

DISSEMINATED *MYCOBACTERIUM BOVIS* AFTER INTRAVESICULAR BACILLUS CALMETTE-GUÉRIN TREATMENTS FOR BLADDER CANCER

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Introduction

Transitional-cell carcinoma of the bladder is an aggressive and potentially fatal malignancy. In 1990, the US Food and Drug Administration approved the use of intravesicular bacillus Calmette-Guérin (BCG) for the treatment of superficial bladder cancer.¹ BCG is a live, attenuated strain of *Mycobacterium bovis* (*M. bovis*) that has been used to treat transitional-cell carcinoma since 1976 and has been reported to eradicate disease in more than 70% of patients with in situ and stage I disease.² The precise mechanism by which BCG acts is unknown, but a local granulomatous inflammation, centered on a T-cell-mediated immunity response, is thought to play a role.³ While the majority of patients tolerate BCG intravesicular treatments well, a number of adverse reactions (eg, fever, hematuria, dysuria, nausea, and malaise) have been reported.^{4,5} More serious complications include granulomatous prostatitis, pneumonitis, and hepatitis. We report a case of disseminated BCG infection causing pneumonitis that required corticosteroids and antitubercular therapy for cure.

Case Report

A 67-year-old man was hospitalized in June 1999 for evaluation of fever and cystitis following intravesicular instillation of BCG. His medical history included pulmonary tuberculosis treated suc-

cessfully with streptomycin and isoniazid in 1954. In 1994, the patient underwent transurethral resection of a bladder tumor with findings of a grade III noninvasive transitional-cell carcinoma. The first six BCG treatments were well tolerated. In 1997, the patient developed carcinoma in situ in the dome of the bladder. When two further instillations led to hematuria, BCG therapy was replaced with intravesicular mitomycin C for a total of four instillations. A recurrence of carcinoma in situ developed in 1998, and BCG therapy was again initiated. Six weekly instillations were administered with no significant side effects, and he began BCG maintenance therapy every 3 months. One week prior to hospital admission, the patient received his second BCG maintenance instillation (his 16th BCG treatment overall). Within hours of his instillation, he developed generalized weakness, fever to 101°F, and dysuria. Five days prior to admission, he presented to clinic and was diagnosed with a Southwestern Oncology Group (SWOG) grade III reaction and was given 300 mg of Isoniazid per day. This treatment was discontinued 3 days later when he developed an elevation in serum transaminases.

Seven days after his last BCG instillation, the patient was admitted to the hospital with dyspnea, generalized weakness, fever to 102.7°F, and dysuria. On admission, he had a temperature of 100.2°F, a pulse rate of 102 beats

per minute, a respiratory rate of 22 breaths per minute, an oxygen saturation of 93% on 2 liters of nasal cannula oxygen, and bibasilar crackles on examination. He was started on empiric, broad-spectrum antibiotic coverage with 500 mg of intravenous levofloxacin given daily and 500 mg of intravenous imipenem/cilastatin given thrice daily. Liver enzymes at the time of admission were elevated with an alkaline phosphatase of 339 U/L, an AST value of 55 U/L, and an ALT value of 50 U/L. Other laboratory findings included a white blood cell count of 8,000/mm³, hemoglobin level of 142 g/L, creatinine clearance of 1.2 mg/dL, and erythrocyte sedimentation rate of 30 mm/h. Two sets of peripheral blood cultures were negative for

bacteria and did not stain or grow acid-fast bacilli in culture. The urine culture grew more than 100,000 colonies/mL of mixed Gram-positive flora but was also negative for acid-fast bacilli by stain and culture. A chest radiograph performed the day after admission revealed bilateral 1- to 3-mm nodules in a miliary pattern without hilar lymphadenopathy (Fig 1). Computed tomography scans of the chest revealed similar bilateral lower-lobe 2- to 3-mm nodules (Fig 2A-B). Polymerase chain reaction (PCR) of a serum specimen was negative for tuberculosis complex that includes both *M. tuberculosis* and *M. bovis*. Subsequently, imipenem/cilastatin was changed to 1,500 mg daily of oral pyrazinamide, and the levofloxacin was continued.

Corticosteroids were added to his treatment, and the patient's condition improved over the next 5 days. He was discharged on an oral 5-day tapering dose of prednisone starting at 60 mg, oral levofloxacin at 500 mg daily, and pyrazinamide at 1,500 mg daily.

He returned to the hospital after 3 days with similar complaints of fever, fatigue, dysuria, and flank pain. He was admitted with a temperature of 100.4°F and bibasilar crackles on examination. Chest radiograph showed a persistent miliary interstitial pattern. The antibiotic regimen was then changed to amikacin, ethambutol, and levofloxacin. The prednisone dose was increased to 60 mg, and oxygen was administered by nasal cannula. Fevers recurred over the next several days. Furthermore, he developed corticosteroid-induced hyperglycemia that required insulin. On day 7 of hospitalization, the patient was afebrile and subsequently discharged with 1,500 mg of oral ethambutol daily, 600 mg of rifampin daily, 500 mg of levofloxacin daily, insulin, and a 6-week tapering schedule of prednisone starting at 60 mg daily.

A second relapse of symptoms (namely, fever and fatigue) occurred, 3 weeks following his hospital discharge when the prednisone dosage was tapered from 40 mg daily to 20 mg daily. The prednisone dosage was increased again to 40 mg per day, and a slower tapering schedule was substituted. Four months following hospitalization, he was free of any respiratory or urinary symptoms and no longer



Fig 1.— Chest radiograph demonstrates small 2- to 3-mm nodules in both lung fields consistent with a miliary pattern of spread.

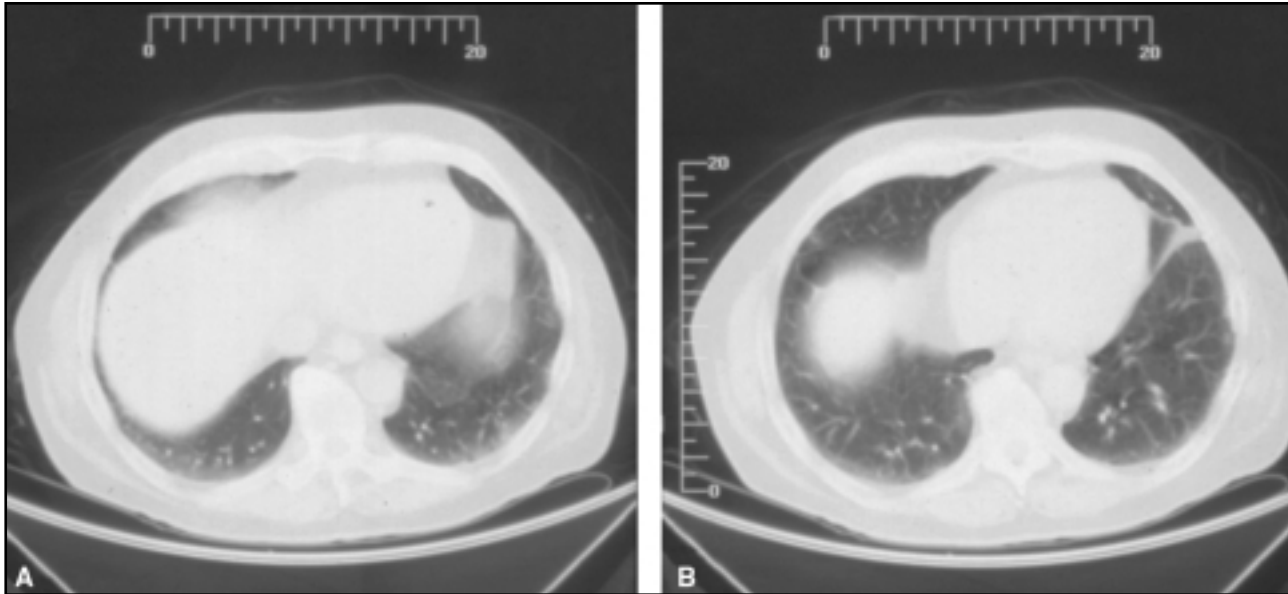


Fig 2A-B.— Computed tomography scans of the chest delineates bilateral lower-lobe 2- to 3-mm nodules from disseminated *M. bovis* infection.

required corticosteroid treatment or insulin. Six months following hospitalization, he remained asymptomatic on a daily regimen of 500 mg of levofloxacin, 1,500 mg of ethambutol, and 600 mg of rifampin. One year later, he completed 12 months of this regimen with no recurrence of bladder cancer or symptoms associated with *M. bovis* infection. He received no further BCG treatments, and subsequent chest radiograph revealed no evidence of miliary *M. bovis*.

Discussion

Immunotherapy with intravesicular BCG is an effective treatment for patients with superficial transitional-cell carcinoma of the bladder. A 1985 study demonstrated that more than 70% of patients with superficial and stage I disease experienced complete remission.²

The method by which BCG provides therapeutic benefit in patients with bladder cancer is unknown. However, it is thought to act as a nonspecific stimulant of the immune system by inducing granulomatous inflammation.^{1,6} Intravesicular BCG is well tolerated with relatively few side effects. The frequency of adverse effects was reported in a study of more than 1,200 patients who received this type of immunotherapy.⁵ The results revealed only a 2.9% incidence of high fever (>39°C), 1.0% major hematuria, 0.9% granulomatous prostatitis, 0.7% granulomatous pneumonitis/hepatitis, 0.5% arthritis or arthralgia, 0.4% epididymo-orchitis, 0.4% life-threatening BCG sepsis, 0.3% urethral obstruction, 0.2% bladder contracture, 0.1% renal abscess, and 0.1% cytopenia. In addition, there have been reports of rare BCG complications such as mycotic aneurysms,

glomerulonephritis, choroiditis, nephrogenic adenoma, suppurative lymphadenitis, cardiac toxicity, and musculoskeletal lesions.^{7,9} Nevertheless, BCG treatment is still considered to be a reasonably safe and effective cancer therapy.

Dissemination of *M. bovis* developed in our patient following an intravesicular treatment with BCG. Although all blood cultures, urine cultures, and PCR analysis for *M. bovis* were negative, a presumptive diagnosis of disseminated BCG was justified by various findings. Cystitis and fever developed within hours of BCG instillation, which eventually progressed to respiratory compromise requiring corticosteroids and supplemental oxygen. Chest radiograph revealed the development of a bilateral miliary interstitial pattern consistent with pulmonary spread of *M. bovis*. The lack of mycobacterial identification

by blood culture is not unusual in cases of *M. bovis* sepsis. A similar case was reported in 1992, in which a patient with disseminated BCG presented with a miliary radiographic pattern and negative urine and blood cultures.¹⁰ Pulmonary dissemination of *M. bovis* was also reported in a 1990 case with bilateral interstitial infiltrates seen on chest radiograph and blood and lung tissue cultures negative for mycobacterium.¹¹ In both cases, the patients improved clinically with antituberculosis treatment. Similarly, our patient exhibited a marked improvement on a regimen of ethambutol, rifampin, and levofloxacin.

Previous reports have speculated as to the cause of BCG dissemination following intravesicular instillation. One accepted risk factor is a recent history of urological trauma that facilitates hematogenous spread.² This was not an issue for our patient as he lacked a history of recent surgery, and the administration of BCG was not reported to be traumatic. A review by Lamm¹ suggests that delaying BCG immunotherapy by at least 1 to 2 weeks after any disruption of the uroepithelium may reduce the risk of subsequent dissemination. In addition, the author suggested that patients who experience traumatic catheterization are not candidates for further BCG instillations.

An immunocompromised state is another important risk factor for BCG dissemination. Current recommendations are that patients who have AIDS, who are taking immunosuppressive agents, who have a

hematological malignancy, who are pregnant, or who are lactating should not receive treatment with this live attenuated strain of mycobacterium.^{5,12} Our patient was immunocompetent, did not experience catheterization trauma, and had no other established risk factors for dissemination.

The mechanism of complications in patients after disseminated BCG infections remains controversial. One theory is that the hematogenous spread of mycobacteria to sites such as liver, bone, or lung induces direct organ damage. Reports of positive cultures for *M. bovis* in sputum and lung biopsy specimens have supported this theory.^{10,13} In addition, noncaseating granulomas have been recovered from liver and bone marrow biopsy specimens of disseminated BCG patients, suggesting mycobacterial spread.^{11,14,15} These patients responded well to antituberculosis regimens, often with complete resolution of symptoms within weeks. This indicates that direct spread of organisms likely has some role in the pathogenesis.

An alternate theory is that a hypersensitivity response to *M. bovis* is important in the pathogenesis of this disease.^{13,14} This concept was proposed after several case reports were unable to demonstrate *M. bovis* on acid-fast bacillus stains of blood or tissue specimens and when PCR analysis for *M. bovis* was negative.^{14,15} More significantly, patients responded well when corticosteroids were added to the antituberculosis treatment regimen.^{1,16}

Our patient demonstrated a significant clinical improvement when prednisone was added as adjunctive therapy followed by a relapse as the corticosteroid dose was tapered too quickly. This indicates that a hypersensitivity response was likely involved in the pneumonitis symptoms.

There is in fact some consensus that both mechanisms play a role. For this reason, it has been suggested that the recommended treatment for patients with *M. bovis* infections in the acute setting is a combination of antimycobacterial therapy and corticosteroids.¹ Current recommendations are that patients with systemic side effects such as fever, malaise, or bladder irritation should be initially treated with 300 mg of isoniazid per day.⁹ If symptoms persist for more than 1 to 2 weeks or worsen, 600 mg of rifampin per day should be added for 2 weeks. Patients with extravesical symptoms such as pneumonitis, hepatitis, or mycotic aneurysm should be treated for 3 to 6 months with an isoniazid-rifampin combination.

In the rare case of BCG sepsis, corticosteroids should be added to the antituberculosis regimen. BCG immunotherapy should be discontinued in all cases of dissemination, and permanent avoidance of BCG therapy should be considered in severe cases.⁵ The efficacy of different treatment protocols was studied in mice with BCG sepsis.¹⁷ Triple-drug therapy with isoniazid, rifampin, and prednisolone resulted in a 53% survival rate compared with 25% with isoniazid and rifam-

Age and Number of BCG Instillations in Published Case Reports⁷⁻²⁰

Age (Years)	Total Number of BCG Treatments
67	4
75	3
59	n/a
49	n/a
68	3
57	13
67	3
68	3
n/a	8
74	6
69	6

pin and 10% with prednisolone alone. Other antituberculosis regimens such as ethambutol, erythromycin, or cycloserine have been used to treat patients with *M. bovis* infections.^{1,5,18} Pyrazinamide, an antituberculosis drug, is ineffective against *M. bovis*.^{5,16} As our patient exhibited hepatocellular injury with isoniazid treatment, we used ethambutol, rifampin, levofloxacin, and prednisone as an alternate therapeutic strategy. Corticosteroids were required in a prolonged dose taper in our patient as he experienced a relapse of symptoms when prednisone was tapered on two separate occasions, thus emphasizing the importance of corticosteroid treatment in this patient.

Our patient received 16 treatments over a 5-year span. This repeated exposure to an inoculum of live attenuated *M. bovis* may have predisposed him to subsequent dissemination. In a review of

current literature, the majority of cases of similar BCG dissemination reported total instillations numbering between 3 and 13 (Table).⁷⁻²⁰ Five patients with disseminated BCG had 4 or fewer instillations. Therefore, dissemination can occur at any time in the course of instillation. However, as therapy recommendations continue to be revised, a growing number of patients may receive large numbers of treatments. Recent experience suggests that the optimal induction therapy is 6 weekly instillations followed by a 6-week rest period and then 3 more weekly instillations.¹

The benefits of monthly maintenance therapy are still being studied, but current evidence suggests there is a significant increase in disease-free survival for patients who receive a maintenance schedule. With this treatment regimen, the number of total instillations can be significant, especially if subsequent recurrences develop and therapy is reinitiated. Thus, the toxicity of repeated BCG treatments may need further evaluation.

Conclusions

Although *M. bovis* is a rare complication of intravesicular BCG treatment, it may result in prolonged fever, miliary lung nodules, or death if inappropriately treated. Symptomatology is probably produced jointly by dissemination of *M. bovis* to the reticuloendothelial system and a hypersensitivity response. Antituberculosis agents other than pyrazinamide in combination with corticosteroids com-

prise the treatment of choice for disseminated BCG infection. Our patient improved clinically with a regimen including both prednisone and antituberculosis agents. Corticosteroids were necessary to control symptoms as demonstrated by improvement in symptoms during prednisone treatment and relapse as the corticosteroid dosage was tapered.

References

1. Lamm D. BCG immunotherapy for transitional-cell carcinoma in situ of the bladder. *Oncology (Huntingt)*. 1995;9:947-952, 955-965 discussion and review.
2. Schellhammer PF, Ladaga LE, Fillion MB. Bacillus Calmette-Guérin for superficial transitional cell carcinoma of the bladder. *J Urol*. 1986;135:261-264.
3. Mungan NA, Witjes JA. Bacille Calmette-Guérin in superficial transitional cell carcinoma. *Br J Urol*. 1998;82:213-223. Review.
4. Lamm DL, Stogdill VD, Stogdill BJ, et al. Complications of bacillus Calmette-Guérin immunotherapy in 1,278 patients with bladder cancer. *J Urol*. 1986;135:272-274.
5. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol*. 1992;147:596-600.
6. Groves MJ. Pharmaceutical characterization of Mycobacterium bovis bacillus Calmette-Guérin (BCG) vaccine used for the treatment of superficial bladder cancer. *J Pharm Sci*. 1993;82:555-562. Review.
7. Bornet P, Pujade B, Lacaine F, et al. Tuberculous aneurysm of the femoral artery: a complication of bacilli Calmette-Guérin vaccine immunotherapy: a case report. *J Vasc Surg*. 1989;10:688-692.
8. Izes JK, Bihle W III, Thomas CB. Corticosteroid-associated fatal mycobacterial sepsis occurring 3 years after instillation of intravesical bacillus Calmette-Guérin. *J Urol*. 1993;150(5 pt 1):1498-1500. Review.
9. Lamm DL. Complications of bacillus Calmette-Guérin immunotherapy. *Urol Clin North Am*. 1992;19:565-572. Review.
10. McParland C, Cotton DJ, Gowda KS, et al. Miliary Mycobacterium bovis induced by intravesical bacille Calmette-Guérin immunotherapy. *Am Rev Respir Dis*. 1992;

146(5 pt 1):1330-1333.

11. Kesten S, Title L, Mullen B, et al. Pulmonary disease following intravesical BCG treatment. *Thorax*. 1990;45:709-710.

12. Talbot EA, Perkins MD, Silva SF, et al. Disseminated bacille Calmette-Guérin disease after vaccination: case report and review. *Clin Infect Dis*. 1997;24:1139-1146. Review.

13. Kristjansson M, Green P, Manning HL, et al. Molecular confirmation of bacillus Calmette-Guérin as the cause of pulmonary infection following urinary tract instillation. *Clin Infect Dis*. 1993;17:228-230.

14. Dederke B, Riecken EO, Weinke T. A case of BCG sepsis with bone marrow and liver involvement after intravesical BCG instillation. *Infection*. 1998;26:54-57.

15. Case records of the Massachusetts General Hospital: weekly clinicopathological exercises. *N Engl J Med*. 1998;339:831-837. Case 29-1998.

16. Molina JM, Rabian C, D'Agay MF, et al. Hypersensitivity systemic reaction following intravesical bacillus Calmette-Guérin: successful treatment with steroids. *J Urol*. 1992; 147:695-697.

17. Koukol SC, DeHaven JI, Riggs DR, et al. Drug therapy of bacillus Calmette-Guérin sepsis. *Urol Res*. 1995;22:373-376.

18. Deresiewicz RL, Stone RM, Aster JC. Fatal disseminated mycobacterial infection following intravesical bacillus Calmette-Guérin. *J Urol*. 1990;144:1331-1334.

19. Griggs H, Cammarata SK. Acute mental changes in a 68-year-old man with bladder cancer. *Chest*. 1998;114:621-23.

20. Iantorno R, Nicolai M, Storto ML, et al. Miliary tuberculosis of the lung in a patient treated with bacillus Calmette-Guérin for superficial bladder cancer. *J Urol*. 1998;159:1639-1640.