Case report

*Mycobacterium bovis* infection of total hip arthroplasty after intravesicular Bacillus Calmette-Guérin

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**ABSTRACT**

Intravesicular application of Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is effective in the treatment of bladder cancer. However, systemic dissemination and subsequent infection of implants have been reported. We present a case of *M. bovis* infection of a total hip arthroplasty 5 years after BCG instillation for bladder cancer. He was treated with debridement, antibiotics, irrigation, and prosthesis retention with appropriate antituberculous therapy. At 4 years after surgery and 3 years after cessation of treatment, he has had no recurrence of infection with a good functional outcome. This case highlights the need to consider *Mycobacteria* infection in patients who have received intravesicular BCG. Debridement and retention of well-fixed implants can be successful in combination with appropriate antituberculous therapy.

**Introduction**

Bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, was originally used in the vaccination against tuberculosis [1]. Intravesicular application of BCG was subsequently recognized to be an effective treatment for superficial bladder cancer, reducing both progression and recurrence of disease [2,3]. However, the treatment is not benign, and the use of a live bacterium produces inherent risks including the potential for systemic dissemination of *M. bovis* and subsequent seeding to artificial heart valves and implanted cardiac defibrillators [4,5]. There have been isolated reports of infections of hip and knee arthroplasties, usually requiring 1- or 2-stage revision [6-14]. We present a case of *M. bovis* infection of a total hip arthroplasty (THA) 5 years after intravesicular BCG treated by debridement, antibiotics, and implant retention (DAIR).

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**Case history**

In August of 2014, a 70-year-old male with ankylosing spondylitis presented with a 6-week history of a painless collection over the anterior aspect of the left thigh. He reported occasional pain over the buttock and left knee with no systemic symptoms. He had previously undergone a primary uncemented left THA in 2005 using a Reflection cup (Smith & Nephew, Memphis, TN) and CSL Spotorno stem (Zimmer, Warsaw, IN). He subsequently was diagnosed with transitional cell carcinoma of the bladder, for which he underwent a transurethral resection of bladder tumor and a course of 6 intravesical BCG instillations from February to March 2008, with a repeat course from November 2008 to January 2009. He ultimately underwent a total cystectomy and ileal conduit formation in October 2009.

His left hip examination was pain free with a range of flexion from 20° to 90°. A fluctuant subcutaneous collection was noted over the anterior aspect of the left thigh. Radiography of the left hip revealed eccentric wear of the polyethylene liner and proximal femoral osteolysis (Figure 1). A magnetic resonance imaging scan showed a lesion of 10 cm length and 2.5 cm diameter overlying quadriceps. The lesion was predominantly high T2 signal with a capsule that was high signal on T1 and enhanced after gadolinium administration (Figure 2). His complete blood count was within...
| Author                  | Age/gender | Original procedure                           | Months from BCG to presentation | Presentation                                      | Imaging                                                                 | Markers                                           | Orthopedic management                               | Medications                                                                 | Follow up                                                                 |
|-------------------------|------------|----------------------------------------------|---------------------------------|--------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Present case            | 70/male    | Uncemented THA 9 years before presentation   | 67                              | Collection over anterior thigh                   | XR: eccentric wear of polyethylene liner and proximal osteolysis; MRI: Collection in thigh | CRP 27 mg/L                                        | Revision of acetabular liner and head components. Washout and debridement ×4 for recurrent wound dehiscence. Repeat revision of modular components | Rifampin 300 mg bd, isoniazid 150 mg bd 12 months, ethambutol 1200 mg daily for 3 months, moxifloxacin 400 mg daily for 9 months | No signs of infection at 24 months after completion of treatment. Mobilizing well with a stick. Stable components. |
| Guerra et al. 1998 [6]  | 66/male    | THA 6 years before presentation              | 20                              | Hip pain for 6 months sweats and rigors          | XR: loosening, osteoblastic and osteolytic changes; Bone scan: intense activity around prosthesis | ESR normal                                         | First stage revision                                | Isoniazid and rifampin for 6 months. Restarted at 9 months after positive biopsy | Failed treatment. Died 1 year later of lung carcinoma                     |
| Segal and Krauss 2007 [7]| 76/male    | Cemented THA 18 years prior for revised hybrid THA and 12 years prior for aseptic loosening | 48                              | Progressive hip pain for 2 years                | XR: loose implants; CT: iliopectos abscess                        | ESR 76 mm/h, CRP 9.09 mg/dl                        | Second stage revision THA, Second stage completed after 12 months of therapy First stage revision uncemented THA | Isoniazid 300 mg, ethambutol 1200 mg, and rifampin 600 mg for 1 year       | No evidence of infection or loosening at 36 months. Uses a cane, pain free. Stable THA at 30 months, pain free, and mobile without crutches at 30 months. Harris hip score: 95 |
| Reigstad and Siewers 2008 [8] | 86/male    | Cemented THA 10 years before presentation (Exeter) | 8                               | Groin pain                                       | Loose cemented THA                                               | ESR 18 mm/h, CRP 12 mg/L                          | First stage revision THA                          | Triple therapy daily for 6 months (rifampin 600 mg, isoniazid 300 mg, pyrazinamid 1.5 g); rifampin and isoniazid at 6–12 months, isoniazid (200 mg) daily 2 years | No evidence of infection or loosening at 36 months. Uses a cane, pain free. Stable THA at 30 months, pain free, and mobile without crutches at 30 months. Harris hip score: 95 |
| Gomez et al. 2009 [9]   | 82/male    | THA (1997)                                    | 20                              | Hip pain                                         | Loose THA                                                        | ESR 51 mm/h                                       | First stage revision of THA, Reoperation at 9 months, femoral head replaced Debridement and washout. Two further washouts at 3 and 4 months after presentation | Rifampin 600 mg, isoniazid 300 mg, ethambutol 1 g, pyrazinamide 2 g, and pyridoxine 25 mg daily for 4 months. Rifampin, isoniazid, ethambutol, and pyridoxine from 4 to 15 months. | Follow-up after 12 months of treatment therapy—no sign of active infection 27 Months after presentation, discharging sinus, clindamycin 300 mg 3 times daily for suppression |
| Aitchison et al. 2015 [10]| 80/male    | Third revision THA 11 years prior             | 9                               | Fluid-filled mass in buttock, associated night sweats, anorexia, weight loss, malaise, and fatigue | XR: ostelysis around acetabular cup & distal prosthesis with bone loss. Nuclear medicine: increased uptake both components | ESR 55 mm/h, CRP 64.6 mg/L                       | Second-stage revision THA after 6 months of antibiotics | Rifampin 600 mg, isoniazid 300 mg, ethambutol, pyrazinamide 2 g, and clindamycin 300 mg 3 times daily for suppression | No sign of infection at 24 months after completion of treatment. Mobilizing well with a stick. Stable components. |
| Metayer et al. 2018 [11]| 70/male    | Uncemented THA 9 years before presentation   | 17                              | Pain in hip, painless mass in inguinal fold      | XR: loose THA and osteolysis CT: 7 × 9 cm mass between acetabulum and femoral neurovascular bundle | CRP 40 mg/L                                       | Excision biopsy first-stage revision THA after 6 months of antibiotics | Rifampin, ethambutol, isoniazid for 1 year. Moxifloxacin stopped after 30 days | No sign of infection at 24 months after completion of treatment. Mobilizing well with a stick. Stable components. |
| Srivastava et al. 2011 [14]| 76/female  | THA 6 years before presentation              | 36 months                       | Hip pain                                         | Second-stage revision THA                                        |                                                                   |                                                                   |                                                                                                                                                  | (continued on next page)
normal limits, although his C-reactive protein level was raised at 27 mg/L (normal <5 mg/L). The collection was aspirated with no organisms seen on Gram staining and small numbers of polymorphs. No cell count was performed. There was no growth on routine culture. The collection was therefore presumed to be secondary to wear debris. He was waitlisted for exchange of his polyethylene liner and head. Owing to service capacity constraints, he finally underwent revision surgery with exchange of the acetabular liner and head components in April 2015. The implants were found to be well fixed. The preoperative C-reactive protein level was retrospectively noted to have risen to 60 mg/L. Multiple tissue samples showed no organisms on gram stain and no growth. Histology was reported as detritic synovitis. He developed a subcutaneous hematoma requiring drainage and further washout procedures at 4 and 5 weeks postoperatively. The aspirate at 4 weeks showed 1880 $\times 10^6$ white blood cells/L with 30% polymorphs and 70% mononuclear cells. Gram staining showed no organisms, and there was no growth on culture.

His wound subsequently dehisced with a direct communication down to the joint requiring a repeat debridement and washout 7 weeks after his initial head and liner exchange. Multiple tissue and fluid samples were sent for microbiology; however, these were again negative. The wound initially healed but broke down again, and a repeat debridement with exchange of head and liner was performed 4 weeks later. Specimens were sent for aerobic, anaerobic, fungal, and mycobacteria culture. Cell count showed 2500 $\times 10^6$ white blood cells/L with 60% mononuclear cells and 40% polymorphs. Histology showed features of a chronic granulomatous inflammatory process. However, no mycobacteria were identified on staining. Mycobacterium was finally identified from tissue cultures 6 weeks later. M. bovis/BCG was confirmed by polymerase chain reaction. Resistance to pyrazinamide was detected, so he started on rifampin (300 mg bd), isoniazid (150 mg bd), ethambutol (1200 mg daily), and moxifloxacin (400 mg daily). After a further wound breakdown, a final debridement and washout was performed in September 2015. By this time, he had been on antituberculous therapy for 3 weeks. A large collection of clear, nonpurulent serous fluid was drained. A full debridement of all possibly infected or devitalized tissue was performed. The implants remained stable, and the head and liner were not exchanged. The wound then healed uneventfully. The ethambutol was ceased after 3 months, moxifloxacin after 9 months, and rifampin/isoniazid after 12 months. Follow-up at 24 months after completion of therapy revealed he remained well, with no systemic symptoms and a well-healed surgical scar with

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Table 1

| Author                | Age/Gender | Original procedure | Months from BCG to presentation | Presentation | Imaging | Orthopedic management | Medications | Follow up |
|-----------------------|------------|--------------------|---------------------------------|--------------|---------|-----------------------|-------------|-----------|
| Chazerain et al. 1993 | 77/male    | TKA 9 years before presentation | 5 months                        | Acute arthritis, fever, progressive knee stiffness, normal bone-implant interface | XR normal, CRP normal | Arthroscopy and synovectomy, positive cultures after 6 weeks | Rifampin 600 mg & isoniazid 300 mg daily for 2 years | No evidence of infection at 5-year follow-up | No evidence of infection at 5-month follow-up |
| Rispler et al. 2015   | 66/male    | Uncemented TKA 5 years before presentation | 12 months                       | ESR normal, CRP normal | XR normal, MR normal, CT scan, X-ray, MRI | Second-stage revision TKA, arthroscopy and synovectomy, positive cultures after 6 weeks | Ethambutol 1200 mg daily, Rifampin 600 mg daily, Isoniazid 300 mg daily for 1 year | Asymptomatic at 2-year follow-up with persistent bladder symptoms | No evidence of infection at 2-year follow-up | No evidence of infection at 2-year follow-up |

CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; TKA, total knee arthroplasty; THA, total hip arthroplasty; XR, X-ray; ESR, erythrocyte sedimentation rate.

Figure 1. AP pelvis radiograph at initial presentation in 2014.
no sign of a sinus tract, discharge, or erythema. He continues to ambulate without pain with a stick due to his ankylosing spondylitis and abductor muscle weakness. Radiographs demonstrated the implants to have remained well fixed (Figure 3). His Oxford hip score at final review was 37/48. The patient gave consent for details of his case to be published.

Discussion

Mycobacterial or other atypical organisms are unusual causes of prosthetic infection [15-18]. A delay in diagnosis is common, and clinicians need to be mindful of the need to consider unusual organisms if routine cultures are negative and wound issues persist. *M. tuberculosis* accounts for just 0.3% of all cases of prosthetic infection and rapidly growing mycobacteria accounting for even less [19]. In retrospect, it is clear that samples should have been sent for atypical organisms including mycobacteria at the initial revision and subsequent procedures. Even when appropriate culture was performed, it took 6 weeks to identify *M. bovis*. Until the organism was identified, it was not clear why there were repeated wound breakdowns. Infection was suspected but could not be confirmed. Therefore, in the presence of well-fixed implants, there was a reluctance to embark on a 2-stage revision. Once the diagnosis was made and appropriate antituberculous treatment commenced, the final debridement was successful with no further wound or implant-related problems.

The attenuated live strain of *M. bovis* is usually well tolerated; however, systemic complications secondary to hematogenous BCG dissemination have been reported. These are rare but potentially severe including sepsis, pneumonitis, and hepatitis [4,20]. *M. bovis* joint infection after intravesical BCG is exceedingly rare, and the majority of involvement is in the form of monoarthritis, oligoarthritis, or polyarthritis [20].

Figure 2. MRI scan (a) of the left thigh axial T1 post gadolinium. (b) MRI left thigh coronal T2 fat-saturated scan. MRI, magnetic resonance imaging.

Figure 3. (a) AP pelvis and (b) lateral left hip at 2018, 3 years after cessation of the antituberculous treatment. AP, anteroposterior.
A review of the literature revealed 9 previously reported cases of prosthetic \textit{M. bovis} infection associated with intravesical BCG [6-14] (Table 1). The time from BCG instillation to presentation ranged from 0 to 48 months, with the majority presenting by 2 years. However, our case did not present for over 5 years, contributing to the delay in diagnosis. All previously reported cases were treated with a minimum of 2 antituberculosis medications, with an average treatment duration of 14 months. Only one case of THA infection was managed with retention of the prosthesis; however, at 27 months, there was a persistent discharging sinus requiring suppressive treatment with clindamycin [10]. Rispler et al. reported successful treatment of a low-grade infection 4 years after BCG treatment in a total knee arthroplasty with arthroscopic debridement and synovectomy [13]. To our knowledge, the present case is the only reported instance of successful management of \textit{M. Bovis} hip infection secondary to BCG with implant retention.

DAIR can be successful in controlling prosthetic infection, although it may be less successful in chronic infection due, in part, to biofilm formation [21-23]. While \textit{Mycobacteria} do form biofilms, studies have indicated that the formation of these biofilms on metalware is poor in comparison to \textit{Staphylococcus} species [24-26]. This may increase their susceptibility to antituberculosis agents. Successful DAIR management has been reported for \textit{M. tuberculosis} and \textit{M. fortuitum} previously [15-18]. Therefore, in the presence of well-fixed components, DAIR including modular exchange, combined with appropriate antituberculosis therapy under the supervision of an infectious disease specialist, may be successful.

Summary

This case report highlights the difficulty of diagnosis and the importance of awareness of the risk of \textit{M. bovis} in patients with a history of BCG treatment presenting with periprosthetic infection. In the presence of well-fixed implants, successful treatment may be achieved through DAIR including multiagent antimicrobials that are effective against atypical \textit{Mycobacteria}.

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