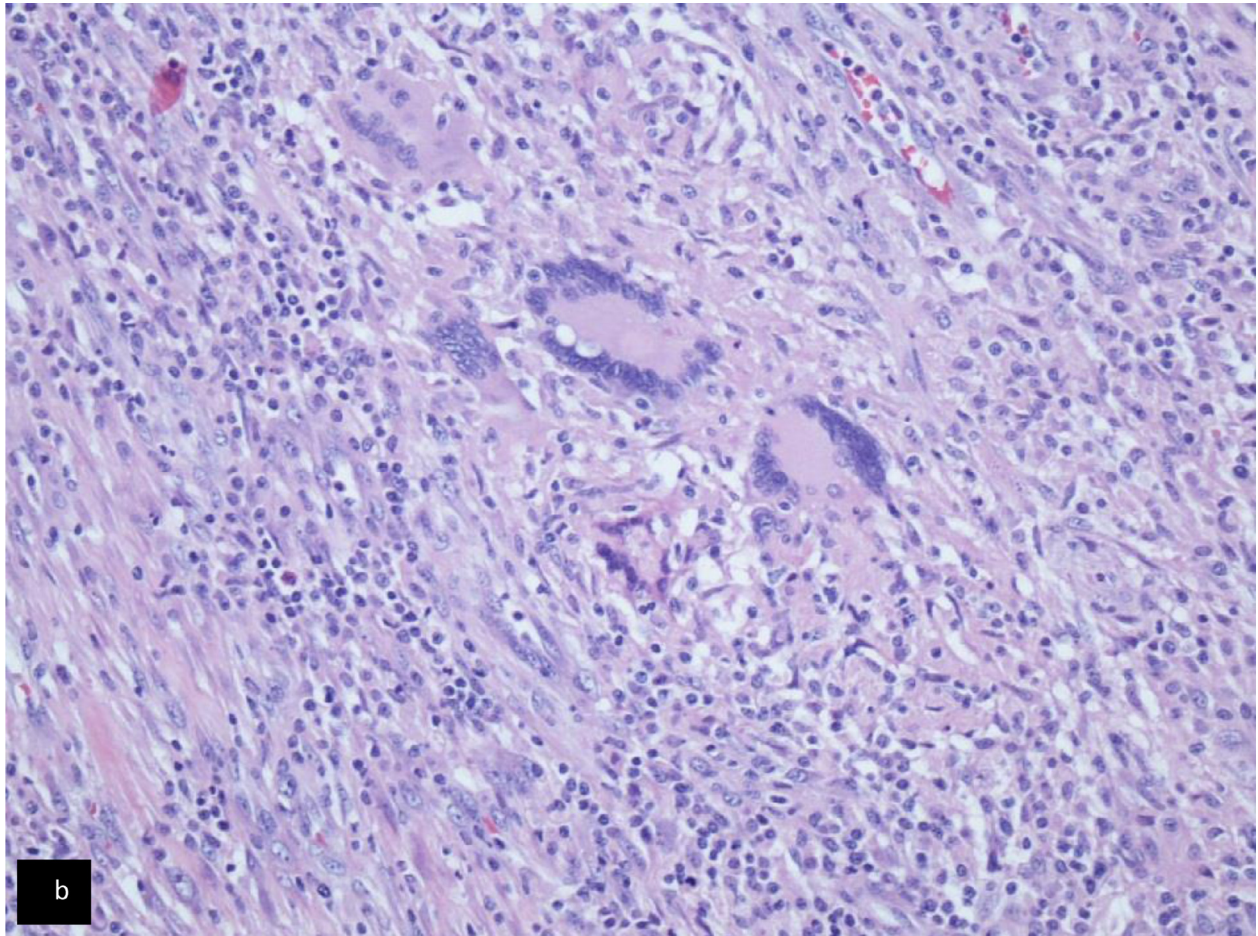


Fig. 4b – High power photomicrograph of orchietomy specimen demonstrating giant cells suggestive of tuberculosis.

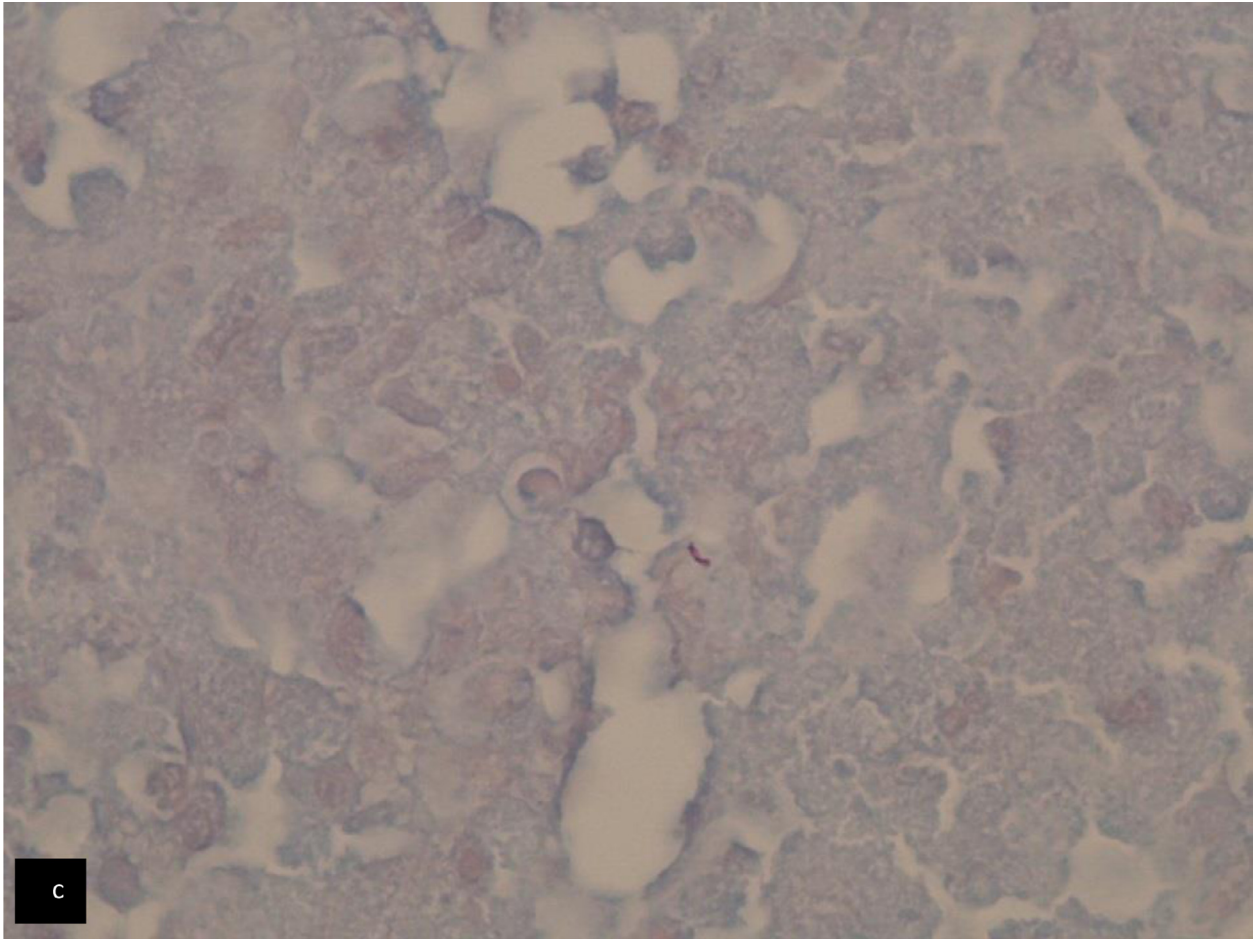


Fig. 4c – Acid fast stain showing sparse acid-fast bacilli.

scrotum includes scrotal skin thickening, blurred separation between the testis and the epididymis, hydrocele, and calcification of the epididymis and tunica vaginalis [8–10].

Testicular TB may be confirmed with fine needle aspiration and cytology or testicular biopsy [11]. Fine needle aspiration may show epithelioid granulomas and acid-fast bacilli staining may be positive for occasional acid-fast bacilli.

Treatment options for testicular TB include anti-TB antibiotic therapy and orchiectomy. While the patient elected to undergo orchiectomy for his suspected testicular TB, an anti-TB antibiotic regimen could include rifampicin, isoniazid, pyrazinamide, and ethambutol with follow-up imaging to document resolution [12]. Ultimately, orchiectomy is the best current treatment option particularly in resistant cases [12].

Drug Names and Instrument Names

BCG vaccine, rifampicin, isoniazid, pyrazinamide, ethambutol.

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