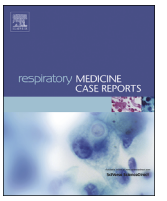
Respiratory Medicine Case Reports 45 (2023) 101902

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

A case of disseminated *M. bovis* bacillus Calmette-Guérin (BCG) disease after one month of BCG bladder infusion therapy and analysis of 77 cases of suspected BCG infection in Japan, 2017–2022

Masashi Nishimura [a, b, *], Masao Okumura [a], Takii Takemasa [c], Takashi Yoshiyama [a], Yoshiaki Tanaka [a], Mikio Saotome [a], Ken Ohta [a]

[a] *Respiratory Disease Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association, Japan*
[b] *Division of Infectious Diseases and Respiratory Medicine, Department of Internal Medicine, National Defense Medical College, Japan*
[c] *Department of Mycobacterium Reference and Research, Research Institute of Tuberculosis, Japan Anti-tuberculosis Association, Japan*

ARTICLE INFO

Keywords:
Miliary tuberculosis
Mycobacterium bovis BCG
Mycobacterium tuberculosis intravesical BCG
Bladder cancer

ABSTRACT

Bacillus Calmette-Guerin (BCG) intravesical injections are used as adjuvant therapy for superficial bladder cancer. We report a case of a 78-year-old man who developed disseminated *M. bovis* BCG disease mimicking miliary tuberculosis early after BCG intravesical infusion. He started coughing after receiving three rounds of BCG for superficial bladder tumors, following transurethral resection of the tumors, approximately one month after initiation. Computerized tomography (CT) images showed diffuse nodular shadows in the bilateral lung fields with a random pattern. Consequently, disseminated BCG disease was diagnosed. Treatment with isoniazid, rifampicin, and ethambutol was initiated. Nine months after initiating treatment, CT showed the disappearance of the miliary shadows. We also discussed 77 cases of suspected BCG infection and the requests for *Mycobacterium bovis* BCG identification at our institution from 2017 to October 2022. Of these, 76 cases were *M. bovis* BCG, and 1 case was *M. tuberculosis*. Since *M. tuberculosis* can be identified in some patients with suspected BCG infection, it is crucial to distinguish between the two based on pathogenicity.

1. Introduction

Mycobacterium bovis BCG (Bacillus Calmette-Guérin) is an attenuated, viable form of *M. bovis*, and BCG intravesical injection is used as an adjuvant therapy for superficial bladder cancer [1]. It inhibits tumor recurrence and progression of superficial bladder cancer whilst prolonging disease-free survival [2]. Although the mechanism is not clearly understood, it is believed to exert an antitumor effect by eliciting various local immune responses [3]. Side effects reported include urinary symptoms such as cystitis (91%), gross hematuria (1%), bladder contractions (0.2%), granulomatous prostatitis (0.9%), epididymitis (0.4%), and urethral obstruction (0.3%) [4].

Abbreviations: BCG, Bacillus Calmette-Guerin; CT, Computerized Tomography; PCR, polymerase chain reaction; COVID-19, Coronavirus disease 2019.

* Corresponding author. Division of Infectious Diseases and Respiratory Medicine, Department of Internal Medicine, National Defense Medical College, 3-2, Namiki, Tokorozawa-shi, Saitama, 359-8513, Japan.
E-mail address: mn0219green@gmail.com (M. Nishimura).

https://doi.org/10.1016/j.rmcr.2023.101902
Received 19 December 2022; Received in revised form 31 March 2023; Accepted 22 July 2023
Available online 22 July 2023

M. bovis is a member of the *Mycobacterium tuberculosis* complex group; it is an important infectious agent of cattle but can also infect humans. Human infection typically occurs after close contact with infected animals or ingestion of contaminated dairy products that have not been pasteurized [5,6]. Although infrequent, cases of BCG infection following intravesical BCG injection have also been reported [4]. However, it is possible that many cases go unreported due to a lack of appropriate microbiological testing.

We encountered a case of disseminated BCG disease one month after the start of intravesical BCG infusion and discussed it here alongside the frequency of *M. bovis* BCG identified at the Research Institute of Tuberculosis, Japan.

2. Case presentation

Our patient was a 78-year-old man. He smoked 20 cigarettes/day from the age of 30–40. After transurethral resection of a superficial bladder tumor, BCG intravesical injection therapy was administered three times at another hospital, and a cough appeared 3 weeks after BCG commencement. A computerized tomography (CT) scan revealed multiple granular shadows suggestive of miliary tuberculosis, and the patient was referred to our hospital. Upon arrival, his temperature was 35.8 °C; respiratory rate, 24 breaths/min; and SpO_2, 97% (room air). Physical examination revealed no head and neck lymphadenopathy, normal heart and respiratory sounds, and no other abnormal findings. Blood tests showed a mildly elevated inflammatory reaction but no other abnormal findings. Sputum and urine smears were negative for acid-fast bacilli. The urine anti-acid test was smear-negative, and the TB-polymerase chain reaction (PCR) result was positive (Table 1). Chest radiography showed diffuse small granular shadows in the bilateral lung fields, and chest CT showed multiple small granular shadows in the bilateral lungs (Fig. 1). Miliary tuberculosis was strongly suspected from the chest CT.

Based on clinical symptoms, imaging findings, and a positive urinary *M. tuberculosis* complex group PCR, a preliminary diagnosis of disseminated *M. bovis* BCG disease mimicking miliary tuberculosis was made. Since BCG infection was suspected from the disease course and the patient was an older adult, treatment was started with three drugs (isoniazid (INH), rifampicin (RFP), and ethambutol (EB)) other than pyrazinamide (PZA) from the beginning of treatment. Anti-tuberculosis chemotherapy with INH 300 mg, RFP 600 mg, and EB 1000 mg was started. Seventeen days later, a urine mycobacteria culture was positive for *M. tuberculosis* complex, and then the cultured microorganism was identified as *M. bovis* BCG using multiplex PCR [7]. Drug sensitivity showed that the patient was resistant to pyrazinamide but sensitive to other drugs, and the treatment was continued without any changes. The patient's subjective symptoms improved over time, and the miliary shadowing disappeared on CT (Fig. 1).

Table 1
Results of Blood Test before treatment.

Hematology		Biochemistry		Serology	
White blood cells	7030/uL	T-Bil	1 mg/dL	CRP	0.48 mg/dL
Neutrophil	38.7%	AST	24 IU/L	T-SPOT	(−)
Lymphocyte	51.2%	ALT	19 IU/L		
Basophil	1.6%	LDH	183 IU/L	Urine	
Eosinophil	1.8%	TP	8.17 g/dL	AFB smear	(−)
Monocyte	6.7%	Alb	4.1 g/dL	AFB culture	(+)
Red blood cells	5.06 × 10^4/mL	BUN	12 mg/dL	AFB PCR	TB(+)
Hemoglobin	15.7 g/dL	Cr	0.85 mg/dL		
Hematocrit	46.8%	Na	140 mEq/L	DDH	
Platelets	29.4 × 10^4/mL	K	4.4 mEq/L	*Mycobacterium bovis* BCG	
		Cl	100 mEq/L		

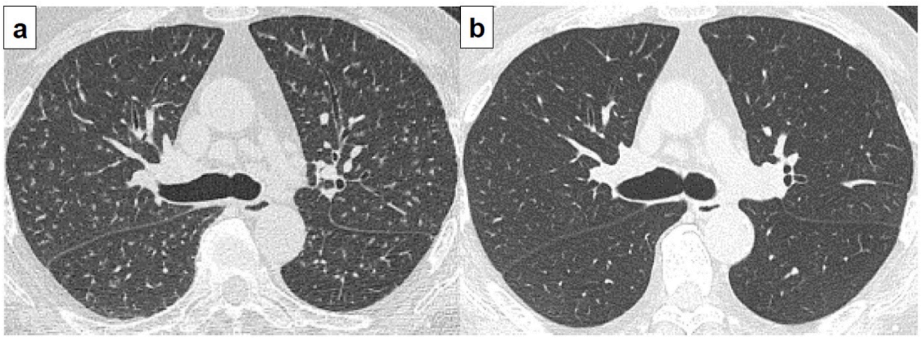


Fig. 1. Imaging studies of the chest. (a) Computed tomography (CT) image showing multiple small granular shadows in the lungs bilaterally. (b) CT after therapy showed resolution of multiple small granular shadows in the lungs bilaterally.

3. Discussion

In a study of 970 *M. tuberculosis* complex strains in tuberculosis patients throughout Japan, 966 (99.6%) *M. tuberculosis*, 2 *M. africanum*, and 2 *Mycobacterium canettii* strains were identified by multiplex PCR, suggesting that human infection with *M. bovis* in Japan is close to zero [8]. From 2017 to October 2022, there were a total of 77 requests for identification of BCG to the Research Institute of Tuberculosis, Japan, due to suspected BCG infection. The difference between *M. tuberculosis* and *M.* BCG was determined by multiplex PCR using the RD1 region as an indicator [7]. Of the samples requested for identification, 76 cases were BCG, and 1 case was *M. tuberculosis* bacilli. Patients detected with BCG bacilli included 64.4% who had received BCG treatment for bladder cancer, 34.2% BCG childhood vaccine, and 1.4% BCG vaccination for COVID-19 (unpublished data). There were approximately 23,000 prescriptions for BCG intravesical injection therapy in Japan between April 2020 and March 2021 (from the National Database published by the Ministry of Health, Labour and Welfare, Japan). Based on these results, it is estimated that 5–12% of all BCG infection cases are identified by the Research Institute of Tuberculosis, Japan. BCG intravesical infusion therapy has been used to prevent the recurrence of superficial bladder cancer [9]. It is reported to cause rare serious complications such as bladder tuberculosis, sepsis, hepatitis, encephalomyelitis, cystitis, pyelonephritis, prostatitis, epididymitis, aneurysms, and spondylitis, and to cause disseminated lesions in 0.3–0.7% of cases [2,10,11]. BCG vaccine reduces the risk of tuberculosis by an average of 50%. [12] It is also suggested that the BCG vaccine could be used as an adjuvant to reduce the impact of SARS-CoV-2 infection and overlapping respiratory infections [13]. The risk of adverse reactions from BCG vaccination is reported to be $<$ 0.1–30 cases of osteitis/osteomyelitis, 0.1–4.3% of suppurative lymphadenitis, and $<$0.1 cases of disseminated BCG infection per 100,000 vaccinations [14].

The predisposing factors for the development of BCG infection after intravesical injection are not well understood. Asín et al. reported that infection development did not correlate with BCG dose, number of treatment courses, or time elapsed since transurethral tumor resection; this suggests that infection is dependent on host characteristics [2]. Among them, immunocompromised status and advanced age have been suggested as predisposing characteristics. BCG can be detected in bladder biopsies and early morning urine cultures more than 1 year after BCG therapy ends; it can cause infection years later, averaging 2.5 years (0.5 months–12 years) after BCG vaccination [15]. The present case of BCG infection occurred in an older patient, but he was not immunocompromised. This was also a case of disseminated BCG disease that developed early, with symptoms occurring after the third injection, one month after the start of BCG treatment. Based on the results of the Research Institute of Tuberculosis, Japan, it is very important to distinguish between BCG and *M. tuberculosis* infection because, rarely, *M. tuberculosis* bacilli can be identified in patients with a background of suspected BCG infection.

Mild dysuria and flu-like symptoms that appear within 24–48 hours after BCG intravesical injection are considered to be an inflammatory reaction caused by BCG and an indicator of adequate anti-tumor effect [16]. However, BCG infection should be suspected in patients who develop systemic symptoms such as severe urinary symptoms or high fever for more than 72 hours after BCG treatment. In a previous report of BCG-related infectious complications after BCG intravesical injection, 4.3% of patients developed systemic BCG infection, most commonly miliary tuberculosis, after 6–14 BCG doses [2].

A specimen is collected for microbiological diagnosis according to symptoms. BCG bacilli cannot be differentiated from *M. tuberculosis* bacilli using the widely used *M. tuberculosis* complex group PCR test; diagnosis requires waiting for culture results. On the other hand, Pérez et al. reported that the microbiological diagnosis of BCG infection was positive in only 118 of 246 patients [17], and BCG infection cannot be ruled out even if results of all microbiological tests are negative. A tissue biopsy specimen showing the presence of granulomas can also aid in the diagnosis [18], but since only about 40% of cases are detected on tissue biopsy, it is recommended that anti-tuberculosis antibacterial agents be started empirically if BCG infection is suspected clinically [19]. In the present case, disease onset occurred after the third treatment dose (approximately one month after treatment commencement), leading to disseminated *M. bovis* BCG disease mimicking miliary tuberculosis, despite the patient lacking systemic symptoms. Bacteriological examination initially revealed a positive TB-PCR on urine culture, and BCG bacilli were detected during culture. Based on the clinical, imaging, and bacteriological findings, a diagnosis of disseminated BCG disease was made.

When deciding on a treatment regimen, pyrazinamide was excluded because all strains of *M. bovis*, a parent bacillus of BCG, are resistant. As recommended by the Centers for Disease Control and Prevention, treatment of disease caused by *M. bovis* usually consists of rifampicin, isoniazid, and ethambutol, and the duration of treatment is generally extended to 9 months [20]. When disseminated BCG disease develops, we recommend the use of prednisolone in addition to the three-drug combination [2,4]. In this case, disseminated BCG disease was suspected at the start of treatment; since the patient had mild symptoms without fever, treatment with rifampicin, isoniazid, and ethambutol was started, and improvement of symptoms and disappearance of miliary shadowing was observed.

BCG infection should be considered when examining a patient with a history of *M. bovis* BCG administration, regardless of the number of doses or doses administered. It is important to differentiate between *M. tuberculosis* and BCG bacilli because some patients with suspected BCG infection may also have *M. tuberculosis*.

4. Conclusions

We experienced a case of disseminated BCG disease one month after the start of BCG bladder infusion therapy. Because disseminated *M. bovis* BCG disease mimicking miliary tuberculosis may develop even early after BCG intravesical infusion commencement, BCG infection should be considered if these patients develop urinary or systemic symptoms, and therapeutic intervention should be provided as early as possible. *M. tuberculosis* bacilli may also be present in patients with suspected BCG infection. Therefore, it is important to differentiate between *M. tuberculosis* and BCG from the standpoint of pathogenicity.

Declaration of competing interest

None.

Acknowledgements

Source of funding -None declared.

References

[1] S. Guallar-Garrido, E. Julián, Bacillus calmette-guérin (BCG) therapy for bladder cancer: an update, ImmunoTargets Ther. 9 (2020) 1–11.
[2] M.A.P.J. Asín, M. Fernández-Ruiz, F. López-Medrano, et al., Bacillus Calmette-Guérin (BCG) infection following intravesical bcg administration as adjunctive therapy for bladder cancer incidence, risk factors, and outcome in a single-institution series and review of the literature, Méd. 93 (17) (2014) 236–254.
[3] N.M. Gandhi, A. Morales, D.L. Lamm, Bacillus Calmette-Guérin immunotherapy for genitourinary cancer, BJU Int. 112 (3) (2013) 288–297.
[4] D.L. Lamm, A.P.M. Van der Meijden, A. Morales, et al., Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer, J. Urol. 147 (3 I) (1992) 596–600.
[5] J.M. Grange, Mycobacterium bovis infection in human beings, Tuberculosis 81 (1–2) (2001) 71–77.
[6] N.M. Gandhi, A. Morales, D.L. Lamm, Bacillus Calmette-Guérin immunotherapy for genitourinary cancer, BJU Int. 112 (3) (2013) 288–297.
[7] E.A. Talbot, D.L. Williams, R. Frothingham, PCR identification of Mycobacterium bovis BCG, J. Clin. Microbiol. 35 (3) (1997) 566–569.
[8] M. Ueyama, K. Chikamatsu, A. Aono, et al., Sub-speciation of *Mycobacterium tuberculosis* complex from tuberculosis patients in Japan, Tuberculosis 94 (1) (2014) 15–19.
[9] S.A. Brossman, Experience with bacillus Calmette-Guerin in patients with superficial bladder carcinoma, J. Urol. 128 (1) (1982) 27–30.
[10] M. Brausi, J. Oddens, R. Sylvester, et al., Side effects of bacillus calmette-guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose an, Eur. Urol. 65 (1) (2014) 69–76.
[11] D.L. Lamm, Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer, Clin. Infect. Dis. 31 (SUPPL. 3) (2000) 86–90.
[12] A. Graham, F. Timothy, S. Catherine, Efficacy of BCG vaccine in the prevention of tuberculosis meta-analysis of the published literature, JAMA 271 (9) (1994) 698–702.
[13] M. Gonzalez-Perez, R. Sanchez-Tarjuelo, B. Shor, E. Nistal-Villan, J. Ochando, The BCG vaccine for COVID-19: first verdict and future directions, Front. Immunol. 12 (March) (2021).
[14] WHO: expanded programme on immunization (EPI) indications and contraindications for vaccines used in the EPI, Wkly. Epidemiol. Rec. 59 (1984) 13–15.
[15] L. Bowyer, R.R. Hall, J. Reading, M.M. Marsh, The persistence of bacille Calmette-Guerin in the bladder after intravesical treatment for bladder cancer, Br. J. Urol. 75 (2) (1995) 188–192.
[16] B. Andreas, B. Sven, Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer, J. Urol. 170 (2003) 964–969.
[17] A. María, F. Mario, L. Francisco, et al., Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature, Medicine (Baltim.) 93 (17) (2014) 236–254.
[18] L. Martin, C. Boiron, J. Poveda, G. Herreman, Generalized BCG Infection after Intravesical Instillations of Calmette-Guerin bacillus, 22, Press Med, 1993, pp. 1352–1356.
[19] M. Elkabani, J.N. Greene, A.L. Vincent, S. VanHook, R.L. Sandin, Disseminated Mycobacterium bovis after intravesicular bacillus Calmette-Guerin treatments for bladder cancer, Cancer Control 7 (5) (2000) 476–481.
[20] American Thoracic Society, CDC and IDS of A, The treatment of tuberculosis, CDC 52 (2003) RR-11.