Vol. 37, No. 6

Mycobacterium bovis BCG Causing Vertebral Osteomyelitis (Pott's Disease) Following Intravesical BCG Therapy

IBRAHIM S. ALJADA,[1] JOHN K. CRANE,[2] NANCY CORRIERE,[3] DATTA G. WAGLE,[4]
AND DANIEL AMSTERDAM[1,2,3,5]*

Erie County Medical Center[3] and Departments of Medicine,[2] Microbiology,[5] Pathology,[1] and Urology,[4] School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York 14215

We report a case of *Mycobacterium bovis* BCG vertebral osteomyelitis in a 79-year-old man 2.5 years after intravesical BCG therapy for bladder cancer. The recovered isolate resembled *M. tuberculosis* biochemically, but resistance to pyrazinamide (PZA) rendered that diagnosis suspect. High-pressure liquid chromatographic studies confirmed the diagnosis of *M. bovis* BCG infection. The patient was originally started on a four-drug antituberculous regimen of isoniazid, rifampin, ethambutol, and PZA. When susceptibility studies were reported, the regimen was changed to isoniazid and rifampin for 12 months. Subsequently, the patient was transferred to a skilled nursing facility for 3 months, where he underwent intensive physical therapy. Although extravesical adverse reactions are rare, clinicians and clinical microbiologists need to be aware of the possibility of disseminated infection by *M. bovis* BCG in the appropriate setting of clinical history, physical examination, and laboratory investigation.

CASE REPORT

We report a case of *Mycobacterium bovis* BCG spinal osteomyelitis affecting a 79-year-old man 2.5 years after intravesical BCG administration for bladder cancer. A 79-year-old man was admitted to the Erie County Medical Center in December 1997 with low back pain, left hip pain, lower extremity weakness, and inability to walk. He first had back pain in June 1996, when he sustained a compression fracture of vertebral body L1. He had additional compression fractures of vertebral bodies L5 and T11 between December 1996 and June 1997; all of these fractures were attributed to osteoporosis. His medical history included hypertension, two myocardial infarctions (in 1974 and 1975), cigarette smoking, Parkinson's disease, and peripheral vascular disease.

The patient had bladder cancer diagnosed in November 1993. A cystoscopy done at another medical center at that time showed a slightly more than 5-cm transitional cell carcinoma (grade 1, stage 0), for which he was treated with transurethral resection the following month. A repeat cystoscopy 18 months later revealed multiple superficial urinary bladder tumors aggregating to less than 5 cm (grade 2, stage 0), and all were resected at the time of cystoscopy. Treatment with intravesical bacillus Calmette-Guérin (BCG) immunotherapy (TICE strain by Organon) was started in June 1995 with one instillation treatment given every week for 8 weeks, followed by one treatment every month for the next 12 months, with the last dose of BCG given in October 1996. Follow-up cystoscopy was performed every 3 months until May 1997; these examinations did not reveal any evidence of a recurrent tumor.

On physical examination for this current admission, he had bilateral lower extremity weakness and pain with hip movement, especially on the left, but no other significant abnormality. X-rays showed the old compression fractures at T11, L1, and L5 plus new destructive changes affecting vertebral bodies

L2 and L3. Magnetic resonance imaging revealed destruction of the vertebral body of L3 with a paraspinal soft-tissue mass extending into the left psoas muscle. The spinal canal was severely compressed at L3. The patient underwent a computerized tomography (CT)-guided needle biopsy of vertebral body L3 and the paraspinal mass, but no tumor cells were seen and stains for bacteria, mycobacteria, and fungi were negative. Therefore, 2 weeks later, a laminectomy was performed which revealed pus in the paraspinal mass and the psoas muscle. Histological examination of the tissue obtained did not show granulomas or acid-fast bacteria (AFB). Cultures for routine bacteria and fungi showed no growth. No AFB were seen on concentrated smears in both biopsies, but BACTEC 12B broth (Becton-Dickinson, Sparks, Md.) was positive for growth after 3 weeks from the initial specimen and eventually all specimens. Subcultures to Lowenstein-Jensen (L-J) and 7H10 media grew the same nonchromogenic rough colonies 3.5 weeks after inoculation from both biopsies. The use of a nucleic acid probe (AccuProbe; Gen-Probe, San Diego, Calif.) for *M. tuberculosis* complex organisms was positive. Nitrate reduction was weakly positive (1+) on colonies recovered from the CT-guided biopsy and negative on those recovered from the open biopsy. Results of additional biochemical testing of the initial biopsy colonies were as follows: niacin production negative, heat-stable catalase reaction (at 68°C) negative, pyrazinamidase negative, semiquantitative catalase of <20 mm, and thiophene-2-carboxylic acid hydrazide (TCH) susceptible. The isolated AFB were susceptible to isoniazid, streptomycin, rifampin, and ethambutol but resistant to pyrazinamide (PZA) as determined by the radiometric BACTEC methods. Repeat testing for PZA susceptibility confirmed resistance to the drug; all isolates reacted similarly. The preliminary identification was *M. tuberculosis* complex. Subsequent testing by high-pressure liquid chromatography (HPLC) performed at North Carolina State University, upon referral from the New York State Health Department, identified the mycobacterium as *M. bovis* BCG.

The patient was started on a four-drug regimen of isoniazid, rifampin, ethambutol, and PZA. When susceptibility results became available, the regimen was changed to a 12-month

---

* Corresponding author. Mailing address: Department of Laboratory Medicine, Erie County Medical Center, 462 Grider St., Buffalo, NY 14125. Phone: (716) 898-3114. Fax: (716) 898-3090. E-mail: AMSTERDAM@LAB.ECMC.EDU.

course of isoniazid and rifampin. Subsequently, the patient was transferred to a skilled nursing facility, where he underwent intensive physical therapy for 3 months to restore strength to his lower extremities. At the time this report was prepared, the patient was unable to walk because of persistent leg weakness. However, he was living at home and using a wheelchair. He had had no recurrence of bladder cancer.

Discussion. BCG is a live attenuated strain of *M. bovis* that was first used for immunization against tuberculosis in 1921. Over 3 billion doses of BCG vaccine have been given since 1948, and it has been considered safe (15). Localized abscesses, regional lymphadenopathy, and disseminated disease in immunocompromised hosts are uncommon but well-recognized complications (8, 13, 15). Intravesical instillation of BCG was first introduced by Morales and associates in 1976 (10) and is currently the most effective agent for therapy and prophylaxis of superficial transitional cell carcinoma of the urinary bladder (i.e., Ta, T1, and carcinoma in situ) and has been used in order to treat existing or residual tumors, prevent tumor recurrence, prevent disease progression, and prolong survival (12). Complications of BCG instillations for cancer therapy are relatively rare but are more frequent than in tuberculosis vaccination programs. While side effects such as hematuria, dysuria, increased urinary frequency, and an influenza-like syndrome are common, intravesical BCG is considered safe and extravesical complications are rare (9). Lamm and associates (7) noted the incidence of the following complications in 2,602 patients: fever (2.9%), hematuria (1.0%), granulomatous prostatitis (0.9%), pneumonitis or hepatitis (0.7%), arthralgia (0.5%), epididymitis (0.4%), sepsis (0.4%), rash (0.3%), ureteral obstruction (0.3%), contracted bladder (0.2%), renal abscess (0.1%), and cytopenia (0.1%). The same authors made treatment recommendations for BCG-related complications.

BCG osteomyelitis is a rare complication of vaccination with BCG for prophylaxis of tuberculosis (1, 11). It has been reported after use of intralesional BCG injections in a melanoma case (14). To our knowledge, it has been reported only once previously after intravesical BCG instillation for bladder cancer (5). In our case, the patient's advanced age and pre-existing osteoporotic compression fractures of the spine may have contributed to the development of vertebral osteomyelitis.

The *M. tuberculosis* complex includes *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. bovis* BCG, and the newly described species *M. canetti*. Nitrate reduction and niacin production are strongly positive in cases of *M. tuberculosis* infection. Colonies grown in our case had weak nitrate reduction and no niacin production, making *M. tuberculosis* a remote possibility. *M. africanum* is a cause of human tuberculosis in tropical Africa. In addition, *M. tuberculosis* and *M. africanum* are both resistant to TCH inhibition and susceptible to PZA. In our case, colonies were susceptible to TCH inhibition and resistant to PZA, results that favor an identification of *M. bovis*. A possible consideration at this point would be *M. bovis* BCG. The treatment history with BCG makes a diagnosis of *M. bovis* BCG more likely. Differentiation of wild-type *M. bovis* and *M. bovis* BCG based on morphology and biochemical criteria is difficult, since the two exhibit similar features. Although both species demonstrate susceptibility to TCH inhibition and resistance to PZA, some differences help to distinguish them. *M. bovis* BCG strains are eugonic, i.e., more rapidly growing (requiring 3 to 4 weeks to grow on L-J medium), having a rough, buff-colored appearance, and in some cases, accumulating niacin (6). *M. bovis*, on the other hand, has a very slow growth rate, producing dysgonic-appearing colonies on L-J medium, frequently requiring 6 to 8 weeks to become observable. Growth of most strains is better on L-J medium than in Middlebrook 7H10 or an equivalent medium, the best being one without glycerol, although repeated subculture permits growth adaptation (17). Typical colonies are buff colored, low, and small and may appear either smooth or rough on egg-based media. On Middlebrook 7H10 agar, colonies are very flat and transparent and often show little or no stranding (referred to as water droplet like) (6). Freshly isolated cultures of *M. bovis* are microaerophilic, and inocula dispersed into liquid, semiliquid, or solid agar media grow in the medium but not on the surface, while *M. bovis* BCG strains grow well aerobically. In addition, *M. bovis* BCG strains grow well on glycerated media (17). In our case, colonies grew after 3 weeks and had a rough, buff-colored appearance, favoring a diagnosis of *M. bovis* BCG.

The four validated methods for the definitive identification of *M. bovis* BCG are phage typing (4), HPLC (2), restriction fragment length polymorphism analysis with the use of insertion element IS*1081* as a probe (i.e., IS*1081* fingerprinting) (16), and amplification of a specific region containing the major polymorphic tandem repeat by PCR, followed by restriction enzyme analysis (3). HPLC was the method used in our case.

This is the second report of Pott's disease caused by intravesical BCG therapy for bladder cancer. The standard mycobacterial culture techniques currently used in the majority of laboratories are capable of recovering the organism as *M. bovis*. More sophisticated techniques are probably needed to confirm a diagnosis of *M. bovis* BCG as mentioned above. Media and growth parameters may have to be adjusted to recover some of the difficult-to-grow nontuberculous mycobacteria. Microbiologists should consider *M. bovis* BCG when a nucleic acid probe is positive but the organism is characterized by negative nitrate reduction, negative niacin production, susceptibility to inhibition by TCH, and resistance to PZA, especially in a patient with a history of intravesical BCG therapy for bladder cancer.

There is no established antimicrobial regimen for the treatment of Pott's disease caused by BCG. In this case, a 12-month regimen of isoniazid and rifampin proved successful. BCG is generally highly susceptible to antituberculosis drugs, including isoniazid, rifampin, paraaminosalicylic acid, ethambutol, and to a lesser degree, kanamycin and gentamicin (7).

REFERENCES

1. **Bottinger, M., V. Romanus, C. de Verdier, and G. Boman.** 1982. Osteitis and other complications caused by generalized BCG-itis (experiences in Sweden). Acta Paediatr. Scand. **74:**471–478.
2. **Floyd, M. M., V. A. Silcox, W. D. Jones, Jr., W. R. Butler, and J. O. Kilburn.** 1992. Separation of *Mycobacterium bovis* BCG from *Mycobacterium tuberculosis* and *Mycobacterium bovis* by using high-performance liquid chromatography of mycolic acids. J. Clin. Microbiol. **30:**1327–1330.
3. **Frothingham, R.** 1995. Differentiation of strains in *Mycobacterium tuberculosis* complex by DNA sequence polymorphisms, including rapid identification of *M. bovis* BCG. J. Clin. Microbiol. **33:**840–844.
4. **Jones, W. D., Jr.** 1975. Differentiation of known strains of BCG from isolates of *Mycobacterium bovis* and *Mycobacterium tuberculosis* by using mycobacteriophage 33D. J. Clin. Microbiol. **1:**391–392.
5. **Katz, D. S., H. Wogalter, R. F. D'esposito, and B. A. Cunha.** 1992. *Mycobacterium bovis* vertebral osteomyelitis and psoas abscess after intravesical BCG therapy for bladder carcinoma. Urology **40:**63–66.
6. **Koneman, E. W., S. D. Allen, W. M. Janda, P. C. Schreckenberger, and W. C. Winn.** 1992. Color atlas and textbook of diagnostic microbiology—1992, p. 703–755. J. B. Lippincott Company, Philadelphia, Pa.
7. **Lamm, D. L., AD. P. M. vander Meijden, A. Morales, S. A. Brosman, W. J. Catalona, H. W. Herr, M. S. Soloway, A. Steg, and F. M. J. Debruyne.** 1992. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J. Urol. **147:**596–600.
8. **Lotte, A., O. Wasz-Hockert, N. Poisson, N. Dumitrescu, M. Verron, and E. Couvet.** 1984. BCG complications: estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv. Tuberc. Res. **21:**107–193.

9. **Miller-Catchpole, R.** 1988. Diagnostic and therapeutic technology assessment (DATTA). JAMA **259:**2153–2155.

10. **Morales, A., D. Eidinger, and A. W. Bruce.** 1976. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J. Urol. **116:**180–183.

11. **Mortensson, W., O. Eklof, and H. Jorulf.** 1976. Radiologic aspects of BCG-osteomyelitis in infants and children. Acta Radiol. Diagn. **17:**845–855.

12. **Nseyo, U. O., and D. L. Lamm.** 1997. Immunotherapy of bladder cancer. Semin. Surg. Oncol. **13:**342–349.

13. **Rosenberg, E. B., S. P. Kanner, R. J. Schwartzman, and J. Closky.** 1974. Systemic infection following BCG therapy. Arch. Intern. Med. **134:**769–770.

14. **Strausser, J. L., and E. A. Quindlen.** 1981. Pott's disease following BCG therapy of melanoma. Cancer **48:**1154–1156.

15. **Talbot, E. A., M. D. Perkins, S. F. M. Silva, and R. Frothingham.** 1997. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. Clin. Infect. Dis. **24:**1139–1146.

16. **van Soolingen, D., P. W. M. Hermans, P. E. W. de Haas, and J. D. A. van Embden.** 1992. Insertion element IS*1081*-associated restriction fragment length polymorphism in *Mycobacterium tuberculosis* complex species: a reliable tool for recognizing *Mycobacterium bovis* BCG. J. Clin. Microbiol. **30:**1772–1777.

17. **Wayne, L. G., and G. P. Kubica.** 1986. The mycobacteria., p. 1435–1457. *In* P. H. A. Sneath, N. S. Mair, M. E. Sharpe, and J. G. Holt (ed.), Bergey's manual of systemic bacteriology. The Williams & Wilkins Co., Baltimore, Md.