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Mycobacterium bovis Osteomyelitis of the Thoracic Spine Mimicking a Metastatic Lytic Lesion in a Patient Exposed to Intravesicular Bacille Calmette-Guérin Treatment☆

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ABSTRACT

An 80-year-old man with previous intravesicular bacille Calmette-Guérin therapy developed mass lesions of the lower thoracic spine. Metastatic disease was suspected. The patient underwent a course of radiation; however, biopsy later demonstrated fibrosis and cultures grew *Mycobacterium bovis*. The patient was treated with a course of isoniazid, rifampin, and ethambutol.

Introduction

Intravesicular bacille Calmette-Guérin (BCG) has become an accepted approach for treating uroepithelial cancers. It is believed to exhibit antitumor effect via activation of an inflammatory cascade. This inflammatory response can also cause a systemic inflammatory reaction or lead to localized or systemic *Mycobacterium bovis* infection. Sites of infection range from localized cystitis to disseminated bacteremia, with possible secondary seeding of lung or bone. Though uncommon, *M bovis* infection should be considered in patients with history of intravesicular BCG therapy when presenting with new lumbar spine pain or destructive bone lesions.

Case presentation

An 80-year-old man with history of bladder cancer underwent treatment with intravesicular BCG between 2008 and 2010. More than 1 year after treatment, he developed progressive neck pain with right arm numbness and tingling. He underwent cervical discectomy and decompression. He subsequently developed difficulty ambulating, fatigue, lethargy, and 40-pound weight loss over the ensuing 5 months. Magnetic resonance imaging and computed tomography scans of the thoracic spine demonstrated a lytic mass at T9-T10. Bone biopsy revealed fibrosis. Positron emission tomography scan showed increased uptake. With concern for malignancy, he was treated with 10 cycles of radiation therapy. The pain did not improve and he had worsening neurologic function. Repeat magnetic resonance imaging showed retropulsion of the remaining vertebral body causing impingement. He was referred for surgical stabilization. At that time, he denied fevers, chills, night sweats, or further constitutional symptoms. He reported no history of BCG vaccination, recent travel, tuberculosis, or animal exposures. On examination, he was afebrile with no notable findings aside from bilateral lower extremity weakness and sensory disturbance. Laboratory revealed a white blood cell count of 6700 (92% neutrophils, 2% lymphocytes, and 6% monocytes), normocytic anemia with hemoglobin 11.9 g, and a platelet count of 85,000. Creatinine and hepatic transaminases were normal, with albumin low at 1.9 g/dL. A T-spot.TB test (Oxford Diagnostic Laboratories, Memphis, TN) was negative.

He underwent T6-L1 minimally invasive thoracolumbar fusion with T9-T10 laminectomy. No purulence was visualized; however, a portion of the posterior lamina was found to have been eroded by soft tissue and the ligament appeared dark in color. A biopsy of the T10 vertebral body was performed and specimens were sent for culture and histopathology (Fig. 1).

He was started on empiric therapy with intravenous vancomycin and ertapenem. Frozen and permanent sections of the associated

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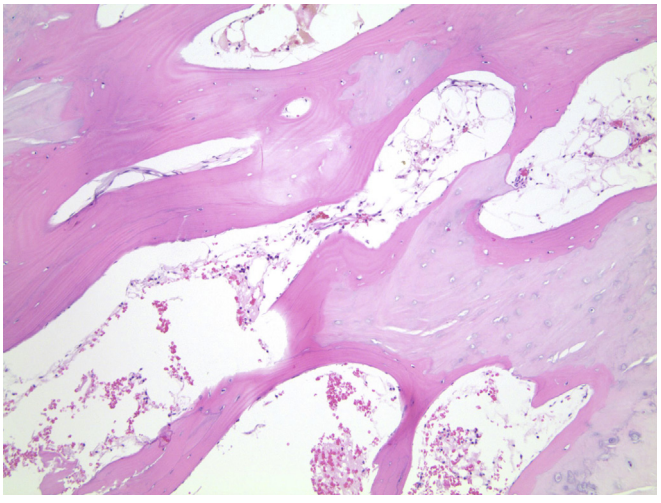

Figure 1. T10 bone and fibrocollagenous tissue; no evidence of malignancy. Image courtesy of Dr. Maura O'Neil, M.D.

soft tissue revealed fibrosis. Culture of the bone later grew *M bovis*. Isoniazid 300 mg orally daily, rifampin 600 mg orally daily, ethambutol 1200 mg orally daily, and pyridoxine 50 mg orally daily were started. Further surgical treatment was not undertaken given the patient's advanced age and deconditioned state. Vancomycin and ertapenem were discontinued. The *Mycobacterium* was later identified as *M bovis*. The isolate was susceptible to isoniazid, rifampin, and streptomycin and resistant to pyrazinamide. He was discharged to a long-term care facility and completed 2 months of ethambutol and 6 months of isoniazid and rifampin along with physical therapy.

Discussion

M bovis is a member of the tuberculosis complex that includes *M tuberculosis*, *M africanum*, and *M microti*. It is the primary cause of tuberculosis complex infections in cattle and other mammals but is also associated with disease in humans (approximately 1%-2% of tuberculosis complex infections). In humans most cases involve consumption of infected cow's milk products or administration of BCG.

BCG is a vaccine prepared from a live attenuated strain of *M bovis*. It has been used since the early 20th century to prevent tuberculosis and other mycobacterial infections. BCG was first used as an immunomodulatory agent for superficial urothelial carcinomas in 1976. When BCG is instilled into the bladder, it binds to fibronectin expressed on the urothelium and is internalized by local cells. This provokes an inflammatory response with mononuclear cell infiltration and class-II major histocompatibility complex molecule expression by the malignant cells. The malignant cell then becomes a target for lymphokine-activated killer cells and BCG antigen-presenting cells.[1] However, intravesiciular BCG administration can also lead to an exaggerated inflammatory response and localized and disseminated infection. Localized disease includes cystitis and prostatitis and generally presents early after treatment. More widespread disease can present as a sepsis syndrome, induced either by a cytokine storm leading to a serum sickness or overt bacteremia. This reaction generally occurs acutely but has been reported several months or rarely years after treatment.[2-4]

More common delayed complications of intravesicular BCG administration include granulomatous hepatitis and osteomyelitis. Bone disease most commonly affects the spine, presumably because of spread from the urinary tract through the Batson venous plexus, although the incidence remains overall very rare. A computer-assisted search of English literature using PubMed identified case reports of BCG infection of the spine intravesicular administration of BCG. Keywords used in the search were "Osteomyelitis and spine and BCG," "Spine and infection and BCG," "Spondylitis and BCG," and "Discitis and BCG". In addition to the PubMed search, publications referenced in the footnotes of other case reports were reviewed for additional cases. Fourteen additional cases of spinal infection with *M bovis* in patients treated with intravesicular BCG treatments were identified. Patient ages ranged from 66 to 94 years. Time from treatment to disease identification ranged from 5 months to 12 years. Most patients were started on a 4-drug antituberculosis regimen that was narrowed to isoniazid, and rifampin with or without ethambutol once *M bovis* was identified, given its inherent resistance to pyrazinamide. Half of the patients required surgical intervention including debridement with or without spinal stabilization. Polymerase chain reaction testing proved helpful in making a diagnosis in several cases, and the rest were diagnosed via culture of *M bovis* from the infected area (Table 1).

Conclusion

Despite the relatively low incidence of spinal infection after BCG therapy, osteomyelitis and discitis secondary to *M bovis* should be considered in patients with an indolent course of back pain with a

Table 1
Published cases of spinal *Mycobacterium bovis* infection

Case	Author	Age	Time to Disease From BCG	Area of Disease	Treatment	Surgical Intervention?
1	Abu-Nader, R[6]	76	7 y	T6-7	INH + RIF + ETM	No
2	Aljada, IS[7]	79	2.5 y	L3	INH + RIF	No
4	Katz, DS[8]	67	1.3 y	L4-5	INH + RIF + PYR	Yes
5	Morgan MB[9]	77	8 mo	T11-L1	INH + RIF + ETM	Yes
6	Nikaido, T[10]	86	1.8 y	T12-L1	INH + RIF + ETM	No
7	Samadian, S[11]	94	5 mo	L1-2	INH + RIF + ETM	No
8	Colebatch, AN[12]	67	5 y	L4-5	INH + RIF	No
9	Civen, R[13]	81	7 mo	T12-L1	INH + RIF	Yes
10	Fishman, JR[14]	90	1.3 y	T11-12	INH + RIF + ETM + PYR	Yes
11	Patel, AR[15]	66	5 mo	T10-11	INH + RIF + ETM	No
12	Mavrogenis, AF[16]	79	12 y	L3-4	INH + RIF + ETM	Yes
13	Rozenblit, A[17]	76	5.8 y	L4-5	INH + RIF + ETM + cipro	Yes
14	Dahl, T[18]	69	1 y	L3-4	INH + RIF	Yes
15	Presented case	80	3 y	T9-10	INH + RIF + ETM	Yes

BCG, bacille Calmette-Guérin; cipro, ciprofloxacin; ETM, Ethambutol; INH, Isoniazid; PYR, Pyrazinamide; RIF, Rifampin.

history of intravesicular BCG therapy. The incidence of *M bovis* infections in general may be under-reported in those patients with additional exposures including infected animals, contaminated cheese products, and prior BCG vaccination.[5] Antituberculous therapy, in addition to standard empiric antimicrobial therapy, should be considered as workup for the pathogen ensues.

Conflict of interest

The authors have no financial disclosures and no actual or potential conflict of interests to disclose.

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