CASE REPORT

Tuberculous epididymitis following intravesical Bacillus Calmette-Guérin immunotherapy

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Intravesical Bacillus Calmette-Guérin (BCG) is widely used as an adjuvant therapy in the treatment of superficial bladder cancer. BCG is administered as a live, attenuated form of Mycobacterium bovis, and acts as an immunomodulary agent to delay tumor progression. BCG is generally well tolerated, though localized and systemic infectious complications may occur. A literature search revealed that tuberculous epididymitis is a rarely reported complication of intravesical BCG therapy. We report the case of an 82-year-old male who developed tuberculous epididymitis while undergoing intravesical BCG treatment for transitional cell carcinoma of the bladder. Right orchiectomy was performed, followed by rifampin and isoniazid therapy once M. bovis was identified as the infectious agent. The patient responded well to these treatments, and made a full recovery. Tuberculous epididymitis is an uncommon complication resulting from intravesical BCG therapy, which is likely explained by retrograde migration from the prostatic urethra in this case.

Key Words: BCG, tuberculous epididymitis, bladder cancer

Case report

An 82-year-old white male was undergoing intravesical Bacillus Calmette-Guérin (BCG) therapy for papillary transitional cell carcinoma of the bladder. A standard course of 6 weekly BCG treatments was initiated in October 2005. Cystoscopy demonstrated that the tumor responded well to treatment, though the patient did suffer side effects including moderate to severe cystitis, mild fever, and malaise. Tumor regrowth was noted in August 2006 during cystoscopy and transurethral resection was performed. Two weekly doses of BCG were subsequently administered before the treatment was discontinued by the patient, as the side effects were not tolerable.

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In March 2007, the patient presented with a painful, right scrotal mass. On clinical examination, the right hemiscrotum was swollen and tender. A 1 cm mass was palpable at the inferior pole of the right testicle. There was evidence of induration upon palpation of the right epididymis. Patient was afebrile with normal vital signs. Abdominal examination and chest x-ray 1 month previous were normal. Urinalysis showed microscopic hematuria, but was otherwise normal.

His past medical history was significant for a previous episode of bacterial epididymitis in 2002, in which *Escherichia coli* was identified as the causative agent. This was successfully treated with a course of tetracycline. He underwent tuberculin purified protein derivative (PPD) skin testing at that time, which was negative at 0 mm.

The patient was treated empirically with tetracycline, and showed improvement, though the scrotal pain worsened upon cessation of the antibiotic treatment.

Testicular ultrasound demonstrated a diffusely heterogeneous texture of the right testicle, Figure 1. A 9 mm diameter cyst was present arising from the head of the right epididymis, along with hypervascularization suggestive of epididymitis.

The patient underwent a right orchiectomy, and incision and drainage of the right scrotal abscess was performed. Pathological examination revealed a 1.3 mm soft nodule within the epididymis showing a large area of central caseous necrosis surrounded by reactive fibroblastic proliferation, mild lymphocytic inflammation, and an occasional multinucleated giant cell. Adjacent area demonstrated granulomatous inflammation with multinucleated giant cells, Figure 2 and 3. The lower pole of the specimen contained a dense fibrous area approximately 3.5 cm x 2.0 cm x 2.5 cm. No testicular involvement was noted. Acid fast bacilli were identified in the necrotic portion of the granulomatous tissue. Cultures were positive for *M. bovis*, and no additional pathogens were identified. The patient was treated with a 6 month course of rifampin and isoniazid, which has proven well tolerated.

Tumor regrowth was noted on cystoscopy in June 2007, which was treated by transurethral resection. He continues to be monitored for tumor recurrence, and is otherwise doing well.

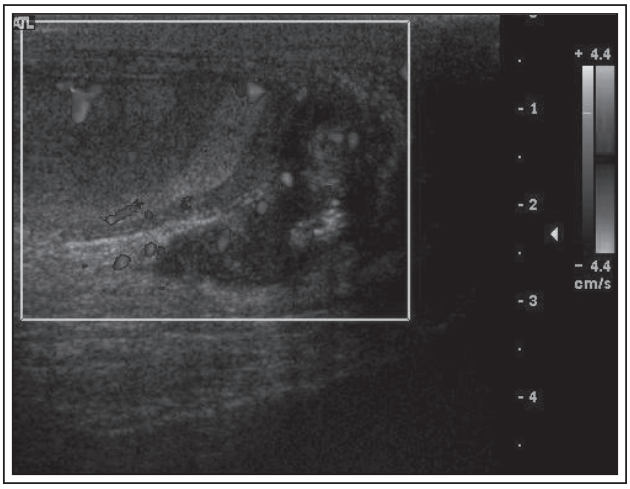

Figure 1. Doppler ultrasound demonstrating a thickened, hypervascular epididymis and normal testicle.

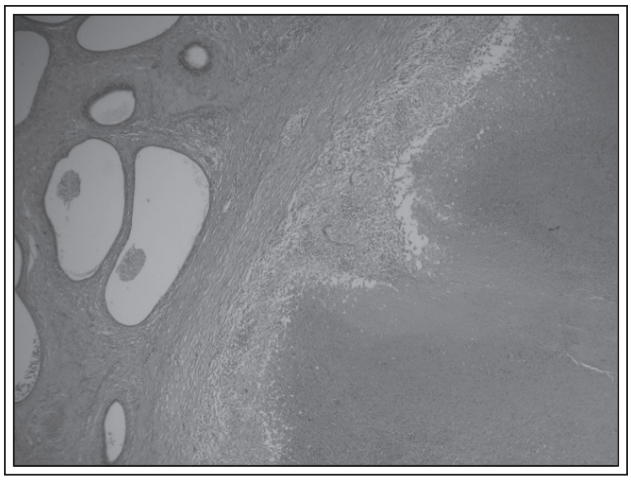

Figure 2. Low power view displaying caseating granuloma adjacent to epididymal ductules. A few acid-fast bacilli were identified (not shown).

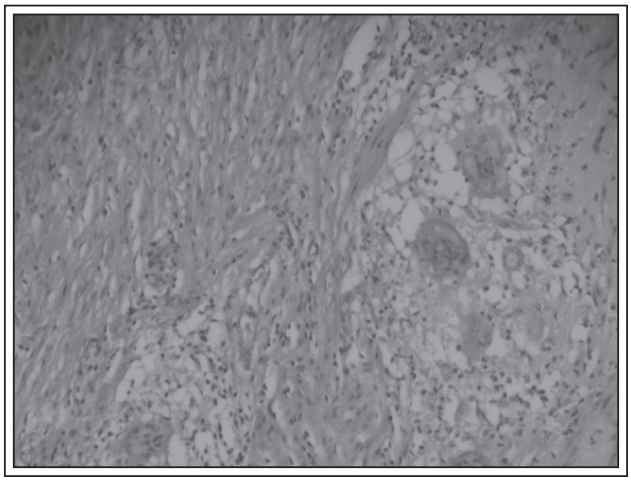

Figure 3. High power view showing granulomas with multinucleated (Langhan's type) giant cells.

Discussion

Superficial transition cell carcinomas of the bladder have a 5 year recurrence rate of 50%-70%.[1] This has necessitated the need for an effective adjuvant therapy in addition to transurethral resection. Intravesical BCG is now considered the adjuvant therapy of choice, as it has been statistically shown to decrease tumor recurrence rate and delay progression.[1]

The mechanism of action of BCG is incompletely understood. It is thought that BCG facilitates a local immune response involving the expression of specific cytokines. BCG may act directly on tumor cells, though T helper cells, cytotoxic T cells, and natural killer cells have been shown to mediate its anti-tumor effects. It has been recently suggested that nitric oxide may play a role in the anti-tumor activity of BCG.[2]

Intravesical BGC therapy is associated with few serious side effects, as > 95% of patients tolerate BCG without significant morbidity. Most patients report mild side effects such as urinary frequency and dysuria, malaise, and a low grade fever as a result of immune stimulation. In patients undergoing BCG therapy, fever has been associated with an improved response to treatment. In patients with an increase in severity of symptoms, the dosage of BCG may be reduced and 300 mg of isoniazid may be given daily. In 2602 patients treated with intravesical BCG, the following complications were reported: fever (2.9%), hematuria (1.0%), granulomatous prostatitis (0.9%), pneumonitis/hepatitis (0.7%), arthralgia (0.5%), epididymitis (0.4%), rash (0.3%), ureteral obstruction (0.3%), contracted bladder (0.2%), renal abscess (0.1%), and cytopenia (0.1%).[3]

Those patients with evidence of BCG related infectious complications, such as prostatitis, pneumonitis, hepatitis, and epididymitis should be treated with isoniazid and rifampin 600 mg daily for 3-6 months.[3]

Tuberculous epididymitis is an uncommon complication resulting from intravesical BCG therapy. Infection may occur via hematogenous spread, though retrograde migration from the prostatic urethra provides a more likely explanation in this case.[4]

Cases of isolated tuberculous epididymitis resulting from intravesical BCG therapy have been reported in the literature.[5,6] Though these reports highlight the rarity of this occurrence, Wilson et al[7] have speculated that this complication may be more common that previous reports have suggested.

The patient in this case report continues to be monitored for tumor recurrence. Due to the previous local and infectious complications, he is not a candidate for further BCG therapy. If further tumor recurrence is identified, he will be managed with transurethral resection of the tumor.

Conclusion

Though tuberculous epididymitis and other infectious sequelae resulting from intravesical BCG therapy are rare, it is essential to recognize and treat such cases promptly. In any patient undergoing BCG immunotherapy who presents with epididymal inflammation or scrotal swelling, consideration should be given to the possibility of BCG as an infectious etiology. □

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