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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).

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 CLS 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

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Table 1
Literature review.

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 (CLS Spotorno stem and Reflection cup)	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: iliopsoas abscess	ESR 76 mm/h, CRP 9.09 mg/dl	Second stage revision THA. Second stage completed after 12 months of therapy	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.
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 uncemented 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	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	Isoniazid and rifampin for 1 year after second revision	Follow-up after 12 months of treatment therapy—no sign of active infection
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: osteolysis around acetabular cup & distal prosthesis with bone loss. Nuclear medicine: increased uptake both components	ESR 55 mm/h, CRP 64.6 mg/L	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.	27 Months after presentation, discharging sinus, clindamycin 300 mg 3 times daily for suppression
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	
Srivastava et al. 2011 [14]	76/female	THA 6 years before presentation	36 months	Hip pain			Second-stage revision THA		

(*continued on next page*)

Table 1 (*continued*)

Author	Age/gender	Original procedure	Months from BCG to presentation	Presentation	Imaging	Markers	Orthopedic management	Medications	Follow up
								Antituberculosis medications for 9 months	No evidence of infection at 5-month follow-up
Chazerain et al. 1993 [12]	77/male	TKA 9 years before presentation	2.5	Acute arthritis, fevers	XR: normal		Second-stage revision TKA	Antituberculosis medications for 2 years	Asymptomatic at 2 year follow-up with persistent bladder cancer
Rispler et al. 2015 [13]	66/male	Uncemented TKA 5 years before presentation	12 months	Progressive knee stiffness	XR: normal bone-implant interface	ESR normal, CRP normal	Arthroscopy and synovectomy, positive cultures after 6 weeks	Rifampin 600 mg & isoniazid 300 mg daily for 1 year	No evidence of infection at 7.5-year follow-up. Returned to high level of function

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

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 1880×10^6 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 2500×10^6 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 was 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

Figure 1. AP pelvis radiograph at initial presentation in 2014.

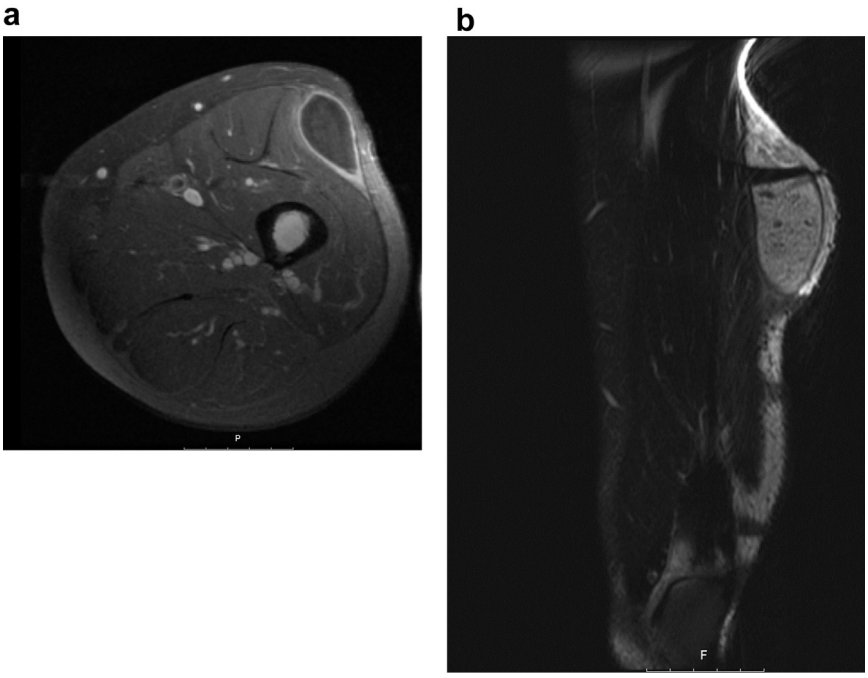

Figure 2. MRI scan (a) of the left thigh axial T1 post gadolinium. (b) MRI left thigh coronal T2 fat-saturated scan. MRI, magnetic resonance imaging.

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].

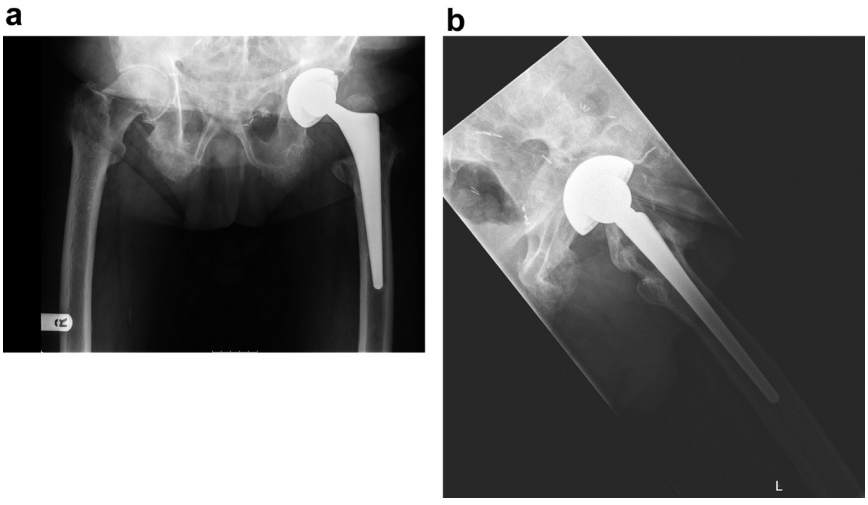

Figure 3. (a) AP pelvis and (b) lateral left hip at 2018, 3 years after cessation of the antituberculous treatment. AP, anteroposterior.

A review of the literature revealed 9 previously reported cases of prosthetic *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 *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 *Mycobacteria* do form biofilms, studies have indicated that the formation of these biofilms on metalware is poor in comparison to *Staphylococcus* species [24-26]. This may increase their susceptibility to antituberculosis agents. Successful DAIR management has been reported for *M. tuberculosis* and *M. fortuitum* previously [15-18]. Therefore, in the presence of well-fixed components, DAIR including modular exchange, combined with appropriate antituberculous 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 *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 *Mycobacteria*.

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