CASE STUDY

Please cite this paper as: Aitchison LP, Jayanetti V, Lindstrom ST, Sekel R. Myobacterium bovis peri-prosthetic hip infection with successful prosthesis retention following intravesical BCG therapy for bladder carcinoma. AMJ 2015;8(9):307–314.

http://doi.org/10.21767/AMJ.2015.2475

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ABSTRACT

Systemic dissemination and peri-prosthetic infection of Mycobacterium bovis (M. bovis) following intravesical Bacillus Calmette-Guerin (BCG) therapy presents a rare but significant complication of treatment for non-muscle invasive bladder carcinoma. We present a patient with Mycobacterium bovis infection of a prosthetic hip nine months following BCG therapy for bladder cancer. The debridement and (implant) prosthesis retention approach in conjunction with anti-tuberculous medication (DAIR) employed in this case, allowed the same prosthesis to be retained. This case report highlights the importance of physician awareness of the possibility BCG peri-prosthetic infections.

Key Words
Intravesical BCG therapy, non-muscle invasive urothelial carcinoma of the bladder, peri-prosthetic infection, Mycobacterium bovis

Implications for Practice:

1. What is known about this subject?
Peri-prosthetic seeding of a hip by Mycobacterium bovis as a complication of BCG therapy is a rare complication with only seven previously reported cases.

2. What is the key finding in this case report?
This case report illustrates eradication of Mycobacterium bovis infection from an afflicted hip joint replacement where the prosthesis has been retained, a first for the hip joint.

3. What are the implications for future practice?
Using anti-tuberculous therapy, BCG peri-prosthetic infections can be overcome without replacing the joint replacement components.

Background

Intravesical application of Bacillus Calmette-Guerin (BCG) immunotherapy is a proven and commonly recognised treatment in reducing both progression and recurrence of urothelial bladder cancer.1–3 Following transurethral resection of bladder tumour (TURBT), peri-operative instillation of BCG has been reported to result in systemic spread of Mycobacterium bovis (M. bovis) microorganisms to cardiac defibrillators, aortic grafts, and orthopaedic implants.4,5 Systemic dissemination of the M. bovis organism used in BCG therapy and subsequent peri-prosthetic seeding and infection is a rare but serious complication with the potential to cause significant morbidity in those affected.

We report a case of M. bovis seeding to a prosthetic hip replacement, clinically presenting nine months after the intravesical instillation of BCG for the treatment of superficial non-muscular invasive urothelial bladder carcinoma.
Case details
An 80-year-old previously active male presented in March 2013 with a cold, painless 10cm diameter fluid-filled mass in the right buttock posterolaterally with no overlying skin changes. This was associated with a one-month history of night sweats (soaking three shirts/night), anorexia, weight loss (6kg in five months), malaise, and fatigue. BCG treatment had been used for his superficial bladder urothelial carcinoma nine months earlier. In 1975, a primary total hip replacement (THR) was implanted, with three subsequent revisions for mechanical failure, with the last being in 2001, following which the patient had full mobility for 11 years.

Following a diagnosis of superficial urothelial carcinoma of the bladder nine years prior to presentation, multiple recurrences required treatment with six-monthly cystoscopies with repeated transurethral resection of bladder tumour (TURBT). Nine months prior to presentation, six well-tolerated rounds of weekly BCG intravesical therapy were administered with no side effects. Two subsequent cystoscopies at six and 12 months post-instillation revealed no tumour recurrence.

On presentation, inflammatory markers were significantly raised with an erythrocyte sedimentation rate (ESR) of 55mm/h (1–30mm/h) and C-reactive protein (CRP) of 64.6mg/L (0–12mg/L). Within a month of presentation, an X-ray of the right hip showed a lysis halo around the acetabular cup (Figure 1) as well as the distal end of the prosthesis (Figure 2). A bony gap had developed from bone resorption presumed to be a result of infection, a change from the nil abnormalities seen four months prior. Nuclear medicine scans (Tc and Ga) revealed soft tissue infection of the right posterolateral buttock, hip joint, and proximal thigh, involving the femoral and acetabular components.

Debridement and washout of the right hip was performed immediately. A large volume (~500cc) of purulent material was evacuated, with pus connecting between the acetabular component and shaft of the femur laterally. The thickened synovial lining was curetted back to normal tissue after removal of all fibrous necrotic material from within the joint. Initial intraoperative cultured specimens from the hip were negative and empirical 1g IV vancomycin bd was commenced. The CRP was reduced to 25mg/L. Two months after presentation polymerase chain reaction (PCR) was positive for Mycobacterium tuberculosis, the day prior to a planned two-stage hip exchange procedure, which was thus cancelled. Rifampicin 600mg, isoniazid 300mg, ethambutol 1.0g, pyrazinamide 2.0g, and pyridoxine 25mg daily was commenced. *M. bovis* was subsequently cultured; sensitivity testing showing resistance to pyrazinamide. Two further washout procedures of the abscess were performed three and four months after presentation.

Cultures from the second right hip washout three months after presentation grew *M. bovis*, as well as *Staph epidermidis* which was treated with two weeks of IV vancomycin, followed by clindamycin long term. Our patient became systemically well at four months from the beginning of treatment. Anti-tuberculous medication was reduced to ethambutol 1.6g, rifampicin 600mg, isoniazid 600mg, and pyroxidine 25mg, three times weekly and ceased 15 months after their commencement.

Further, and what is most remarkable to note, is that his previous bony defects around the femoral shaft and behind the acetabular cup filled in with new bone formation (Figures 3 and 4). This is a most integral process in the retention of the prosthesis, its functional viability being dependant on reversal of the loosening. Twenty-seven months from initial presentation, our patient remains systemically well, fully weight bearing and mobile without pain. There is a small 3mm sinus at the hip wound with minimal discharge but no surrounding erythema for which the patient is continuing to take 300mg clindamycin tds for its suppressive effect. There has been no clinical evidence of relapse of the *M. bovis* infection.

Discussion
The bladder intravesicular application of a live attenuated strain of *M. bovis* in the form the BCG is now routinely used in the treatment of carcinoma of the bladder and is superior to TURBT alone in preventing tumour recurrence.1,6-12

Localised side effects of BCG intravesical therapy to the bladder, including dysuria, urgency, frequency, and a low-grade fever are to be expected following treatment and are usually self-limiting within 48 hours.13 However, systemic complications have the potential, as with this patient, to cause significant morbidity and mortality.14-16 BCG bacteraemia was reported by Lamm to occur in 0.4 per cent of 2,602 patients,7 of which those with prostheses, such as cardiac pacemakers, orthopaedic hardware, or artificial valves, present a theoretically increased risk of bacterial seeding at these sites.17-19 Dissemination of bacteria around orthopaedic prostheses is an extremely rare occurrence with only seven cases reported in the literature (Table 1), with all but one having the original prosthesis removed.20-26
While fever is a common side effect of therapy (28 per cent of patients)\textsuperscript{27} and may even be associated with improved response to immunotherapy,\textsuperscript{28} a temperature lasting more than 48 hours or >39°C is an indication of organism dissemination, and the literature recommends that empirical anti-tuberculous treatment be commenced and further BCG therapy withheld until symptoms have resolved.\textsuperscript{7,14,29} Immuno-compromising and healing impairing factors such as previous pelvic irradiation, systemic steroid administration, diabetes, and persistent cystitis also need to be considered.\textsuperscript{14} Our patient had none of these risk factors or indications of dissemination.

With the increased morbidity and mortality associated with revision joint replacement surgery, it is preferable to overcome a BCG infection with non-operative treatment as described in this case; i.e., retention of joint prosthesis with prolonged anti-tuberculous treatment.

The BCG organism is known to be sensitive to anti-tuberculous therapy.\textsuperscript{30,31} There have been five reported cases of successful treatment of prosthetic \textit{M. bovis} infection post-BCG using revision arthroplasty with employment of at least two anti-tuberculosis drugs.\textsuperscript{20,21,23–25}

As such, two popular methods of surgical management for prosthetic joint infection were considered:

1. the debridement, antibiotics and implant retention strategy (DAIR); and
2. two-stage implant revision.

In view of the solidly ingrown large prosthetic stem used at the last revision 13 years ago, removal would have been extremely difficult, and a DAIR treatment approach for this case was adopted. This process involves surgical debridement of the joint, antibiotic therapy, and irrigation with retention of the prosthesis while replacing the modular stem ball and cup liner.\textsuperscript{32,33} Due to this combination of surgical management and long-term antibiotic therapy, this strategy allows conservation of the prosthesis with the potential for infection suppression or clearance, a first for the treatment of periprosthetic hip infection post-BCG instillation.\textsuperscript{35}

On identification of acid-fast bacilli, a regimen of anti-tuberculous drugs must be commenced alongside simultaneous further testing to differentiate between Mycobacterium species and to determine antibiotic sensitivities and resistances, subsequently allowing tailored antibiotic therapy. Furthermore, joint washouts should be considered to decrease the infection burden for the anti-tuberculosis drugs to overcome, thus augmenting drug therapy.

There has been previous consideration of prophylactic anti-tuberculous drugs for patients with prosthetic devices,\textsuperscript{17,34} but in a randomised controlled trial (RCT) of 952 patients, isoniazid was found to be ineffective as prophylaxis, given at three days for each BCG instillation for reducing both local and systemic side effects of BCG therapy.\textsuperscript{25} Furthermore, due to the rarity of peri-prosthetic \textit{M. bovis} infection following BCG therapy and the potential toxicities of anti-tuberculous drug therapy,\textsuperscript{15,36–38} further research is necessary to determine the risk-to-benefit ratio for prophylaxis.

It is important to be aware that bladder intravesical BCG therapy can disseminate still viable organisms around orthopaedic prosthetic implants, not just pacemakers and aortic plaques.\textsuperscript{4,5} If infection in any of these areas is suspected, it is important to culture not only for common organisms, but also for mycobacteria in these patients, and to order for PCR on cell block tissue for tuberculosis. If positive, further sequencing can lead to determination of \textit{M. bovis}. Our patient was treated successfully with repeated joint washouts, and anti-tuberculous therapy without removal of the hip replacement implants.

**Conclusion**

Dissemination of \textit{M. bovis} from bladder intravesical BCG therapy to protheses can occur. We present a case of hip prosthesis infection with \textit{M. bovis} that was successfully treated with anti-tuberculous medication and washouts without the need of prosthesis removal.

**References**

3. Sylvester RJ, Brausi MA, Kikrks WJ, et al. Long-Term Efficacy Results of EORTC Genito-Urinary Group Randomized Phase 3 Study 30911 Comparing Intravesical Instillations of Epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus Isoniazid in...


ACKNOWLEDGEMENTS
None

FUNDING
None

PATIENT CONSENT
The authors, Aitchison LP, Jayanetti V, Lindstrom S, Sekel R declare that:
1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

PEER REVIEW
Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.
Figure 1: X-ray of the right hip taken at presentation showing a lysis halo around the acetabular cup

Figure 2: X-ray of the right femur taken at presentation showing a lysis halo around the distal end of the prosthesis
Figure 3: X-rays of the right hip, left taken at presentation, right taken a year after presentation, note resolution of lysis around prosthesis

Figure 4: X-rays of the right femur taken left at presentation, right taken a year after presentation, note resolution of lysis around prosthesis
Table 1: Summary of published case reports involving *M. bovis* infection of orthopaedic prostheses following BCG treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Previous Orthopedic Operation/Time Until Presentation (Years)</th>
<th>Presentation</th>
<th>Diagnostics</th>
<th>Treatment/Joint Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chazerain et al.21</td>
<td>77/Male</td>
<td>TKA/9</td>
<td>Febrile, sterile monoarthritis of knee</td>
<td>Synovial and bone samples positive for AFB culture</td>
<td>Two years of antituberculous drugs (two drugs not mentioned) and two-stage arthroplasty / Asymptomatic at two years</td>
</tr>
<tr>
<td>Guerra et al.22</td>
<td>66/Male</td>
<td>THA/6</td>
<td>Progressive buttock pain radiating to knee and foot. Rigors and sweats present.</td>
<td>Cultures from prosthesis removal operation positive for AFB</td>
<td>Cement spacer implanted and six months of INH and RIF before passing away of other causes</td>
</tr>
<tr>
<td>Segal and Krauss24</td>
<td>76/Male</td>
<td>THA/4</td>
<td>Groin pain</td>
<td>Elevated ESR, CRP; THA loosening on imaging; Surgical debridement cultures positive for BCG</td>
<td>INH, RIF, ETA for one year with successful two-stage revision arthroplasty/ Asymptomatic at three years</td>
</tr>
<tr>
<td>Reigstad and Sieweres23</td>
<td>86/Male</td>
<td>THA/10</td>
<td>Groin pain</td>
<td>Elevated CRP; THA loosening on imaging; Surgical debridement cultures positive for BCG</td>
<td>One-stage revision arthroplasty with INH, RIF, PZA for six months, INH, RIF for six months, INH for one year. All antituberculous drugs ceased at two years/ Asymptomatic at 2.5 years</td>
</tr>
<tr>
<td>Gomez et al.20</td>
<td>82/Male</td>
<td>THA/10</td>
<td>Hip pain</td>
<td>THA loosening on imaging; <em>M. bovis</em> cultured from fluid acquired DI</td>
<td>One-stage revision arthroplasty with INH, RIF for one year/ Asymptomatic at one year</td>
</tr>
<tr>
<td>Srivastava et al.25</td>
<td>76/Female</td>
<td>THA/6</td>
<td>Painful hip</td>
<td>Intraoperative cultures showed <em>M. bovis</em></td>
<td>2-stage revision arthroplasty with nine months of antituberculous drugs/ Asymptomatic at five months</td>
</tr>
<tr>
<td>Rispler et al.26</td>
<td>66/Male</td>
<td>TKA/5</td>
<td>Joint effusion and stiff knee</td>
<td>Arthroscopy fluid cultures positive for AFB, identified as <em>M. bovis</em></td>
<td>Arthroscopic incision and drainage with Rif, INH for 12 months/ Asymptomatic at six years</td>
</tr>
<tr>
<td>Present Case</td>
<td>79/Male</td>
<td>THA/11</td>
<td>Cold, painless fluid filled mass on posterolateral buttock. 1 month of night sweats, anorexia, weight loss, malaise, and fatigue</td>
<td>Elevated ESR, CRP; THA loosening on imaging; DI drainage fluid PCR positive for <em>M. bovis</em>, later culture positive for <em>M. bovis</em></td>
<td>Two joint washouts undertaken with 13 months of Rif, INH, ETH/ Asymptomatic at two years</td>
</tr>
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