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Case report

A rare case of vertebral osteomyelitis with associated epidural abscess complicating BCG immunotherapy for transitional cell carcinoma of the bladder

Massimo Berneri [a], Fionnuala Murray [b,c,*], Sue Davel [a]

[a] Joondalup Health Campus, Cnr Grant Blvd &, Shenton Ave, Joondalup, WA 6027, Australia
[b] St John of God Hospital Subiaco, WA 6008, Australia
[c] Fiona Stanley Hospital, 11 Robin Warren Drive, Murdoch, WA 6150, Australia

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ABSTRACT

Bacillus Calmette-Guérin (BCG), a live attenuated strain of Mycobacterium bovis was first described as a vaccine against tuberculosis in 1921. The use of intravesical BCG to treat non-muscle invasive bladder cancer (NMIBC) was first described by Morales in 1921. The therapeutic effect of BCG is related to stimulation of the immune system following direct contact with tumour cells. As a result of this intended immune response some minor symptoms including fever, malaise and bladder irritation manifesting as dysuria, urinary frequency and mild haematuria, are expected. These side effects are however, generally easily managed and well tolerated. Severe complications are rare and can be temporally remote from the instillation of therapy. In this report we describe the case of a 74-year-old immunocompetent man with biopsy confirmed BCG T11/12 discitis and adjacent osteomyelitis of the T11/T12 vertebral bodies with an associated an epidural abscess following intravesical administration of BCG therapy for recurrent bladder transitional cell carcinoma (TCC).

Background

Bacillus Calmette–Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, was first described as a vaccine against tuberculosis in 1921 [1]. Since then, then the utility of BCG as an oncological immunotherapy has been studied in a variety of cancers both in vivo and in vitro [2–5]. Morales was the first to describe the use of intravesical BCG instilled via catheter as a beneficial treatment for superficial bladder cancers [6]. Intravesical BCG is now a widely used and successful treatment for superficial or "non-muscle invasive bladder cancers".

Though not fully elucidated, the mechanism of action of BCG relies on a primary immune response toward BCG which has secondary anti-tumour effects. The most pertinent mechanism is direct cytotoxicity mediated by CD4+/CD8+ lymphocytes, NK cells and granulocytes [7]. In patients with superficial bladder cancers, BCG is an extremely efficacious therapy at preventing muscle invasive disease. A large, randomised control trial by Lamm and colleagues showed an 84 % complete response rate in superficial disease, with 70 % of therapy responsive individuals remaining disease free at 5 years.

Whilst generally well-tolerated, the adverse effect profile of intravesical BCG is varied, and ranges from cystitis/haematuria to sepsis and potentially death [8]. It is thought that serious adverse events occur in less than 5 % of patients, most of which are immunocompromised [9]. Additionally, concurrent cystitis and traumatic catheterisation are thought to increase risk of serious adverse events to therapy [10,11].

We report the first Australian case of confirmed *M. bovis* vertebral osteomyelitis with associated epidural abscess from BCG therapy in an immunocompetent man. The case highlights a rare but serious adverse event following BCG therapy as well as the multimodal, multidisciplinary approach required to manage spinal BCG.

Case report

Our patient is a 74-year-old gentleman with a history of Transitional Cell Carcinoma of the bladder diagnosed in 2018, for which he initially underwent transurethral resection of the bladder tumour (TURBT) followed by 4 rounds of adjuvant cisplatin and gemcitabine. He was subsequently found to have a recurrence on routine surveillance cystoscopy 15 months after his initial diagnosis and went on to receive 6 intravesical BCG instillations. There was no known history of concurrent

* Corresponding author at: Fiona Stanley Hospital, 11 Robin Warren Drive, Murdoch, WA 6150, Australia.
E-mail address: Fionnuala.murray@health.wa.gov.au (F. Murray).

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bacterial cystitis or traumatic catheterisation during the time of his BCG therapy, however he did present with an episode of frank haemturia following his second instillation of BCG therapy. He has a history of macular degeneration and chronic lower back pain related to a previous L3 disc herniation but is otherwise fit and active and is not known to be immunocompromised. Approximately 14 months after his last BCG instillation, he presented with a 3-month history of worsening of his chronic lower back pain. He was afebrile and denied any associated weight loss, night sweats or lower limb weakness.

The white cell count was within normal limits, with a CRP of 38. An MRI of the spine subsequently demonstrated evidence of T11/12 discitis with adjacent osteomyelitis of the T11/T12 vertebral bodies and an epidural abscess (Fig. 1). A CT-guided aspirate was performed and was sent for microscopy and culture as well as 16S PCR. Serial blood cultures were negative. The biopsy material became smear positive for acid fast bacilli on day 3. GeneXpert PCR was positive for Mycobacterium tuberculosis complex with subsequent culture growing *Mycobacterium bovis* BCG strain, confirming epidural abscess due to intravesical BCG. At the time, a brief immunodeficiency screen was performed. Serum globulins were not decreased, HIV and hepatitis serology were negative. Standard anti-tuberculous therapy with rifampicin, isoniazid, pyrazinamide and ethambutol (RIPE) was initiated with vitamin-B6 while awaiting formal mycobacterial culture. Pyrazinamide was subsequently ceased upon confirmation of *Mycobacterium bovis* on culture, in light of the strains' inherent resistance to this agent. Chest plain film at the time did not reveal evidence of active TB.

The patient was subsequently transferred to our hospital with a severe worsening of lumbar back pain with bilateral radicular features. Neurological examination revealed normal tone and reflexes with 4+/5 power in left ankle dorsiflexion and plantar flexion. All other myotomes were preserved. Sensory and proprioceptive examination was unremarkable. Multimodal analgesia was used to good effect. He continued treatment with magnesium/manganese/pyridoxine complex, Isoniazid 300 mg OD, Ethambutol 1200 mg OD, Rifampicin 600 mg OD. He was commenced on prednisolone 50 mg OD on advice from infectious disease and continued on this for 2 months.

A month later, the patient was reviewed by a neurosurgeon who determined surgical intervention was indicated. He underwent decompression and surgical washout with spinal fusion/bone graft. Operative cultures were obtained and were again positive for *Mycobacterium bovis* BCG. The patient was managed in a brace post operatively and subsequently graduated off, with a good functional outcome. At present he has had 12 months of anti-TB therapy which he has tolerated well, with normal transaminases, renal function, and no ophthalmological sequelae of ethambutol. He is currently not using any opioid analgesia.

Discussion

Disseminated BCG is a rare but potentially life-threatening complication of BCG therapy. The true incidence of disseminated disease in contentious, with few cases of spinal BCG represented in the literature [12–14]. To the best of our knowledge, we report the first Australian case of spinal BCG from intravesical BCG therapy. The present case highlights several aspects of the medical and surgical management of BCG abscesses.

Evidence based management of *M. bovis* is difficult given the paucity of data pertaining to ecologically acquired *M. bovis*, let alone iatrogenic infection. Due to limited surveillance data, the true proportion of human TB infections caused by *M. bovis* remains to be accurately elucidated. In general, the proportion of clinically significant human TB attributable to *M. bovis* is lower in developed countries; perhaps owing to stricter bovine control and pasteurisation processes [15,16].

Our patient presented primarily with back pain, with subsequent imaging confirming osteomyelitis and epidural abscess. After surgical biopsy and microbiological analysis, he was commenced on multi agent therapy for mycobacterial spine infection based on microbiological specimens. However, limited retrospective data suggests that outcomes (including death) are less favourable in *M. bovis* infections [17,18].

For rifampicin susceptible *M. bovis*, a regimen on Rifampicin, Isoniazid and ethambutol is appropriate. Duration of therapy should be minimum of 9 months total for pulmonary and extrapulmonary disease; with potential for conversion to a maintenance regime of rifampicin/isoniazid dual therapy at 2 months [19,20]. Data from biopsy specimens in TB abscesses suggest that traditional agents penetrate well into the abscess, with therapeutic concentrations being found in biopsy specimens of patients treated with oral Rifampicin, isoniazid and pyrazinamide [21]. If there is a sclerotic boundary to the lesion, there is variable penetration [21] and surgical intervention may be warranted. In general, patients without neurological compromise and spinal instability have good outcomes with medical management alone (RIPE for

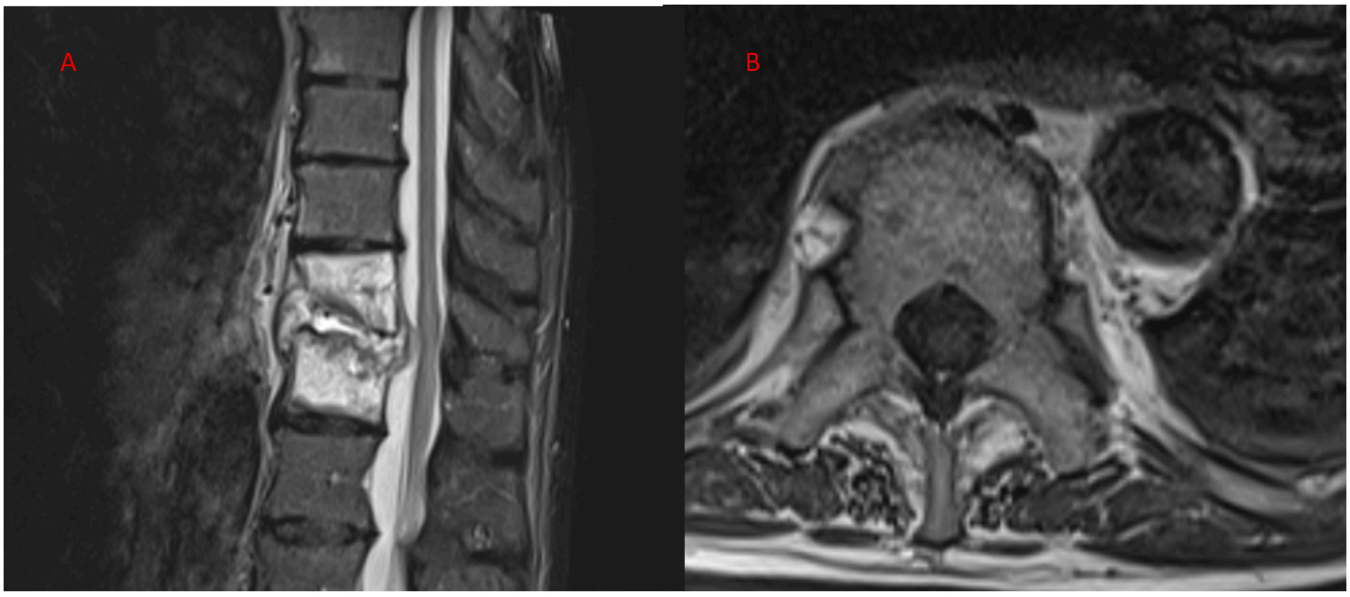

Fig. 1. A: STIR weighted sagittal lumbar/thoracic spine MRI revealing T11/12 Mycobacterium osteomyelitis, discitis and epidural abscess. B: T1 weighted transverse MRI highlighting epidural abscess approx. 13 mm in diameter.

6–18 months) and rarely require surgical management [21–23]. It is uncertain whether rates of failure of medical therapy are different in *M. bovis* infections.

After specialist team consultation, a course of steroid therapy was recommended. The role of steroids in spinal TB is highly contentious. The therapeutic rationale for corticosteroids is to reduce oedema associated with the lesion and/or progression to neurological compromise. There is sparse evidence for the use of corticosteroids in spinal TB, mainly reserved for specific clinical situations (arachnoiditis and non-osseous disease) [24]. Consequently, the prevalence of corticosteroid use in spinal TB is quite variable, with no study assessing dose, length of course, or route of administration [25,26].

The present case outlines a rare but significant adverse reaction to a commonly used bladder cancer therapy. Though there is significant data surrounding spinal TB infection, there is little for *M. bovis* and only sparse case reports for *M. bovis* BCG specifically. Accordingly, this condition is best treated by obtaining appropriate microbiological specimens and the involvement of a multi-disciplinary team consisting of infectious diseases, urology, and spinal surgeon. We acknowledge that severe reactions to BCG are quite rare, and that therapy should always be commenced in a shared care setting where a patient's risk of adverse outcome is balanced with the significant benefit BCG confers in superficial TCC. The optimal management of spinal *M. bovis* BCG is a potential area for future research regarding optimal duration of antimicrobial therapy and use of corticosteroids as adjunct therapy.

CRediT authorship contribution statement

Massimo Berneri: Conceptualization, Writing – original draft. **Fionnuala Murray:** Design, Writing – review & editing. **Sue Davel:** Conceptualization, clinical management, Supervision.

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Ethical approval

Not required.

Consent

Ethical approval was not required for the reporting of this case. The patient gave us written informed consent for the publication of this case report.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Data Availability

The data that supports the findings of this case study are available from the corresponding author upon request.

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