

CASES

Attenuated but live: a pelvic abscess caused by bacille Calmette–Guérin

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A 64-year-old man presented with a three-week history of a tender suprapubic mass. His medical history included superficial (stage T1) transitional cell carcinoma of the bladder for which he had undergone transurethral resection of the tumour 10 months earlier. At the time of surgery, he had received one dose of intravesical mitomycin followed by six intravesical instillations of bacille Calmette–Guérin (BCG), without complication. Follow-up cystoscopy performed three months before his current presentation had shown an ulcerative lesion that was suspicious for recurrence of cancer, and his BCG therapy had been resumed. Following his third weekly instillation of BCG, he had developed fever, chills and scrotal pain. His treatment had been discontinued; however, his pain had worsened over a three-week period to the point where he was no longer able to walk.

On examination, the patient was grimacing in pain. His blood pressure was 110/74 mm Hg, heart rate was 100 beats/min and temperature was 38.4°C. A firm, tender, nonmobile suprapubic mass was palpated that extended into the scrotum. Inguinal lymph nodes were not enlarged.

The results of laboratory investigations showed a hemoglobin concentration of 93 (normal 140–180) g/L, a leukocyte count of 7.0 (normal 4.0 – 11.0) $\times 10^9$ /L with a normal differential, and a platelet count of 357 (normal 150–400) $\times 10^9$ /L. The creatinine level was 83 (normal < 109) $\mu\text{mol/L}$, and results of urine and blood cultures for bacteria were negative. Magnetic resonance imaging (MRI) of the pelvis showed a small area of nodular enhancement on the anterior aspect of the bladder neck that was contiguous with the pubic symphysis. In addition, there was a large collection in the soft tissue anterior to the pubic symphysis with extension into the left adductor muscles (Figure 1).

The timing of the patient's symptoms in relation to his BCG therapy raised the possibility of a complication from the treatment; specifically,

infection with *Mycobacterium bovis*–BCG. Specimens of first morning urine were taken for mycobacterial culture. An ultrasound-guided biopsy and drainage of the collection in the soft tissue was performed and the sample submitted for pathologic examination and culture. The patient was given isoniazid and rifampin, empirically, for the treatment of presumed infection with *M. bovis*–BCG. Three specimens of morning urine subsequently grew an organism belonging to the *Mycobacterium tuberculosis* complex that was later confirmed to be *M. bovis*–BCG. Results of acid-fast staining of the ultrasound-guided aspirate were positive. In addition, culture of the aspirate grew *M. bovis*–BCG, which was susceptible to isoniazid and rifampin, but resistant to pyrazinamide. Tissue biopsy showed focal fat necrosis and chronic inflammation, without evidence of malignancy. The patient completed a one-year course of therapy with isoniazid and rifampin, and follow-up MRI of the pelvis showed complete resolution of the collection. There was no recurrence of infection more than four years after the completion of therapy.

Discussion

Transitional cell carcinoma of the bladder has an incidence of 27 cases per 100 000 people per year and is the fourth most common cancer among Canadian men.¹ About 70% of incident

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KEY POINTS

- Bacille Calmette–Guérin (BCG), a live, attenuated strain of *Mycobacterium bovis*, is used as adjuvant immunotherapy for the treatment of superficial bladder cancer.
- Infection with *M. bovis*–BCG is a complication of intravesical BCG therapy that can present as local or disseminated infection.
- Biopsy and culture are paramount to distinguish between BCG-related infection and recurrence of cancer.
- Bacille Calmette–Guérin is intrinsically resistant to pyrazinamide, but susceptible to other first-line antituberculous drugs.

cases of transitional cell bladder cancer do not invade muscle.² Standard treatment in this setting includes transurethral resection of the tumour followed by adjuvant intravesical therapy, usually with BCG.

Bacille Calmette–Guérin is a live, attenuated strain of *M. bovis* that has been used as a vaccine against tuberculosis for nearly a century. Its role as an immunotherapeutic agent for the treatment of cancer has been recognized since the 1970s, notably in the treatment of superficial transitional cell carcinoma of the bladder and malignant melanoma. The antitumour effect of BCG is thought to be mediated through the stimulation of local cytotoxic T cell responses that are directed against tumour cells.³ Adjuvant intravesical BCG therapy for superficial transitional cell carcinoma has been repeatedly shown in randomized controlled trials to reduce the risk of tumour recurrence.² When compared with intravesical chemotherapy, treatment with weekly BCG for six weeks is superior in terms of complete response and disease-free survival.²

Infections complicating intravesical BCG therapy

Although most patients do not experience complications of intravesical BCG therapy, there is considerable literature on clinical infections caused by *M. bovis*–BCG in this particular set-

ting. Clinical manifestations of infection with *M. bovis*–BCG range from local genitourinary infections to disseminated disease with organ involvement (Box 1).^{4,7}

The incidence of these complications was best studied in a review of 2602 patients who received intravesical BCG for the treatment of superficial bladder cancer.⁵ Greater than 95% had no important adverse events, whereas 2.9% experienced fever. Less than 1% experienced granulomatous prostatitis, granulomatous pneumonitis or hepatitis, epididymitis, sepsis or renal abscess. A review of the records from the Public Health Laboratories of the Ontario Agency for Health Protection and Promotion showed that there were 27 unique patient samples that grew *M. bovis*–BCG for the period of 2007–2010, inclusive (Dr. Frances Jamieson, Public Health Laboratories, Ontario Agency for Public Health Protection and Promotion: personal communication, 2011).

Infections related to BCG may occur within weeks of intravesical therapy or may manifest months to years following its completion. Case series of patients who developed *M. bovis*–BCG infection following intravesical therapy with BCG have compared clinical presentations in relation to the time lapsed from the instillation.⁴ Those patients with early-presentation disease (occurring within three months of the first treatment) frequently present with prominent sys-

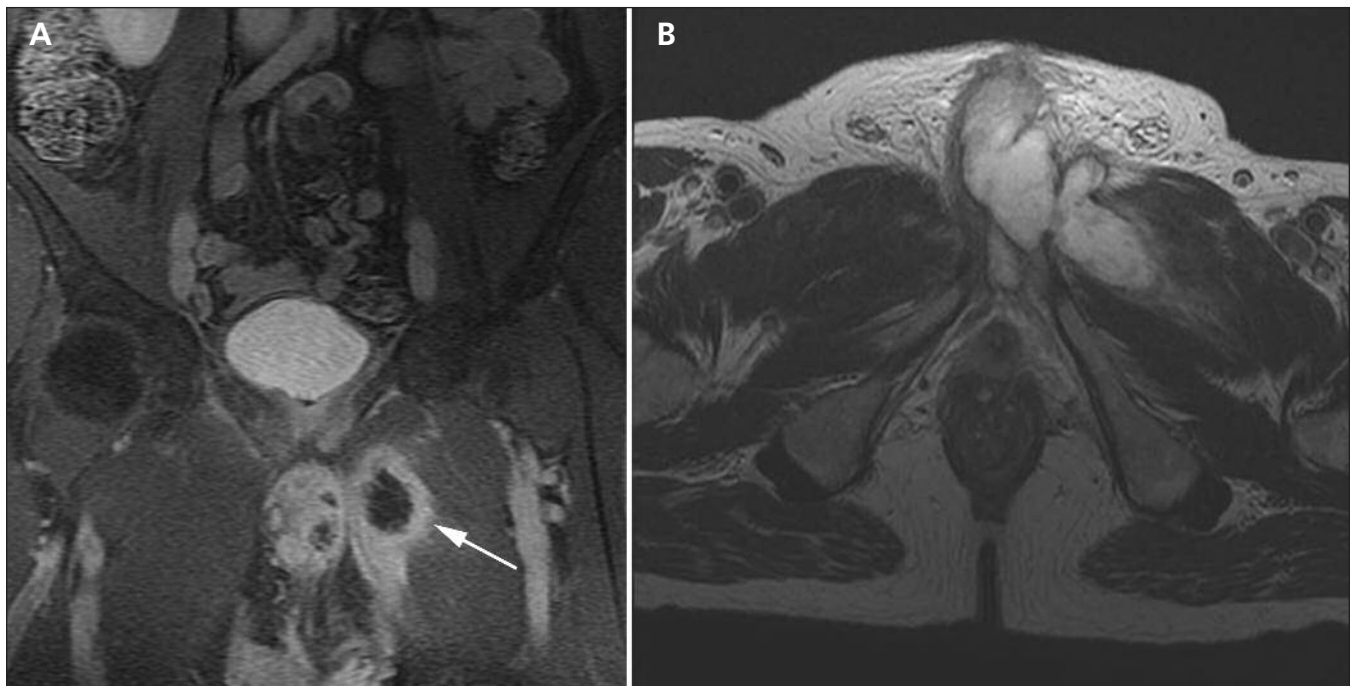


Figure 1: Gadolinium-enhanced magnetic resonance imaging of the pelvis of a 64-year-old man with fever, chills and scrotal pain, within one month after intravesical instillation of bacille Calmette–Guérin for transitional cell carcinoma of the bladder. (A) Coronal view showing active gadolinium extravasation from the bladder to an abscess in the left adductor muscles (arrow). (B) Axial view showing the presence of a multifocal collection anterior to the symphysis pubis.

temic symptoms including fever, chills, sweats and weight loss. Arthralgias have also been reported. Pulmonary infiltrates may suggest a diagnosis of granulomatous pneumonitis, whereas elevation of liver enzymes may suggest a diagnosis of granulomatous hepatitis. Because intravesical BCG is intended to elicit both local and systemic immune responses, it may be difficult to distinguish intended BCG-mediated immune responses from clinical infections caused by *M. bovis*-BCG.

In contrast, late-presentation infections following BCG immunotherapy (occurring more than one year following therapy) typically manifest as local reactivation within the genitourinary tract. Presentations include mass lesions in the prostate and testes. In these patients, systemic symptoms are generally absent. Late-presentation infections may also occur outside of the genitourinary system. Subclinical dissemination of *M. bovis*-BCG may occur at the time of the initial intravesical instillation of BCG, with late reactivation during periods of immunosuppression.

Our patient presented early, within one month of restarting BCG therapy. He had prominent systemic symptoms and local genitourinary disease, without evidence of hepatitis or pneumonitis. One possible explanation for this presentation is that the ulcerative lesion in his bladder played an important role in the pathogenesis of his infection by allowing for the extravasation of BCG into the surrounding tissues, resulting in an abscess.

Prophylaxis with antituberculous medications at the time of BCG instillation was not shown to reduce the incidence of *M. bovis*-BCG infection in one study.⁸ The best form of prevention appears to be the careful selection of patients who are to receive BCG therapy. Risk factors for infection with *M. bovis*-BCG include frequent BCG treatments, active cystitis and traumatic catheterization at the time of instillation, advanced age and congenital or acquired cellular immunodeficiency states.^{5,9}

Diagnosis and management of BCG-related infection

Biopsy and culture remain the gold standard for the diagnosis of BCG-related infections.^{4,5} Serial cultures of morning urine to test for mycobacteria may establish the diagnosis in local genitourinary infections, although cystoscopy and biopsy are still required to exclude the possibility of local tumour recurrence and progression.² The recovery of *M. bovis*-BCG from specimens submitted for culture may be low, especially in early-presentation diseases such as granulomatous hepatitis and pneumoni-

Box 1: Infections complicating intravesical bacille Calmette-Guérin for the treatment of superficial bladder cancer

Local genitourinary infections

- Testicular abscess^{4*}
- Epididymitis^{5*}
- Prostatitis^{5*}
- Renal abscess^{4*}

Disseminated infections

- Sepsis^{4,5†}
- Endophthalmitis^{6*}
- Hepatitis^{4,5†}
- Pneumonitis^{4,5†}
- Mycotic aneurysm[†]
- Septic arthritis^{7*}
- Other metastatic abscesses^{4,5**†}

*Late presentation.

†Early presentation.

tis.⁴ If cultures remain negative, evidence of granulomatous inflammation in a biopsy specimen is supportive of a diagnosis of BCG infection.^{4,5} Our patient's abscess was extravascular and required ultrasound-guided biopsy and culture for diagnosis.

Antituberculous therapy is the mainstay of treatment of BCG-related infection with appropriate drainage of abscess collections. *Mycobacterium bovis*-BCG is intrinsically resistant to pyrazinamide,¹⁰ a first-line agent for *M. tuberculosis*. The combination of isoniazid and rifampin is generally used for the treatment of *M. bovis*-BCG infection, based on small case series that have reported favourable outcomes.^{5,11} Patients usually receive treatment for 6–12 months, although the optimal duration of therapy is not known.⁴ Canadian guidelines recommend a minimum of nine months of therapy with isoniazid and rifampin for instances of pyrazinamide-resistant *M. tuberculosis* infection, although the treatment of *M. bovis*-BCG infection is not specifically addressed.¹⁰ Based on evidence from case reports, corticosteroids have sometimes been added in early-presentation disease when features of hypersensitivity may be prominent, but this practice has not been studied prospectively.^{4,12}

Clinicians should be aware of the potential for intravesical BCG to cause both localized and disseminated infections. Because infection with *M. bovis*-BCG may occur long after treatment of the bladder cancer, the link with prior BCG therapy may be missed. In these circumstances, patients may seek medical attention from physicians other than their treating urologists. A remote history of bladder cancer should prompt questions regarding previous BCG therapy in

patients who present with signs and symptoms compatible with BCG-related infection.

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