AMJ Australasian Medical Journal [AMJ 2015;8(10):307–314]

Myobacterium bovis peri-prosthetic hip infection with successful prosthesis retention following intravesical BCG therapy for bladder carcinoma

Lucy Ping Aitchison, Viran Jayanetti, Steven T Lindstrom, and Ronald Sekel

Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

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

Corresponding Author:
Prof Ronald Sekel
Level 5, Unit 14,
St George Private Hospital
1 South St, Kogarah, NSW 2217, Australia
Email: r.sekel@unsw.edu.au

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-tuberulous 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 Mycobaterium 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)[27] and may even be associated with improved response to immunotherapy,[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.[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.[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.[30,31] There have been five reported cases of successful treatment of prosthetic *M. bovis* infection post-BCG using revision arthroplasty with employment of at least two anti-tuberculosis drugs.[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.[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.[33]

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,[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.[35] Furthermore, due to the rarity of peri-prosthetic *M. bovis* infection following BCG therapy and the potential toxicities of anti-tuberculous drug therapy,[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.[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 *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 *M. bovis* from bladder intravesical BCG therapy to prostheses can occur. We present a case of hip prosthesis infection with *M. bovis* that was successfully treated with anti-tuberculous medication and washouts without the need of prosthesis removal.

References

1. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168(5):1964–70.
2. Sylvester RJ, van der Meijden APM, Witjes JA, et al. Bacillus Calmette-Guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: A meta-analysis of the published results of randomized clinical trials. J Urol. 2005;174(1):86–91.
3. Sylvester RJ, Brausi MA, Kirkels 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

Patients with Intermediate- and High-Risk Stage Ta T1 Urothelial Carcinoma of the Bladder. Eur Urol. 2010;57(5):766–73.
4. Stone DR, Estes NA 3rd, Klempner MS. Mycobacterium bovis infection of an implantable defibrillator following intravesical therapy with bacille Calmette-Guerin. Clin Infect Dis. 1993;16(6):825–6.
5. Wolf YG, Wolf DG, Higginbottom PA, et al. Infection of a ruptured aortic aneurysm and an aortic graft with bacille Calmette-Guerin after intravesical administration for bladder cancer. J Vasc Surg. 1995;22(1):80–4.
6. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013;64(4):639–53.
7. Lamm DL. Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am. 1992;19(3):573–80.
8. Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56(2):247–56.
9. Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int. 2001;88(3):209–16.
10. Han RF, Pan JG. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urol 2006;67(6):1216–23.
11. Shelley MD, Wilt TJ, Court J, et al. Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: A meta-analysis of randomized trials. BJU Int. 2004;93(4):485–90.
12. Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003;169(1):90–5.
13. Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol. 2000;37 Suppl 1:33–6.
14. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol. 2006;175(6):2004–10.
15. Paterson DL, Patel A. Bacillus Calmette-Guerin (BCG) immunotherapy for bladder cancer: review of complications and their treatment. ANZ J Surg. 1998;68(5):340–4.
16. Parker SG, Kommu SS. Post-intravesical BCG epididymo-orchitis: Case report and a review of the literature. Int J Surg Case Rep. 2013;4(9):768–70.
17. Rosevear HM, Lightfoot AJ, Nepple KG, et al. Safety and efficacy of intravesical bacillus Calmette-Guerin plus interferon alpha-2b therapy for nonmuscle invasive bladder cancer in patients with prosthetic devices. J Urol. 2010;184(5):1920–4.
18. Gallo J, Kolar M, Novotny R, et al. Pathogenesis of prosthesis-related infection. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia. 2003;147(1):27–35.
19. Trampuz A, Zimmerli W. Prosthetic joint infections: update in diagnosis and treatment. Swiss Med Wkly. 2005;135(17-18):243–51.
20. Gomez E, Chiang T, Louie T, et al. Prosthetic Joint Infection due to Mycobacterium bovis after Intravesical Instillation of Bacillus Calmette-Guerin (BCG). Int J Microbiol. 2009;2009:527208.
21. Chazerain P DN, Mamoudy P, Leonard P, et al. Prosthetic total knee infection with a Bacillus Calmette-Gu´erin (BCG) strain after BCG therapy for bladder cancer. J Rheumatol. 1993;20(12):2.
22. Guerra CE, Betts RF, O'Keefe RJ, et al. Mycobacterium bovis osteomyelitis involving a hip arthroplasty after intravesicular bacille Calmette-Guerin for bladder cancer. Clin Infect Dis. 1998;27(3):639–40.
23. Reigstad O, Siewers P. A total hip replacement infected with mycobacterium bovis after intravesicular treatment with Bacille-Calmette-Guerin for bladder cancer. J Bone Joint Surgery Br. 2008;90(2):225–7.
24. Segal A, Krauss ES. Infected total hip arthroplasty after intravesical bacillus Calmette-Guerin therapy. J Arthroplasty. 2007;22(5):759–62.
25. Srivastava A, Ostrander J, Martin S, et al. Mycobacterium bovis infection of total hip arthroplasty after intravesicular bacille Calmette-Guerin therapy. Am J Orthop. 2011;40(11):E226–8.
26. Rispler DT, Stirton JW, Gilde AK, et al. Mycobacterium bovis Infection of Total Knee Arthroplasty After Bacillus Calmette-Guerin Therapy for Bladder Cancer". Am J Orthop. 2015;44(2):E46–8.
27. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992;147(3):596–600.
28. Lamm DL. Efficacy and safety of bacille Calmette-Guerin immunotherapy in superficial bladder cancer. Clin

Infect Dis. 2000;31 Suppl 3:S86–90.
29. Serretta V. Management, and prevention, of intravesical therapy complications. Urologia. 2009;76(1):19–28.
30. Shishido Y, Mitarai S, Otomo K, et al. Anti-tuberculosis drug susceptibility testing of Mycobacterium bovis BCG Tokyo strain. Int J Tuberc Lung Dis. 2007;11(12):1334–8.
31. Rousseau PD, M. Antituberculous drug susceptibility testing of Mycobacterium bovis BCG strain Montreal. Can J Microbiol. 1990;36(10):3.
32. Moran E, Byren I, Atkins BL. The diagnosis and management of prosthetic joint infections. J Antimicrob Chemother. 2010;65 Suppl 3:iii45–54.
33. Kuiper JW, Vos SJ, Saouti R, et al. Prosthetic joint-associated infections treated with DAIR (debridement, antibiotics, irrigation, and retention): analysis of risk factors and local antibiotic carriers in 91 patients. Acta orthopaedica. 2013;84(4):380–6.
34. Lamm DL, Stogdill VD, Stogdill BJ, et al. Complications of bacillus Calmette-Guerin immunotherapy in 1,278 patients with bladder cancer. J Urol. 1986;135(2):272–4.
35. Van der Meijden AP, Brausi M, Zambon V, et al. Intravesical instillation of epirubicin, bacillus Calmette-Guerin and bacillus Calmette-Guerin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and Treatment of Cancer genito-urinary group randomized phase III trial. J Urol. 2001;166(2):476–81.
36. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167(11):1472–7.
37. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996;9(10):2026–30.
38. Thompson NP, Caplin ME, Hamilton MI, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J. 1995;8(8):1384–8.

ACKNOWLEDGEMENTS

None

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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.

Figure 1: X-ray of the right hip taken at presentation showing a lysis halo around the acetabular cup

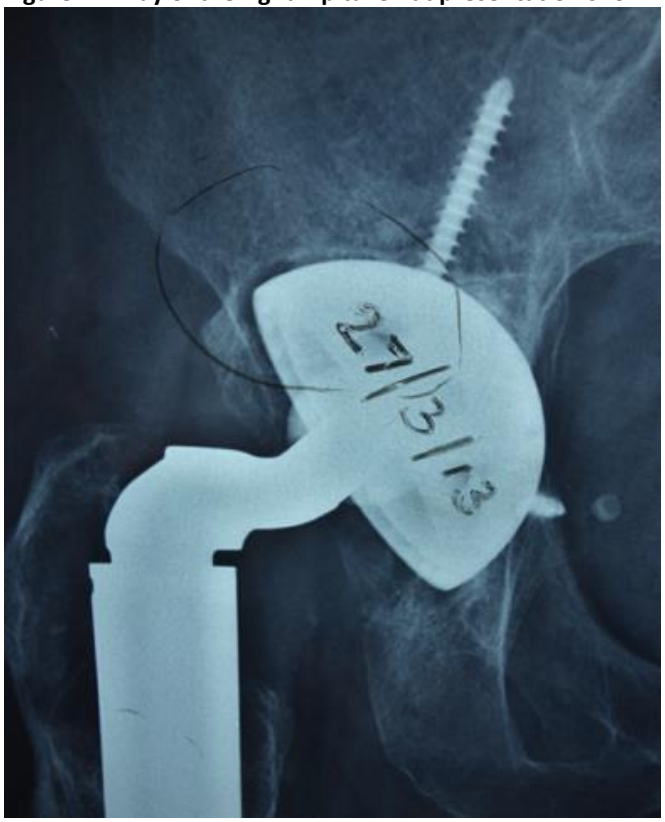

Figure 2: X-ray of the right femur taken at presentation showing a lysis halo around the distal end of the prosthesis

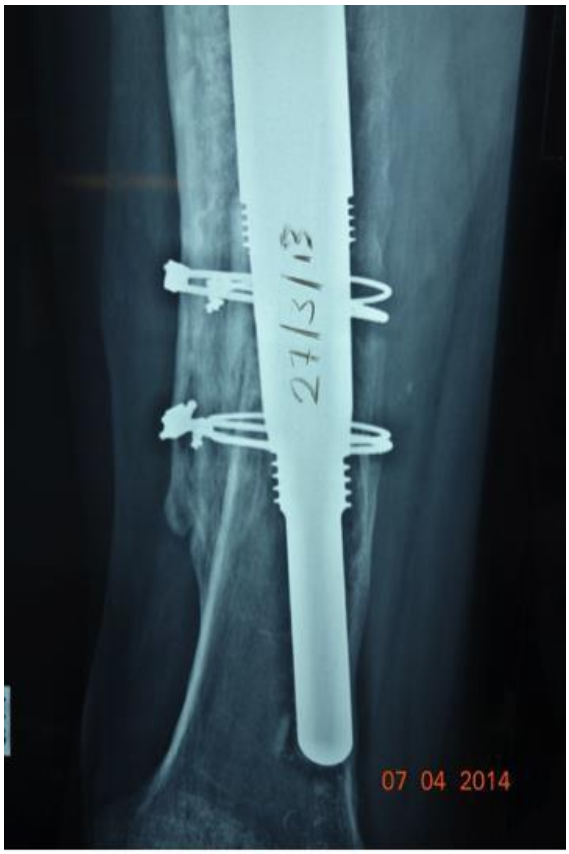

Figure 3: X-rays of the right hip, left taken at presentation, right taken a year after presentation, note resolution of lysis around prosthesis

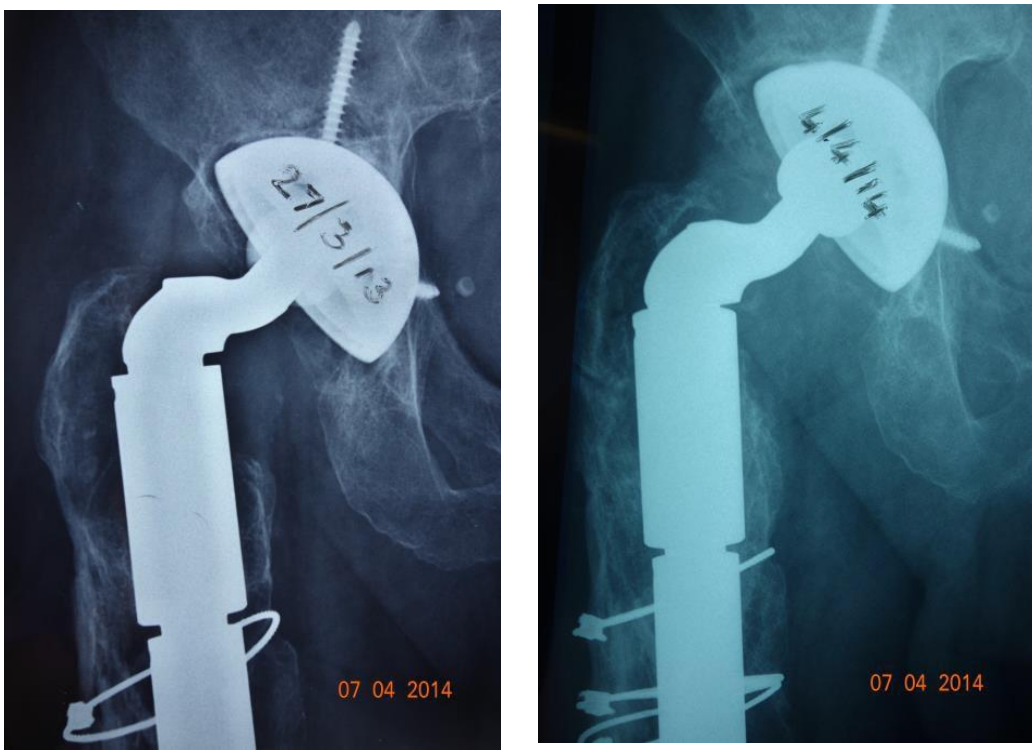

Figure 4: X-rays of the right femur taken left at presentation, right taken a year after presentation, note resolution of lysis around prosthesis

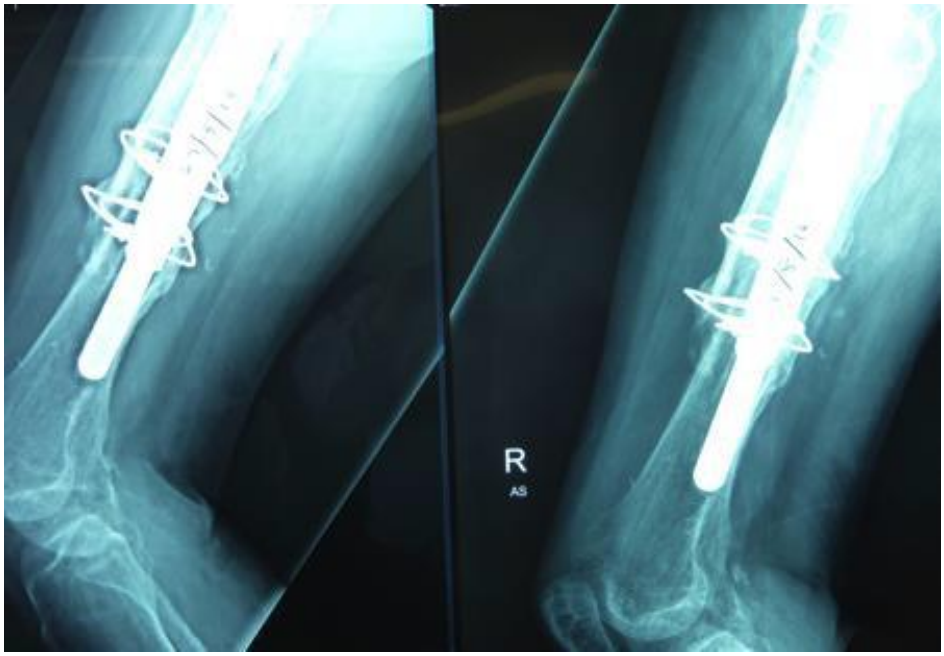

Table 1: Summary of published case reports involving *M. bovis* infection of orthopaedic prostheses following BCG treatment

Case	Age/ Gender	Previous Orthopedic Operation/ Time Until Presentation (Years)	Presentation	Diagnostics	Treatment/Joint Outcome
Chazerain et al.[21]	77/Male	TKA/9	Febrile, sterile monoarthritis of knee	Synovial and bone samples positive for AFB culture	Two years of antituberculous drugs (two drugs not mentioned) and two-stage arthroplasty / Asymptomatic at two years
Guerra et al.[22]	66/Male	THA/6	Progressive buttock pain radiating to knee and foot. Rigors and sweats present.	Cultures from prosthesis removal operation positive for AFB	Cement spacer implanted and six months of INH and RIF before passing away of other causes
Segal and Krauss[24]	76/Male	THA/4	Groin pain	Elevated ESR, CRP; THA loosening on imaging; Surgical debridement cultures positive for BCG	INH, RIF, ETA for one year with successful two-stage revision arthroplasty/ Asymptomatic at three years
Reigstad and Sieweres[23]	86/Male	THA/10	Groin pain	Elevated CRP; THA loosening on imaging; Surgical debridement cultures positive for BCG	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
Gomez et al.[20]	82/Male	THA/10	Hip pain	THA loosening on imaging; *M. bovis* cultured from fluid acquired DI	One-stage revision arthroplasty with INH, RIF for one year/ Asymptomatic at one year
Srivastava et al.[25]	76/Female	THA/6	Painful hip	Intraoperative cultures showed *M. bovis*	2-stage revision arthroplasty with nine months of antituberculous drugs/ Asymptomatic at five months
Rispler et al.[26]	66/Male	TKA/5	Joint effusion and stiff knee	Arthroscopy fluid cultures positive for AFB, identified as *M. bovis*	Arthroscopic incision and drainage with RIF, INH for 12 months/ Asymptomatic at six years
Present Case	79/Male	THA/11	Cold, painless fluid filled mass on posterolateral buttock. 1 month of night sweats, anorexia, weight loss, malaise, and fatigue	Elevated ESR, CRP; THA loosening on imaging; DI drainage fluid PCR positive for *M. bovis*, later culture positive for *M. bovis*	Two joint washouts undertaken with 13 months of RIF, INH, ETH/ Asymptomatic at two years