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Case of *Mycobacterium bovis* Prosthetic Joint Infection from Intravesicular BCG

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Abstract: An 89-year-old man was seen for worsening left hip pain. He had a history of bladder cancer status post-transurethral resection of bladder tumor followed by intravesicular instillations of bacillus Calmette-Guérin (BCG). About one year later, he developed worsening pain in his left prosthetic hip that continued to worsen over the next three months. A computed tomography scan of the hip revealed loosening hardware and periprosthetic fluid collection. Aspiration and operative cultures revealed *Mycobacterium bovis* BCG. Susceptibility testing revealed resistance to pyrazinamide. The patient underwent a surgical washout with retention of hardware. Treatment with isoniazid, rifampin, ethambutol, and pyridoxine was initiated. This case highlights an extremely rare and delayed complication of intravesicular BCG leading to prosthetic joint infection.

Keywords: *Mycobacterium bovis*; prosthetic joint infection; Bacillus Calmette–Guerin

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An 89-year-old male was seen by the infectious disease service for evaluation of weakness and joint pain after left total hip arthroplasty (THA) for three months. The pain had progressed with limitation of activity and the use of a walker. The patient underwent a computed tomography scan of the hip, which revealed loosening of hardware with periprosthetic fluid collection anterior to the hip joint extending into the vastus intermedius muscle. It measured 10.8 cm in length. The patient did not have associated fever, chills, erythema, warmth, swelling, or dehiscence of previous incision. Prior orthopedic history is significant for left THA performed in 2001, a revision in 2013, and right total knee arthroplasty in November 2020, which was complicated by dislocation and revision. Past medical history included hypertension, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease stage 3, bladder cancer status post-transurethral resection with chemotherapy, and previous bacillus Calmette-Guérin (BCG) treatment with last therapy over one year ago.

At the time of evaluation, the patient reported weakness and joint pain and had no cardiac or pulmonary concerns, no constitutional symptoms of weight loss, and no fever, night sweats, or fatigue.

Examination revealed stable vitals with a temperature of 98.1 °F, stable blood pressure of 130/68, and normal oxygen saturation and respiratory rate.

The patient was alert, in no distress, and appeared his stated age. No regional adenopathy was noted. Pulmonary examination revealed equal air entry with clear breath sounds. A cardiac examination noted normal heart rate and rhythm. Abdominal examination showed normal bowel sounds and no hepatosplenomegaly. The left hip evaluation revealed the incision to be clean and dry without evidence of inflammation, with no erythema and no significant pain with a passive range of movement.

Laboratory evaluation was abnormal, with an elevated erythrocyte sedimentation rate of 57 mm/Hr (normal range 0–12 mm/Hr) and C-reactive protein of 5.5 mg/dL (normal < 0.30 mg/dL). White blood cell count (WBC) was 8700/mL, hemoglobin 10.8 g/dL, and platelets 276,000/mL. Serum creatinine was elevated to 1.41 mg/dL.

Aspiration of left hip synovial fluid had been performed a month earlier, revealing a WBC of 62 per cubic millimeter with 72% neutrophils, with bacterial and fungal cultures showing no growth. However, acid-fast bacilli (AFB) were seen and were eventually identified as *Mycobacterium bovis* BCG by MALDI-TOF and polymerase chain reaction (PCR). The patient underwent left revision THA of the acetabular component, which was found to be grossly loose. Operative synovial fluid showed a WBC of 3895 per cubic millimeter with 89% neutrophils. All five cultures grew the same organism. Treatment with isoniazid, rifampin, ethambutol, and pyridoxine was initiated. However, due to poor tolerance and patient preference, therapy was discontinued.

Bladder Cancer and Bacillus Calmette-Guérin

According to the World Health Organization, bladder cancer is the ninth most common cancer worldwide, with an estimated 456,000 cases and 200,000 deaths occurring in 2018. In the United States in 2022, bladder cancer affected approximately 81,180 people, of whom 50,290 were males and 19,480 were females, and was estimated to have caused 17,100 deaths [1]. Risk factors for bladder cancer include advanced age, with an average age of diagnosis between 79–84 years, and exposure to carcinogens such as smoking, benzene compounds, and aromatic amines [2]. Bacillus Calmette-Guérin therapy with a live attenuated form of *M. bovis* for treatment of non-muscle invasive bladder cancer was established as a first-line therapy in 1976 [3], and is now a firmly established immunomodulating therapy used to treat early bladder cancer. Installation of BCG for 90–120 minutes once weekly for six weeks as induction with quarterly maintenance for three years is recommended with cystoscopy. More than 95% of patients receiving BCG tolerate the instillation without significant morbidity. Most symptoms are due to immune reactivity, which is the mechanism of tumor eradication. Symptoms of urinary frequency, burning, malaise, and fever are common; fever is associated with improved response to BCG treatment [4]. Complications include chemical cystitis with voiding symptoms and malaise in up to 60% of patients. Other complications include granulomatous prostatitis (23% of patients) and pneumonitis and/or hepatitis (18% of patients) with complications. Approximately 1 in 15,000 patients treated with intravesical BCG will have a septic reaction due to systemic absorption or hypersensitivity, requiring discontinuation of therapy and possible treatment for dissemination or immune modulation with steroids [4].

Bacillus Calmette Guérin and Disseminated Infections

Bacillus Calmette Guérin, a live attenuated strain of *M. bovis*, has been used since 1921 to prevent tuberculosis and is now used in high-incidence settings in children as it interacts with T lymphocytes and interferon-g (IFN-g) to produce immunity. The most widely used vaccine in the world [3], BCG

was first demonstrated to be useful in superficial transitional bladder cancer in 1976 [5]. This effect is mediated via a complex immune response with presentation of mycobacterial antigens and the interaction of CD4/CD8 response [6]. Tumor cells infected with BCG are presented by phagocytes to T helper cells. This requires a class 11 major histocompatibility complex (MHC) antigen and CD4, lymphocyte function antigen 1 (LFA-1) and intercellular adhesion molecule (ICAM-1), CD28 and CD80. The bladder tumor cells take up characteristics of phagocytes during and after BCG therapy. The change in phenotype from HLA-1 to HLA-2 seems to be an important step as IFN-g release is stimulated, leading to a local immune response mediated by cytokines.

Disseminated infection with BCG occurs in children with severe combined immunodeficiency and other immunosuppressive states where IFN-g is decreased or absent. Several case reports of dissemination after BCG vaccine in families with IFN-g deficiency have been described [7]. Dissemination and sepsis occur infrequently with BCG instillation and increase with traumatic catheterization, urethral stenosis, immunosuppression, and urinary tract infection. Dissemination may present with early onset, defined as 8–12 weeks after instillation, or late disease, defined as symptoms presenting more than two years after instillation [8].

Early infection progresses similarly to disseminated tuberculosis, with fever, chills, malaise associated with sweats, and systemic signs of disseminated infection. Diffuse infiltrates on chest radiography are described. Diagnosis is made by finding non-caseating granulomas in biopsied tissue. Cultures and molecular diagnoses are recommended [1]. In a review of cases involving disseminated BCG infection in the US and Canada from January 1966 through May 2002, 20 patients had early-onset disease, and 15 had late-onset disease. Early infection usually presented within 9.4 $\pm$ 5.8 weeks of instillation. Of 20 patients, 18 (90%) presented with pneumonitis and/or hepatitis. Cultures were positive in only 5 of 17 cases.

Late-onset disease presents 75.9 $\pm$ 48.3 weeks from the last instillation [8] and usually presented with localized infection and without systemic symptoms. Only 4 of the 15 patients in the late-onset group presented with pneumonitis or hepatitis. Nine of the 15 patients (60%) had localized disease. Late-onset disease is thought to be due to the reactivation of infection after initial immunologic control of infection, similar to the breakdown of Ghon's complex in primary tuberculosis. Granulomas were present, and culture was positive in 10 of the 15 cases. Four of the late-onset patients presented with symptoms and signs of disseminated infection similar to those seen in early-onset disease. In the review, BCG infections of aneurysm were noted in 4 cases of late-onset disease and 1 case of early-onset disease [8].

Discussion

Disseminated BCG infections of prosthetic joints are distinctly rare. A review of Google Scholar and PubMed reveals that approximately 14 cases have been reported in the literature, including the current case [9–17]. Joints involved were predominantly hips (10 cases), total knee arthroplasty (3 cases), and one case of shoulder prosthetic joint infection [16] are reported. Most cases presented with late-onset disease had indolent features and lacked symptoms and signs of infection. Acute presentation after the instillation of BCG is thought to be due to local bladder inflammation and dissemination [9]. Diagnosis was complicated by low suspicion of infection and insidious onset many years after joint replacement. In many cases, AFB cultures were not sent, which resulted in a delay of diagnosis. Localized pain at the site of prior arthroplasty and evidence of abnormal lucencies on radiographs are common. When cultures are performed, PCR testing improves accuracy in the differentiation of M. TB complex. M.TB complex consists of *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium microti*. *Mycobacterium bovis* is inherently resistant to pyrazinamide. On review of cases, surgical management varied from surgical debridement to removal of the prosthesis along with antituberculous therapy to antituberculous therapy alone.

Conclusions

Prosthetic joint infection should be considered with BCG infection in all patients who have undergone intravesical BCG instillation, even if it occurs many years after arthroplasty. The most common presentation involves symptoms localized to the joint with pain. Fever is absent in most late-onset cases. Joint fluid should be routinely cultured for AFB in all cases of patients with bladder cancer who have undergone BCG instillation. Therapy directed towards *M. bovis* is recommended. Medical therapy with local debridement and prolonged therapy directed against *M. bovis* is required. Most cases required the removal of the prosthesis and two-stage revision. Surgical therapy may be warranted based on mechanical complications. BCG infection in prosthetic joints is a rare complication and requires a high index of suspicion for accurate and timely diagnosis and treatment.

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