Mycobacterium bovis Infection of Total Knee Arthroplasty After Bacillus Calmette-Guérin Therapy for Bladder Cancer

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Abstract

We present a case of *Mycobacterium bovis* infection of a total knee arthroplasty. This infection developed after use of bacillus Calmette-Guérin immunotherapy used to treat superficial bladder cancer. The patient presented with joint stiffness. Radiographs and inflammatory markers were normal. Six weeks after arthroscopy for synovectomy and biopsy, cultures showed *M bovis* infection of the knee joint. The patient was switched to antitubercular chemotherapy treatment, which resulted in the successful retention of implants. Seven and a half years later, the patient is symptom-free with high function in the joint. To our knowledge, this is the first time that this type of joint infection did not lead to removal.

Intravesicular instillation of bacillus Calmette-Guérin (BCG), an attenuated form of *Mycobacterium bovis*, is the most effective treatment for superficial bladder cancer.[1,2] Minor local reactions to this treatment, such as cystitis and hematuria, are common, but more severe systemic complications[3,4] have also been documented, including sepsis, pneumonitis, granulomatous hepatitis, vertebral osteomyelitis,[5,6] and rarely, total joint infection.[7-11]

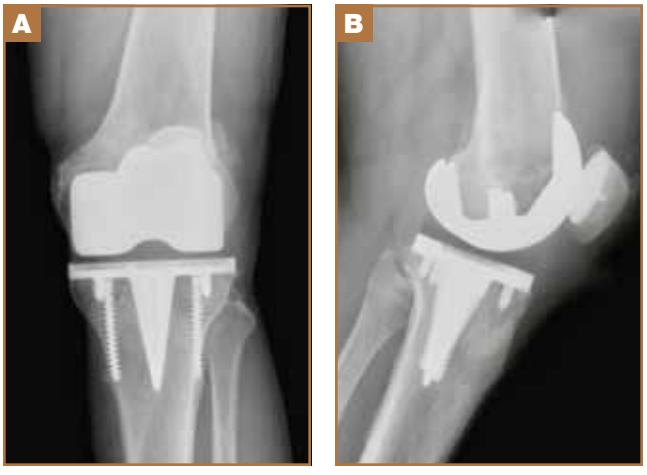
We present a case of *M bovis* infection of a total knee arthroplasty (TKA) after BCG immunotherapy for bladder cancer that was successfully treated with antitubercular chemotherapy and retention of implants. We include a review of the literature addressing this rare mode of infection. The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 66-year-old man presented with a chief complaint of progressive left knee stiffness over several months. Five years earlier, he underwent uncemented left TKA. His knee was functioning well with active range of motion from 0° to 126°, and he had returned to strenuous cycling. One year after his TKA and 4 years prior to the onset of stiffness, he had been diagnosed with superficial transitional cell carcinoma of the bladder. His treatment included intravesicular BCG therapy weekly for 6 weeks followed by semi-annual maintenance therapy.

Initial examination upon presentation with left knee stiffness showed a significant effusion and diminished range of motion but little discomfort. The patient denied fever, chills, night sweats, and weight loss. Radiographs were normal with good component positioning and normal-appearing bone-implant interfaces (**Figures A, B**). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell count (WBC) were within normal limits, and aspirate of the knee revealed no organisms. Based on these findings, the presumptive diagnosis was an adverse reaction to polyethylene wear. Because of persistent stiffness, the patient underwent an examination under anesthesia, arthroscopy, and major synovectomy with biopsy. Intraoperative findings included normal polyethylene but a marked hypertrophic synovitis and abnormal, semi-turbid fluid. The fluid WBC count was 5.35×10^9/L but no organisms were isolated initially. Histologic samples showed chronic inflammation with patches of acute inflam-

Figure. (A) Anteroposterior and (B) lateral radiographs of the left knee at the time of initial presentation with stiffness. There is good alignment and normal bone-implant interfaces.



Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

mation. Approximately 6 weeks after surgery, cultures became positive for acid-fast bacillus, which was identified as *M bovis*.

Maintenance BCG therapy was discontinued, and antitubercular chemotherapy was initiated, consisting of 12 months of rifampin 600 mg daily and isoniazid 300 mg daily. Because symptoms significantly improved after arthroscopic incision and drainage and synovectomy, the TKA implants were maintained and symptoms closely monitored. Subsequent cultures and biopsies remained negative, and the patient continued to do well clinically with no residual stiffness.

At 7½-year follow-up, there is no clinical evidence of infection, and the patient continues to enjoy a high level of function with no pain and no recurrent stiffness. He has returned to cycling, logging more than 40,000 miles. However, a recurrence of bladder cancer is being treated with mitomycin C and gemcitabine, alternative to BCG.

Discussion

Mycobacterial infection in total joint arthroplasty (TJA) is uncommon;[12] *M bovis* infection of joint arthroplasty after intravesicular BCG therapy is exceedingly rare. Joint infection is thought to be the result of dissemination of BCG throughout the bloodstream.[13]

A review of the literature of BCG infection of TJA after intravesicular therapy for bladder cancer revealed only 5 case reports (**Table**). The average age on presentation was 77 years, and all patients were men, with 4 total hip arthroplasties (THAs) and 1 TKA. The average time from index procedure to initial presentation was 7.8 years, and the average time from cancer diagnosis to initial presentation was 20 months. Patients received an average of 8.6 consecutive weeks of BCG treatments, and maintenance therapy was not noted in any of the published reports. The average duration of antitubercular therapy was 13 months, and it comprised either 2- or 3-agent therapy. All reported cases were treated with removal of primary implants in either a 1- or 2-stage fashion. To our knowledge, this is only the second case of BCG infection of TKA reported in the literature and the first report of successful treatment with retention of primary implants.

There are several possible explanations for the success of a more conservative treatment approach in our patient. First, this TKA was uncemented. Second, BCG is an attenuated form of *M bovis*, which is itself a relatively less virulent species than *M tuberculosis*. Finally, mycobacterial species do not produce the biofilm that is seen in other bacterial arthroplasty infections, which typically necessitate removal of implants in cases of chronic infection.[14]

This case was unique because the patient lacked signs of infectious symptoms, there were normal inflammatory markers, and arthroscopy was necessary to aid in the diagnosis. The

Table. Summary of Published Case Reports Involving Infection of Joint Arthroplasty and Bladder Cancer Treatment with BCG in Men

Case Report	Year	Age, y	Prior Orthopedic Procedure (y)	Time From Cancer Diagnosis to Presentation, mo	BCG Duration, wk	Presenting Symptoms	Diagnostic Studies	Treatment	Condition at Follow-up
Chazerain et al.[7]	1993	77	Unreported left TKA (9)	2.5	8	Knee pain, fever	Labs: NR; radiographs: normal	2-stage rev THA; 2-agent therapy NR for 2 y	Asymptomatic at 2 y; persistent bladder cancer
Guerra et al.[8]	1998	66	Unreported right THA (6)	20	12	Hip pain, rigors, sweats	ESR, WBC: wnl; radiographs: osteolytic/blastic change, loosening	2-stage rev THA; INH/RIF for 6 mo	Died from unrelated carcinoma prior to 2nd-stage revision
Segal and Krauss[9]	2007	76	Hybrid left THA (4)	48	Multiple	Groin/hip pain	ESR, 76 mm/h; CRP, 9 mg/L; WBC, 7.1×10^9/L; radiographs: multiple radiolucencies	2-stage rev THA; INHRIF/ETA for 1 y	Asymptomatic hip at 3 y
Reigstad and Siewers[10]	2008	86	Cemented left THA (10)	10	9	Groin pain	ESR, 18 mm/h; CRP, 12 mg/L; radiographs: loosening, femoral cement fixation	1-stage rev THA; INH/RIF/PZA for 6 mo; INHRIF for 6 mo; INH for 1 y	Asymptomatic hip at 2.5 y
Gomez et al.[11]	2009	82	Hybrid right THA (10)	20	6	Hip pain	ESR, CRP: wnl; WBC, NR; radiographs: radiolucency, loosening	1-stage rev THA; INH/RIF for 1 y	Asymptomatic hip at 1 y
Present case	2015	66	Uncemented left TKA (5)	46	6	Effusion, stiffness	ESR, CRP: wnl; radiographs: normal	Arthroscopic I&D; implant retention; INH/RIF for 1 y	Asymptomatic at 6 y; recurrent bladder cancer

Abbreviations: BCG, bacillus Calmette-Guérin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ETA, ethionamide; I&D, incision and drainage; INH, isoniazid; INHRIF, combination of isoniazid and rifampin; NR, not reported; rev, revision; PZA, pyrazinamide; RIF, rifampin; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count; wnl, within normal limits.

definitive diagnosis in this case was significantly delayed to attain a positive M *bovis* culture. Definitive treatment was provided by arthroscopy, implant salvage, and antitubercular chemotherapy only. The standard of care for an infected modular TKA normally involves revision of the polyethylene tibial insert with irrigation and débridement, or removal of components and insertion of new implants in a 1- or 2-stage procedure. Despite the unusual algorithm to reach a definitive diagnosis of an infected joint arthroplasty in this case, we do not recommend arthroscopic biopsy, washout, and antimicrobial therapy as definitive treatment for infected joint arthroplasty, and we continue to support the removal of infected components in a staged manner.

Conclusion

Joint replacement patients with bladder cancer represent a relatively small cohort. Based on current demographics and the increasing demand for joint arthroplasty, it is likely that this unique subset of patients will grow. No current standard of care exists for the treatment of these patients. One preventative measure is to consider alternative types of chemotherapy for bladder cancer treatment, such as mitomycin. Another potential solution would be administration of prophylactic doses of antitubercular agents concomitantly with intravesicular BCG, which would allow for the local effects of BCG immunotherapy while controlling the potential for systemic dissemination. The optimal dose range to achieve this dual effect is not known and is an area for research.

It is important for both arthroplasty surgeons and urologists to be aware of this potential complication in order to appropriately counsel this unique subset of patients. Our case report is the first to demonstrate that a successful outcome can be obtained with retention of primary components. Through research and continued data acquisition, a more concrete standard of care can be established. Until then, we recommend a collaborative approach between informed parties to devise a patient-specific plan of care.

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Am J Orthop. 2015;44(2):E46-E48.

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