**Mycobacterium bovis** Osteomyelitis Involving a Hip Arthroplasty After Intravesicular Bacille Calmette-Guérin for Bladder Cancer

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Bacille Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is one of the most effective agents in the treatment of superficial bladder cancer. BCG osteomyelitis is an infrequent complication of intravesicular BCG therapy; only five cases of BCG vertebral osteomyelitis have been reported in the literature. Similarly, the infection of an indwelling extravascular device by BCG is rare; there is only one previous report documenting infection associated with an automated implantable cardiac defibrillator. We report a case of BCG osteomyelitis involving a hip arthroplasty that occurred after intravesicular administration of BCG for bladder cancer, and we review the risk factors predisposing to such infections and their treatment.

BCG is a live, attenuated strain of *Mycobacterium bovis* that was originally developed in 1921 for vaccination against tuberculosis. More recently, there has been growing interest in the use of BCG in the treatment of patients with neoplastic diseases. Randomized, controlled trials have shown that BCG is the most effective treatment for superficial bladder carcinoma.

As the use of BCG immunotherapy increases, we learn more about the spectrum of the complications that follow treatment. The complications following bladder instillation of BCG are largely confined to local tissues and most commonly consist of cystitis (90%), hematuria (30%–40%), and granulomatous prostatitis (1%–2%) [1]. Because of the low virulence of this organism, systemic complications occur in <1% of the patients but include BCG sepsis, pneumonitis, hepatitis, and, rarely, BCG osteomyelitis. There are only five cases of the latter reported in the literature, all representing cases of vertebral osteomyelitis.

Similarly, BCG infection involving an extravascular device is rare; only one case report of infection associated with an automated implantable cardiac defibrillator (AICD) has been published [2]. We report herein a case of *M. bovis* osteomyelitis involving a hip arthroplasty following intravesicular administration of BCG for superficial papillary transitional cell carcinoma of the bladder.

**Case Report**

In October 1995 a 66-year-old man with non-insulin-dependent diabetes presented with progressive right-buttock and right-lateral-hip pain that radiated to his right knee and foot. Six years before presentation, he underwent a total right-hip replacement. Twenty months before presentation, papillary transitional-cell bladder carcinoma in situ (CIS) was diagnosed. He was treated with 12 weekly instillations of intravesicular BCG (TICE strain, 60 mg) and then 12 weekly cycles of intravesicular mitomycin (40 mg); ultimately he underwent radical cystectomy for persistent CIS. Bilateral iliac and obturator nodes were free of metastatic disease.

Six months prior to admission to our institution, he developed right-hip pain, which was intermittently associated with rigors and sweats. He denied fevers, weight loss, weakness, anesthetics, and paresthesias. Radiography of the right hip revealed both osteolytic and osteoblastic changes. An extensive, inconclusive evaluation followed, which revealed that the complete blood cell count and erythrocyte sedimentation rate were normal and that two bacterial cultures of joint aspirates were negative. A bone scan showed intense activity around the prosthesis, needle and core biopsies showed lytic bone without metastatic disease, and a second set of bacterial cultures was negative. A technetium-labeled WBC scan showed no localization, and an MRI revealed no metastatic disease.

Intraarticular administration of bupivacaine hydrochloride and oral analgesics failed to relieve the patient’s pain, but a 2-week course of ciprofloxacin, administered for possible cellu- litis of the right thigh, brought significant relief. However, the pain recurred after completion of the antibiotic therapy. At our hospital, an arthrogram confirmed the loosening of the patient’s hip arthroplasty, and he underwent removal of the prosthesis along with extensive open bone biopsies.

Histopathologic examination of the right femur revealed noncaseating granulomas. Cultures for bacteria and fungi were negative; however, two acid-fast bacilli (AFB) cultures yielded *M. bovis*. A search for other sites of active mycobacterial infection included chest radiography (normal) and Isolator (Wampole Laboratories, Cranbury, NJ) blood cultures (negative). He was anergic on PPD testing.

We concluded that our patient had BCG osteomyelitis of the bone surrounding the joint prosthesis, a delayed complication...
of his treatment with BCG. *M. bovis* is susceptible to ciprofloxacin, which explained the patient’s significant improvement during this therapy.

The patient’s hip was stabilized with cement beads and a proximal tibial pin, and treatment with isoniazid and rifampin was initiated. An open surgical biopsy of the right hip was again performed in September 1996 (3 months after completion of 6 months of therapy), and AFB cultures were negative. However, histopathologic examination revealed granulomas containing fluorescence-positive bacilli.

The patient began receiving isoniazid and rifampin again but discontinued treatment shortly afterward when his spouse suddenly died. On 8 December 1997 small-cell carcinoma of the lung was diagnosed, of which he subsequently died on 16 March 1998.

**Discussion**

This patient presented with BCG osteomyelitis, a rare complication of bladder cancer treatment with intravesicular BCG. Review of the English-language literature reveals only five case reports of BCG osteomyelitis [2–6], and all are cases of vertebral osteomyelitis presenting months to years following administration of intravesicular BCG. To our knowledge, this represents the first reported case of *M. bovis* osteomyelitis involving a joint prosthesis, and although this raises concern for the safety of patients with indwelling foreign devices who must undergo treatment with intravesicular BCG, the literature contains only one other case report of infection of an AICD by *M. bovis* [2].

It is unclear what factors led to dissemination of BCG in our patient. Dissemination of BCG is believed to occur hematogenously, and the risk of dissemination is thought to increase with traumatic instillation of BCG and instillation during active cystitis, both of which our patient denied. In addition, the risk of dissemination increases in the presence of immunosuppression. It is unclear what effect our patient’s well-controlled, non-insulin-dependent diabetes and his then-occult secondary malignancy played in compromising the integrity of his immunity.

It has also been discovered that in a few patients, BCG can persist in the bladder biopsy specimens and early-morning urine cultures for up to 16.5 months after completion of intravesicular BCG instillations [7]. Thus, the period of exposure to BCG may extend long beyond the completion of therapy, and invasive urologic procedures or immunosuppression, even if they occur long after treatment, may continue to pose a risk of dissemination. After our patient’s treatment with BCG failed, he received intravesicular instillations of mitomycin and subsequently underwent a radical cystectomy, any of which may have caused disruption of the uroepithelium and thus a port of entry for persistent BCG.

Given the paucity of data, it is premature to conclude whether or not patients with indwelling foreign devices (such as pacemakers and joint prostheses) who undergo intravesicular instillations of BCG require prophylaxis to prevent dissemination of BCG to the device. However, even if prophylaxis were to be considered, it appears to be ineffective in preventing the dissemination of BCG. In a case reported by Fishman et al. [4], BCG vertebral osteomyelitis resulted despite the administration of isoniazid (300 mg q.d.) throughout the duration of a 6-week course of intravesicular BCG. Thompson and Cumming [8] also have reported a case of granulomatous hepatitis that occurred despite prophylaxis with isoniazid (600 mg for 2 days) after each bladder instillation of BCG. Furthermore, there is the theoretical concern that prophylaxis will alter the antitumor activity of BCG; however, there are no data validating this concern.

What is clear is that even long after patients have completed intravesicular BCG therapy, the index of suspicion for BCG infections at distant sites, including sites containing an indwelling foreign device, must remain high. Successful treatment likely mandates removal of the infected device, in addition to administration of two to three antimycobacterial drugs. The appropriate duration of therapy is unclear and may require histopathologic and culture guidance.

**References**