"BCGitis": A rare case of tuberculous epididymo-orchitis following intravesical Bacillus Calmette-Guérin therapy

Virginie Demers¹, Vincent Pelsser¹

¹Department of Diagnostic Radiology, Jewish General Hospital, Montreal, Canada

Correspondence: Virginie Demers, MD BSc, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec, Canada, H3T 1E2 (virginie.demers@mail.mcgill.ca)

ABSTRACT

Tuberculous epididymo-orchitis is a rare complication of intravesical Bacillus Calmette-Guérin (BCG) therapy for urothelial cancer of the bladder. We present such a case, describe its sonographic appearance and review the literature. The difficulties in diagnosing this condition based on imaging alone, given the extensive overlap with the appearance of bacterial epididymo-orchitis, malignant testicular disease and testicular torsion, are discussed. Adequate knowledge of tuberculous epididymo-orchitis is of capital importance in order to ensure a proper diagnosis and treatment.

CASE REPORT

A 76-year-old man, with a history of diabetes mellitus type II, hypertension, pericarditis, coronary artery disease and without any previous urological history presented to the emergency room with an intermittent history of hematuria. He was diagnosed with papillary urothelial carcinoma of the bladder and treated with transurethral resection of bladder tumor (TURBT) as well as six treatments of intravesical instillation of BCG. During the following 7 years, he had several recurrences for which he had other transurethral resections and mitomycin chemotherapy.

Seven years after his initial diagnosis of bladder cancer, the patient presented to the emergency room with left testicular pain. He was clinically diagnosed with epididymo-orchitis and treated with a 7-day course of antibiotics which partially relieved his symptoms. Two months later, the patient returned to the emergency room with similar symptoms and was diagnosed and treated for another episode of epididymo-orchitis.

Five months later, the patient returned for the third time with left testicular pain, swelling and a new testicular mass. An ultrasound of the testicle was performed (Figure 1), showing a heterogeneous 3.2 x 3.2 x 2.8 cm mass in the inferior portion of the left testicle which appeared continuous with the epididymal tail. Low-grade internal flow was noted upon Doppler interrogation as well as peripheral linear flow. In addition, the testicular mass was contiguous with a second medial extra-testicular nodule, also demonstrating peripheral linear flow and measuring 2.7 x 2.2 cm. A small hydrocele was present. There was no significant skin thickening. The upper portion of the left testicle, the left epididymal head and body and the right scrotal content were normal. A malignancy was initially suspected by imaging.

The patient was treated with a 2-week course of ciprofloxacin and given a urological follow-up appointment. One month following this treatment, he was seen in the urology clinic. A left radical orchiectomy was planned and performed on the basis of increasing size of the left testicular mass and lack of response to antibiotics.

Macroscopically, the left testicle contained an exophytic mass which, upon dissection, demonstrated a necrotic nodule measuring 3.2 x 3.2 x 2.8 cm (Figure 2). The mass was partly intra-testicular and partly extra-testicular, extending beyond the tunica albuginea and the testicular capsule to the tail of the epididymis. On pathological analysis (Figure 3), the left testicle showed multiple necrotizing granulomas with presence of rare acid-fast bacilli. The assay for M. tuberculosis DNA by
PCR method was positive. Final cultures grew Mycobacterium bovis, the organism used in BCG therapy. The patient was started on anti-tuberculous treatment.

**DISCUSSION**

“BCGitis”, or BCG-induced tuberculous epididymo-orchitis, is a rare granulomatous infection caused by Bacillus Calmette-Guérin therapy. It has been described in a small number of cases to affect several anatomic locations including the lungs [1], the liver [2,3], the bone marrow and bones [4], the kidneys [5], the eyes [6], the vessels [7,8], the prostate, the epididymis and the testicles [10].

The bacillus of Calmette-Guérin (Figure 4, Table 1) is an attenuated strain of Mycobacterium bovis, initially produced as a vaccine against tuberculosis, but introduced in 1972 as an intravesical treatment for urethral cancer of the bladder. When instilled into the bladder, these mycobacteria cause an inflammatory/immune reaction responsible for the destruction of tumor cells. It is currently considered, in combination with TURBT, as the treatment of choice for lesions staged T1 (carcinoma extending to the lamina propria but not involving the muscular layer) or less [11].

We report a case of tuberculous epididymo-orchitis following intravesical treatment with BCG.

Granulomatous epididymo-orchitis is a rare complication from intravesical BCG therapy for urethral bladder cancer, with only 12 previous cases described, to our knowledge, in the English literature. A previous extensive study showed that genito-urinary complications occurred in only 0.9% of patients treated with intravesical BCG [9]. Risk factors for “BCGitis” include intravesical treatment with BCG, recent instrumentation or catheterization, immunocompromised state and recent urological trauma.

Clinically, patients usually present with painful or painless scrotal enlargement. Local symptoms may rarely be accompanied by fever and leukocytosis [11].

The infection usually starts as discrete or conglomerate necrotic areas in the epididymis. Whether it begins in the tail of the epididymis [12,13] or initially involves its entire body [14] remains a point of contention. The testis may become involved, either from direct extension from the epididymis or from hematogenous spread [15]. Isolated tuberculous orchitis from hematogenous spread without epididymal involvement is rare [14,17].

Distinct gray scale sonographic patterns of granulomatous epididymitis have been described and include 1) diffuse enlargement of the testis with either a heterogeneous or homogeneous hypoechoic appearance, 2) nodular enlargement of the testis with heterogeneous hypoechoic appearance and 3) multiple small hypoechoic nodules (miliary appearance) in the enlarged testis [12-14].

Other associated sonographic findings include thickened scrotal skin, hydrocele, lack of clear separation between the epididymis and the testis, intra-scrotal extra-testicular calcification (in the epididymis and in the tunica vaginalis of the testis), scrotal abscess, and scrotal sinus tract [15].

The radiological appearance of granulomatous or tuberculous epididymo-orchitis can be a diagnostic challenge, especially given its similarity to bacterial epididymo-orchitis, malignant testicular disease and testicular torsion. Its diagnosis however remains of critical importance for clinical management.

**Differentiating tuberculous epididymo-orchitis from bacterial infection**

In cases of bacterial infection, patients typically present with fever, dysuria, and severe scrotal pain. Sonographically, diffuse enlargement of the epididymis with hypoechoigenicity is usually characteristic of non-tuberculous epididymitis while in most of the reported case of tuberculous epididymo-orchitis, heterogeneity of the epididymis, which is thought to be caused by the various stages of granulomatous infection (caseation necrosis, granuloma formation and fibrosis), was a distinctive sonographic feature [12-14]. The presence of calcifications from chronicity or of a sinus tract draining necrotic pus from a caseous abscess may also enhance the heterogeneous echotexture of the epididymis in tuberculous epididymitis [14]. On color Doppler sonography, non-granulomatous epididymitis usually shows Doppler signal within the affected epididymis whereas granulomatous epididymitis may show linear or focal Doppler signal at the periphery of the epididymis [17].

**Differentiating tuberculous epididymo-orchitis from testicular malignancy**

The presence of epididymal enlargement together with a testicular lesion is suggestive of an infection rather than a neoplastic process because orchitis is almost always caused by epididymitis, whereas tumors usually partially involve the epididymis from direct extension only in the advanced stage [18]. The sonographic detection of skin thickening and hydrocele is also suggestive of infection rather than testicular tumors.

**Differentiating tuberculous epididymo-orchitis from testicular torsion**

The sonographic appearance of testicular torsion in the acute phase is usually a diffuse hypoechoic enlargement of the testis while in the later phase, it is heterogeneous secondary to hemorrhage and necrosis. Reactive hydrocele and skin thickening may also occur. In such circumstances where the findings of tuberculous epididymo-orchitis and testicular
torsion overlap, color Doppler ultrasound is useful, as venous blood flow in patients with testicular torsion is reduced or absent, whereas it is increased in cases of infection.

Lastly, a history of intravesical BCG instillation and failure of conventional antibiotic therapy are helpful clues in establishing the diagnosis of "BCGitis". Knowledge of the sonographic appearance of tuberculous epididymo-orchitis and its common mimickers help ensure an accurate diagnosis and appropriate management.

The most recent recommendations for the treatment of localized M. Bovis BCG infection consist of 300 mg of isoniazid for 3 months supplemented with rifampin and isonicotinylhydrazine (INH) with or without fluoroquinolones for 3-6 months [19]. The regimen varies for systemic M. Bovis BCG infection and/or sepsis. Although the diagnosis is often established after orchietomy because of a suspicion of testicular cancer, as in this case, if BCG-induced granulomatous epididymo-orchitis is part of the differential diagnosis, a biopsy should first be performed.

TEACHING POINT

The radiological appearance of granulomatous or tuberculous epididymo-orchitis can be a diagnostic challenge, especially given its similarity to bacterial epididymo-orchitis, malignant testicular disease and testicular torsion. While the diagnosis of tuberculous epididymo-orchitis has traditionally been made by histological examination following surgery, awareness of its sonographic appearance should help avoid unnecessary orchietomy.

REFERENCES


FIGURES

Figure 1: 76-year-old male with left tuberculous epididymo-orchitis. Sonographic views of the left testicle, including Doppler ultrasound. A Longitudinal image shows a heterogeneous mass in the inferior portion of the testicle; B transverse image of the lower testicle shows continuity (white arrow) of the testicular lesion (right side) with an extra-testicular lesion medially; C longitudinal image demonstrates extension of the epididymal mass (dotted arrow) into the lower pole of the testicle (white arrow); D Doppler ultrasound of the testicle and epididymis shows internal hypovascularity and peripheral increased flow. (All images obtained with a 12 MHz linear transducer)
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Figure 2: 76-year-old male with left tuberculous epididymo-orchitis. Macroscopic pathology. Transection of the left testicle and epididymis demonstrates a necrotic caseating nodule measuring 3.2 x 3.2 x 2.8 cm (white arrow).

Figure 3: 76-year-old male with left tuberculous epididymo-orchitis. Microscopic pathology, Hematoxylin and Eosin (H&E) stain. Low power view reveals multiple necrotizing granulomas with central areas of necrosis surrounded by collections of epithelioid histiocytes as well as many Langerhans multinucleated giant cells and a chronic inflammatory infiltrate.

<table>
<thead>
<tr>
<th>Etiology</th>
<th><em>Mycobacterium bovis</em>, used as an intravesical treatment for urothelial cancer of the bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.4% of patient treated with intravesical BCG</td>
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<tr>
<td>Gender Ratio</td>
<td>Male only</td>
</tr>
<tr>
<td>Age predilection</td>
<td>Generally, men older than 60 years old</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Intravesical treatment with BCG, recent instrumentation or catheterization, immunocompromised state, recent urological trauma</td>
</tr>
<tr>
<td>Treatment</td>
<td>300 mg of isoniazid for 3 months supplemented with rifampin and isonicotinylhydrazine (INH) with or without fluoroquinolones for 3-6 months +/- corticosteroids</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Orchietectomy can be avoided if promptly diagnosed and treated</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Variable. Classically, diffuse enlargement with heterogeneous hypoechoic appearance of the epididymis, nodular enlargement of the testis with heterogeneous hypoechoic appearance, linear or focal Doppler signal at the periphery of the epididymis, intra-scrotal extra-testicular calcifications, caseous abscess, sinus tract and skin thickening</td>
</tr>
</tbody>
</table>

Table 1: Summary table for BCG-related tuberculous epididymo-orchitis.
### Table 2: Sonographic appearance of different testicular lesions included in the differential diagnosis of granulomatous or tuberculous epididymo-orchitis

<table>
<thead>
<tr>
<th>Granulomatous or tuberculous epididymo-orchitis</th>
<th>Testis</th>
<th>Doppler</th>
<th>Other possible characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse enlargement with heterogeneous or rarely homogeneous hypoechoic appearance</td>
<td>Nodular enlargement with heterogeneous hypoechoic appearance or Diffuse testicular enlargement with multiple small hypoechoic nodules</td>
<td>Linear or focal Doppler signal at the periphery of the epididymis</td>
<td>Intra-scrotal extra-testicular calcifications</td>
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<td></td>
<td></td>
<td></td>
<td>Caseous abscesses</td>
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<td></td>
<td></td>
<td></td>
<td>Sinus tract</td>
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<td></td>
<td></td>
<td></td>
<td>Skin thickening</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacterial epididymo-orchitis</th>
<th>Testis</th>
<th>Doppler</th>
<th>Other possible characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse enlargement with homogeneous hypoechoic appearance</td>
<td>Diffuse enlargement with heterogeneous or homogeneous hypoechoic appearance</td>
<td>Diffuse increased blood flow in the epididymis</td>
<td>Fever</td>
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<td></td>
<td></td>
<td></td>
<td>Dysuria</td>
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<td></td>
<td></td>
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<td>Scrotal pain</td>
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<td></td>
<td></td>
<td></td>
<td>Hydrocele</td>
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<td></td>
<td></td>
<td></td>
<td>Skin thickening</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant testicular lesion</th>
<th>Testis</th>
<th>Doppler</th>
<th>Other possible characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal unless rare direct extension</td>
<td>Mass of mixed echogenicity</td>
<td>Mixed vascularity in the testis</td>
<td>Calcifications</td>
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<td></td>
<td></td>
<td></td>
<td>Cysts</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Testicular torsion</th>
<th>Testis</th>
<th>Doppler</th>
<th>Other possible characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal appearance or Diffuse enlargement with hypoechoic appearance</td>
<td>Normal parenchymal or Diffuse enlargement with hypoechoic (early) or heterogeneous (late) appearance</td>
<td>Reduced or absent blood flow in the testis</td>
<td>Hydrocele</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Skin thickening</td>
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<tr>
<td></td>
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<td>Pain</td>
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</tbody>
</table>

### ABBREVIATIONS

BCG: Bacillus Calmette-Guérin  
TURBT: Transurethral resection of bladder tumor  
PCR: Polymerase chain reaction

### KEYWORDS

Tuberculous epididymo-orchitis; intravesical Bacillus Calmette-Guérin; BCGitis; granulomatous epididymo-orchitis; tuberculosis; epididymitis

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