Mycobacterium Bovis BCG Strain Osteomyelitis Masquerading as Spinal Metastasis from Bladder Cancer
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Introduction
Mycobacterium Bovis, Bacillus Calmette-Guérin (BCG) strain, osteomyelitis is a rare complication of intravesical BCG treatment of bladder cancer.1 It is clinically and radiologically indistinguishable from Mycobacterium tuberculosis. M. bovis is the main cause of tuberculosis in cattle. Human infections occur in the setting of animal domestication, infected cow's milk products, BCG vaccination, or intravesical BCG instillation for bladder cancer treatment. Approximately 1-2 percent of human tuberculosis cases are attributable to M. bovis. Among patients diagnosed with tuberculosis, the possibility of M. bovis should be considered in the setting of foreign born individuals, Hispanic ethnicity, age less than 15 years, immunosuppression, HIV infection, extra pulmonary disease, history of intravesical BCG, and non-responsiveness to standard TB treatment.1

Case Report
An 80-year-old man was admitted from an outside hospital for further work-up of low back pain, bilateral lower extremity weakness, and gait instability of six-month duration. He also reported unintentional weight loss of 40 pounds and fatigue over past 5-6 months. He had no fever or night sweats. He was diagnosed three years earlier with bladder cancer and had cystoscopy with tumor removal. He subsequently had 15 instillations of BCG therapy. At the end of BCG therapy, he was declared as being in remission from bladder cancer. His other past medical history included hypertension and supraventricular tachycardia.

On exam, the patient was lethargic and had severe lower extremity weakness. Labs showed an erythrocyte sedimentation rate of 81 mm/hr, C-reactive protein of 11.73 mg/L, thrombocytopenia with platelets of 67,000, and anemia with hemoglobin of 9.4 gm/dL and hematocrit of 28.3%.

At the outside hospital, computed tomography (CT) of the spine showed a T10 mass (Figures 1 and 2). CT of the chest, abdomen, and pelvis did not show any abnormality. Positron emission tomography showed increased uptake at T10. A CT-guided needle biopsy showed non-specific inflammation and fibrosis but no cancer. Due to his worsening lower extremity weakness and low back pain, a documented spinal mass, and history of bladder cancer, it was presumed that patient had a recurrence of bladder cancer and he received ten radiation therapy treatments to the T10 area. The last treatment was a week prior to the admission to our hospital. As he did not improve with radiation treatment, he was referred for spinal surgery at our hospital.

The patient underwent a T9-T10 thoracic laminectomy and decompression with T6-L1 posterior fusion with associated tissue
biopsy of the T10 vertebral body, which showed no evidence of malignancy. After surgery, he had some improvement in his left extremity weakness.

The patient was transferred to a long-term acute care facility to be followed by a neurosurgeon. Three weeks later, the acid-fast bacilli culture of the T10 tissue taken from the back surgery was positive for mycobacterium bovis. This organism was sensitive to isoniazid, ethambutol, and rifampin, but resistant to pyrazinamide.

The patient was readmitted with a diagnosis of BCG strain osteomyelitis three years after he received BCG treatment for his bladder cancer. A chest x-ray was without evidence for pulmonary tuberculosis. An HIV test was negative. Further exploration of spine to look for any residual infection and debridement was deferred due to moderate malnutrition and poor functional status (due to his recent spine surgery from which he was still recovering and had ongoing weakness).

The patient’s spine infection was managed medically. He was started on isoniazid, ethambutol, and rifampin and transferred to a long-term acute care facility. He completed two months of isoniazid, ethambutol, and rifampin followed by seven months of isoniazid and rifampin. With treatment, his strength and low back pain improved and he was discharged home.

Discussion

BCG is an attenuated derivative of the virulent strain of M. bovis. Intravesical instillation of BCG was first introduced by Morales and associates and is an effective agent for therapy and prophylaxis of superficial transitional cell carcinoma of the urinary bladder. It has been used to treat existing or residual tumors, prevent tumor recurrence, prevent disease progression, and prolong survival. Common complications of BCG immunotherapy include cystitis (up to 90%), hematuria (up to 34%), and fever (3%). Severe complications, including sepsis and systemic infections, are rare (less than 1%). Severe systemic disease also can present with disseminated intravascular coagulopathy, respiratory failure, jaundice,
and leukopenia. Late organ-specific manifestations (pneumonitis, hepatitis, pyelonephritis, osteomyelitis, and bone marrow infection) are due to a reactivation of BCG infection.

Risk factors for complications from BCG instillation include traumatic catheterization, urethral injury during BCG instillation, bladder biopsy, hematuria, active infection, immunosuppression, bladder outlet obstruction, radiation cystitis, and transurethral resection of the prostate and deep bladder tumor within two weeks of instillation. BCG organisms have been documented in the bladder up to 16.5 months after completion of BCG intravesical instillation therapy. Long lasting and persistent BCG DNA in the bladder wall after intravesical BCG therapy may account for long-term immune-activation and immune anticancer effects, and may explain why patients are still at risk of disseminated infection for months and even years after BCG therapy.

M. bovis can manifest with primary and reactivation forms. Involvement may be pulmonary, extra pulmonary, or disseminated and is indistinguishable from tuberculosis. The prognosis for disease is worse than M. tuberculosis.

Susceptibility testing of a mycobacterial isolate with resistance to pyrazinamide or individuals known to have contact with M. bovis often leads to identification of M. bovis. Staining for acid-fast bacilli, PPD skin test, mycobacterial culture, and the interferon gamma release assay are capable of detecting Mycobacterium infections, but cannot identify M. bovis versus M. tuberculosis. Differentiation of M. bovis from M. tuberculosis includes colony morphology, biochemical assays (M. bovis has negative niacin production and negative nitrate reduction tests), susceptibility tests (e.g., resistance to pyrazinamide), and PCR genomic analysis. Based on colony morphology, M. bovis BCG strain can be distinguished from M. bovis wild strain. M. bovis BCG strains are eugonic and grow more rapidly (3-4 weeks to grow on Löwenstein-Jensen medium), have a rough, buff-colored appearance, and in some cases, accumulate niacin. M. bovis wild strains, on the other hand, have a very slow growth rate, produces dysgonic-appearing colonies on Löwenstein-Jensen medium, and frequently require 6 to 8 weeks to become observable.

One should consider M. bovis BCG strain when a nucleic acid probe is positive, but the organism is characterized by negative nitrate reduction, negative niacin production, susceptibility to inhibition by thiopehene-2-carboxylic acid hydrazide (TCH), and resistance to pyrazinamide, especially in a patient with a history of intravesical BCG therapy for bladder cancer. For conclusive identification of M. bovis, the isolate should be sent to the state public health laboratory or a mycobacteria reference laboratory, which was done in our case. The duration of therapy for pulmonary and extra pulmonary disease should be nine months; genetic resistance of M. bovis to pyrazinamide precludes use of a short-course (6-month) regimen. The regimen consists of isoniazid, rifampin, and ethambutol for the first two months, followed by isoniazid and rifampin for seven months and for meningitis up to a total of twelve months.

At least fifteen cases of M. bovis BCG strain osteomyelitis have been reported following intravesical therapy. The range for presentation post instillation varies between two weeks and 12 years. In one report, 1.5 years after diagnosis and surgical and anti-tuberculous treatment, the patient was pain-free with no functional limitations or clinical and imaging findings of recurrent infection. Notably, 8 of 15 patients with vertebral osteomyelitis required surgical
intervention with debridement and spinal stabilization similar to our case.\textsuperscript{1,13,15,16,19-21,24,27} One patient received a presumptive diagnosis of metastatic lung cancer and underwent empiric radiation therapy to the back and chest similar to our case. Another case developed pancytopenia from bone marrow infection with BCG two years after intravesical instillation of BCG for bladder cancer.\textsuperscript{22} Mycobacterium bovis osteomyelitis involving a hip arthroplasty\textsuperscript{17} and infected aortic aneurysm along with vertebral osteomyelitis also has been reported.\textsuperscript{26}

Although the systemic complications are known from the use of intravesical BCG, osteomyelitis is a rare complication and recognition of this syndrome is critical to institution of appropriate therapy and prevention of long-term complications in patients treated with intravesical BCG. Timely diagnosis is important, because chemotherapy, when initiated early in the disease, can preclude the necessity for surgical intervention.

References
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