Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3288-19
Intern Med 59: 733-737, 2020
http://internmed.jp

【 CASE REPORT 】

Tuberculous Spondylitis Caused by Intravesical Bacillus Calmette-Guerin Therapy

Tomokazu Minakata[1], Yoshio Nakano[2], Shinobu Tamura[3], Yamanishi Kazuki[2], Kana Hayakawa[2], Takahiro Hayakawa[2], Takayuki Oota[2], Tokuzou Fuzimoto[2], Yukiko Yamano[1] and Takemasa Takii[4]

Abstract:
A 74-year-old man underwent intravesical bacillus Calmette-Guerin (BCG) therapy for bladder cancer and later presented with lower left back pain. Magnetic resonance imaging of the spine showed high signal intensity, diagnosed as a cystic lesion in the epidural and bilateral intestinal psoas muscle. A computed tomography-guided needle biopsy and histological examination revealed bacteria from the family Mycobacteriaceae, and *Mycobacterium bovis* was identified using multiplex polymerase chain reaction. If lower back pain appears in a patient who has undergone BCG therapy, it is necessary to test for tuberculous spondylitis. In addition, QuantiFERON is useful for the differential diagnosis of *M. bovis* BCG infection.

Key words: tuberculous spondylitis, *Mycobacterium bovis*, bacillus Calmette-Guerin

(Intern Med 59: 733-737, 2020)
(DOI: 10.2169/internalmedicine.3288-19)

Introduction

Bacillus Calmette-Guerin (BCG), an attenuated strain of *Mycobacterium bovis,* is used for vaccination of infants. The onset of disseminated BCG infection, such as disseminated lymphadenitis or osteomyelitis, has rarely been reported (1). BCG has also been used to prevent superficial bladder cancer recurrence (2) and its serious complications such as bladder tuberculosis, sepsis, hepatitis, encephalomyelitis, cystitis, pyelonephritis, nephritis, prostatitis, epididymis, aneurysms and spondylitis are rare (3). However, many cases may not have been reported because of the lack of a proper microbiological examination. To our knowledge, only 13 cases of tuberculous spondylitis as complications have been reported to date.

We herein report a case of *M. bovis* tuberculosis spondylitis that developed three months after intravesical BCG therapy based on hospital records. We present this case study because of its rare occurrence and the severe consequences of a delayed diagnosis. An ethics statement and informed consent were obtained.

Case Report

A 74-year-old man presented with a 7-month history of lower left back pain following an operation. A year and a half before admission, the patient had been diagnosed with bladder cancer and received intravesical BCG therapy. While receiving therapy, he developed a fever of 40℃ that ameliorated after a few days. He also had a history of hypertension.

At the time of hospital admission for lower back pain, the patient's vital signs were stable. He experienced buttock pain when getting up, but walking was possible. A lower limb extension elevation test was negative. Deep tendon reflexes were normal, and there was no motor weakness or paresthesia.

Initial routine laboratory examinations showed microcytic anemia, a normal white blood cell count, an erythrocyte

[1]Department of Nephrology, Kinan Hospital, Japan, [2]Department of Internal Medicine, Kinan Hospital, Japan, [3]Division of Hematology, Department of Internal Medicine, Wakayama Medical University, Japan and [4]Department of Mycobacteriology, The Research Institute of Tuberculosis, Japan Anti-tuberculosis Association, Japan
Received for publication July 16, 2019; Accepted for publication September 3, 2019
Correspondence to Dr. Tomokazu Minakata, tminakata@kinan-hp.tanabe.wakayama.jp

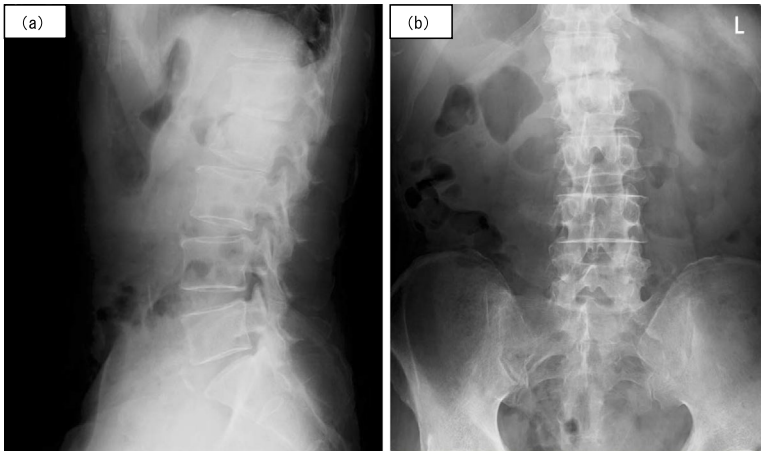

Figure 1. **Plain radiograph showing T1 and L2 compression fractures.**

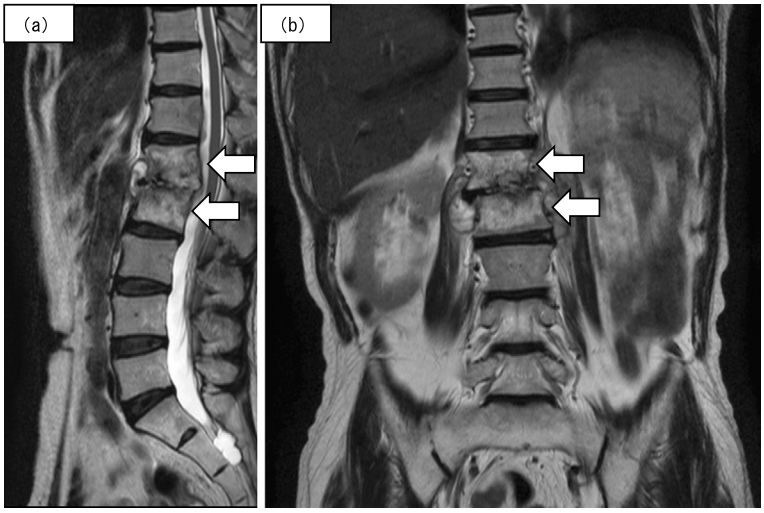

Figure 2. **Magnetic resonance imaging (MRI) of the spine showing high signal intensity in the L1 and L2 vertebral body, diagnosed as a cystic lesion in the Th2 to L2 level epidural and bilateral intestinal psoas muscle.**

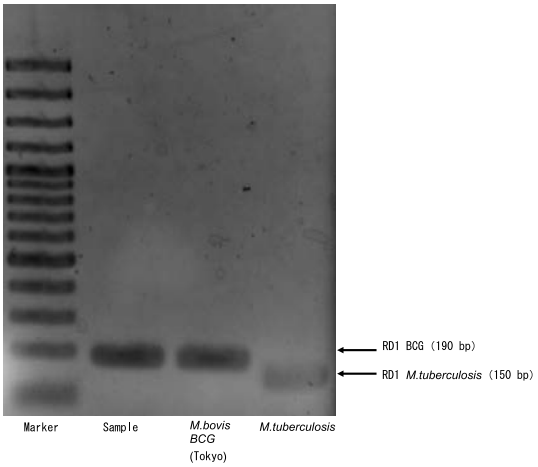

Figure 3. ***Mycobacterium bovis*** **was identified using a multiplex polymerase chain reaction assay.**

sedimentation rate of 29 mm/first hour, and a C-reactive protein level of 0.68 mg/dL. No immunodeficiency was observed, and the QuantiFERON-TB (QFT) (Cellestis, Chadstone, Australia) test result was negative. Plain radiographs showed T1 and L2 compression fractures (Fig. 1). Magnetic resonance imaging (MRI) of the pine showed a high signal intensity in the L1 and L2 vertebral body, diagnosed as a cystic lesion at the T2 to L2 level epidural and bilateral intestinal psoas muscle (Fig. 2).

Because purulent spondylitis and iliopsoas abscess were suspected based on the imaging findings, on the same day, a computed tomography (CT)-guided needle biopsy was performed under suspicion of an infection. Bacterial cultures of the biopsy specimens revealed infection with *M. tuberculosis* group, and antimicrobial susceptibility testing showed that only pyrazinamide was resistant. Because the QFT test result was negative and there was a history of BCG administration, purulent spondylitis caused by BCG was suspected, and an anti-tuberculosis treatment of isoniazid (300 mg/day), rifampicin (450 mg/day), and ethambutol (750 mg/day) was started. At a later date, *M. bovis* was identified using multiplex polymerase chain reaction (4) (Fig. 3). Two months

Table. **Only 14 Cases of Tuberculous Spondylitis Caused by Intravesical Bacillus Calmette-Guerin (BCG) Therapy for Bladder Cancer have been Reported since 1992.**

Reference	Patient age (year)	Dose	Site of infection	Time of onset after BCG therapy	History of tuberculosis or vaccination with BCG	Quanti-FERON-TB test results	Tuberculin test	Diagnosis and culture	Antimicrobial therapy and outcome
(5)	67	40 mg/month for 12 months	Vertebral or psoas abscess	6 months	No history	Unknown	Unknown	Positive tissue biopsy cultures for *M.*[1] *bovis*	Isoniazid and rifampin; discharged after 2 months
(6)	90	Weekly instillation for 6 weeks	Vertebral	1 months	No history	Unknown	Anergy	Open surgical biopsy; culture positive for *M. bovis*	Isoniazid and rifampin, ethambutol; not specified
(7)	81	One instillation per week for 6 weeks, then 1 per month for 2 months	Vertebral	7 months	No history	Unknown	Negative	Open surgical biopsy; blood culture positive for *M. bovis*	Isoniazid and rifampin for 1 year; alive 1 year later
(9)	77	2 cycles (6 treatments/ cycle)	Vertebral	2 weeks	Unknown	Unknown	Unknown	Positive tissue biopsy cultures for *M. bovis*	Isoniazid, rifampin and ethambutol for 6 months, then isoniazid and rifampin for 6 months; alive 1 year later
(18)	66	60 mg/week for 12 weeks	Hip arthroplasty	1.7 years	Unknown	Unknown	Anergy	Positive surgical culture for *M. bovis*	Isoniazid and rifampin; died of lung cancer 3 years later
(10)	79	One instillation per week for 8 weeks	Vertebral	2.5 years	Unknown	Unknown	Unknown	Surgical tissue cultures positive for *M. bovis*	Isoniazid and rifampin for 12 months; alive 1 year later
(11)	76	6 weekly cycles	Vertebral	7 years	No history	Unknown	Negative	Positive tissue biopsy cultures for *M. bovis*	Isoniazid, rifampin and ethambutol for 12 months; not specified
(12)	72	Weekly instillation for 6 weeks	Vertebral	12 years	Unknown	Unknown	Anergy	Open surgical biopsy; culture positive for *M. bovis*	Isoniazid, rifampin and ethambutol for 12 months; alive 1.5 years later
(13)	58	Unknown	Vertebral and aortic graft	3 years	Unknown	Unknown	Negative	Positive tissue biopsy cultures for *M. bovis*	Isoniazid, rifampin for 12 months; alive 1.5 years later
(14)	94	Unknown	Vertebral	5 months	Unknown	Unknown	Unknown	Positive tissue biopsy cultures for *M. bovis*	Unknown
(15)	70	12.5 mg every week for 6 weeks	Vertebral and aortic aneurysm	1 month	Unknown	Unknown	Unknown	Open surgical biopsy; culture positive for *M. bovis*	Isoniazid, rifampin and ethambutol for 12 months; alive 1.5 years later
(16)	82	8 cycles	Vertebral	16 months	Unknown	Negative	Unknown	Open surgical biopsy; culture positive for *M. bovis*	Isoniazid, rifampin and ethambutol for 6 months; alive 1 year later
(17)	64	5 instillations	Vertebral	6 months	Unknown	Unknown	Unknown	Positive tissue biopsy cultures for *M. bovis*	Isoniazid, rifampin, ethambutol, cycloserine and moxifloxacin for 12 months; not specified
This case	74	Unknown	Vertebral	1.5 years	No history	Negative	Unknown	Positive tissue biopsy cultures for *M. bovis*	Isoniazid, rifampin and ethambutol for 12 months; alive 1 year later

[1]M.: Mycobacterium

Intern Med 59: 733-737, 2020 DOI: 10.2169/internalmedicine.3288-19

later, the patient's lower left back pain had resolved completely. One year after antituberculous treatment had been started, the patient was pain-free with no functional limitations or recurrent infection.

Discussion

Intravesical BCG therapy for the treatment of superficial bladder cancer has a low risk of extravesical complications, which are rare (5), but adverse effects such as cystitis, a fever, hematuria, prostatitis, arthralgias, and reactive arthritis are relatively common. The first study to mention tuberculous spondylitis caused by intravesical BCG therapy was reported in 1992, but only 13 cases related to intravesical BCG therapy for bladder cancer have been reported since (6-17) (Table). In most cases, BCG spondylitis develops several months after intravesical BCG therapy, while some cases may develop several years later, but the cause is unknown (13). It is important to confirm the history of intravesical BCG for the differential diagnosis because *M. bovis* BCG may spread hematogenously to distant sites over the course of months or years and develop into *M. bovis* BCG infection.

Several risk factors are associated with an incidence of disseminated BCG infection, such as bladder epithelium injury, urethral injury during BCG installation, deep bladder tumor resection, pelvic radiation, severe cystitis, a bladder biopsy, and prostate resection (5, 7, 18). However, since these risk factors were not observed in the present case, it was necessary to differentiate tuberculous spondylitis, despite the absence of any risk factors.

The QFT test is useful for the differential diagnosis of *M. bovis* BCG and *M. tuberculosis* when there is no history of tuberculosis. Specific antigens used in QFT testing are present in non-BCG *M. tuberculosis* complex but are not present in *M. bovis* BCG; therefore, they are useful for differentiation. When the QFT test is negative and the histological examination reveals the presence of pathogenic bacteria from the Mycobacteriaceae family, clinicians should strongly suspect *M. bovis* BCG infection. Of course, this method is not useful if the patient already has a history of infection with *M. tuberculosis* and is already positive for QFT. The existence of anti-interferon γ autoantibody in the present case was very unlikely because the successful evaluation by QFT suggested that IFNγ in the positive control had been normally measured.

During differentiation, we also performed a multiplex polymerase chain reaction (PCR) assay using a dual-priming oligonucleotide system targeting the RD1 gene for simultaneous identification of the *M. tuberculosis* complex and *M. bovis* BCG (4). In our case, the QFT test was negative, and multiplex PCR revealed that the *M. tuberculosis* complex was *M. bovis* BCG.

All strains of *M. bovis* are resistant to pyrazinamide, but *M. tuberculosis* is not. Therefore, isoniazid and rifampicin with ethambutol should be used as first-line agents to treat *M. bovis* infections (11). There is no clear evidence concerning the ideal duration of treatment for BCG spondylitis. For general treatment of tuberculosis when pyrazinamide cannot be used, RFP, INH and EB are continued for two months, and RFP and INH are continued for seven months. This case was resistant to pyrazinamide, and after confirming clinical symptoms and improvement in CRP, RFP, INH and EB were continued for three months and RFP and INH for four and a half months. If tuberculous spondylitis is resistant to antibiotics, or if neurological symptoms or instability of the spinal column appears, surgery should also be considered (19).

In conclusion, this case highlighted two important issues. First, BCG spondylitis can occur several years after intravesical BCG. Thus, it is necessary to test for tuberculous spondylitis if lower back pain appears in a patient who has undergone BCG therapy. Second, the QFT test is useful for the differential diagnosis of *M. bovis* BCG infection.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

I deeply appreciate the the help and support of the Department of Orthopedics, Kinan Hospital, Wakayama, Japan.

References

1. Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guérin disease after vaccination: case report and review. Clin Infect Dis **24**: 1139-1146, 1997.
2. Brossman SA. Experience with bacillus Calmette-Guerin in patients with superficial bladder carcinoma. J Urol **128**: 127-130, 1982.
3. Hughes RA, Allard SA, Maini RN. Arthritis associated with adjuvant mycobacterial treatment for carcinoma of the bladder. Ann Rheum Dis **48**: 432-434, 1989.
4. Talbot EA, Williams DL, Frothingham R. PCR identification of Mycobacterium bovis BCG. J Clin Microbiol **35**: 566-569, 1997.
5. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol **147**: 596-600, 1992.
6. Katz DS, Wogalter H, D'Esposito RF, Cunha BA. Mycobacterium bovis vertebral osteomyelitis and psoas abscess after intravesical BCG therapy for bladder carcinoma. Urology **40**: 63-66, 1992.
7. Fishman JR, Walton DT, Flynn NM, Benson DR, deVere White RW. Tuberculous spondylitis as a complication of intravesical bacillus Calmette-Guerin therapy. J Urol **149**: 584-587, 1993.
8. Civen R, Berlin G, Panosian C. Vertebral osteomyelitis after intravesical administration of bacille Calmette-Guérin. Clin Infect Dis **18**: 1013-1014, 1994.
9. Morgan MB, Iseman MD. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical administration of bacille Calmette-Guérin. Am J Med **100**: 372-373, 1996.
10. Aljada IS, Crane JK, Corriere N, Wagle DG, Amsterdam D. Mycobacterium bovis BCG causing vertebral osteomyelitis (Pott's Disease) following intravesical BCG therapy. J Clin Microbiol **37**: 2106-2108, 1999.
11. Abu-Nader R, Terrell CL. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical BCG use. Mayo Clin Proc **77**: 393-397, 2002.
12. Mavrogenis AF, Sakellariou VI, Tsiodras S, Papagelopoulos PJ. Late Mycobacterium bovis spondylitis after intravesical BCG ther-

apy. Joint Bone Spine **76**: 296-300, 2009.

13. Santbergen B, Vriens PH, de Lange WC, Van Kasteren ME. Combined infection of vertebroplasty and aortic graft after intravesical BCG treatment. BMJ Case Report **2013**: bcr2012008161, 2013.

14. Samadian S, Phillips FM, Deeab D. Mycobacterium bovis vertebral osteomyelitis and discitis with adjacent mycotic abdominal aortic aneurysm caused by intravesical BCG therapy: a case report in an elderly gentleman. Age Ageing **42**: 129-131, 2013.

15. Nam EY, Na SH, Kim SY, et al. Infected aortic aneurysm caused by Mycobacterium bovis after intravesical bacillus Calmette-Guérin treatment for bladder cancer. Infect Chemother **47**: 256-260, 2015.

16. Miyazaki M, Yoshiiwa T, Ishihara T, Kawano M, Tsumura H. Tuberculous spondylitis following intravesical bacillus Calmette-Guerin for bladder cancer. Case Rep Orthop **2016**: 6741284, 2016.

17. Mackel CE, Burke SM, Huhta T, Riesenburger R, Weller SJ. Mycobacterial osteomyelitis of the spine following intravesical BCG therapy for bladder cancer. Cureus **8**: e545, 2016.

18. Bowyer L, Hall RR, Reading J, Marsh MM. The persistence of bacille Calmette-Guerin in the bladder after intravesical treatment for bladder cancer. Br J Urol **75**: 188-192, 1995.

19. Andreas FM, Vasilios I, Tsiavos K, et al. When and how to operate on spondylodiscitis: a report of 13 patients. Eur J Orthop Surg Traumatol **26**: 131-140, 2016.