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Septic Shock after Intravesical BCG Instillation—A Case Report*

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ABSTRACT

Bacillus Calmette-Guérin (BCG) is a live attenuated form of *Mycobacterium bovis*, initially used in medicine as a vaccination agent only. The discovery of its antineoplastic effects in bladder cancer has led to the widespread recognition of BCG intravesical instillation as a therapeutic option. Although sepsis following BCG intravesical instillation is rare, it is nonetheless a dreadful and potentially fatal complication. Therapy usually relies on antituberculous therapy and steroids, alongside with intensive care unit admission. The authors report a case of a 67-year-old male patient who developed septic shock with multiple organ dysfunction after intravesical BCG instillation and review the currently available knowledge concerning the risk factors, diagnosis, management and prevention of BCG sepsis.

Keywords: Bacillus Calmette-Guérin; BCG; Sepsis; Shock

1. Introduction

Bacillus Calmette-Guérin (BCG) is a low-virulence mycobacteria originated from successive cultures of *Mycobacterium bovis* [1], and intravesical instillation of BCG is a therapeutic option in bladder cancer [2]. Sepsis is a rare complication of this procedure, and certain aspects concerning its diagnostic and treatment are still debatable. We report the case of a patient who developed septic shock with multiple organ dysfunction after intravesical BCG instillation and review the currently available knowledge concerning the risk factors, diagnosis, management and prevention of BCG sepsis.

2. Case Report

We report the case of a 67-year-old male patient, with known Alzheimer's and cerebrovascular disease, who had been diagnosed with a vesical urothelial carcinoma (pT1) on February 2012 and underwent transurethral resection (TUR) in the following month. He began monthly intravesical Bacillus Calmette-Guérin (BCG) instillation on May 2012. After each session he complained of low-grade fever, which spontaneously waned on the following 24 - 48 h.

On May 10th of 2013 (Day 1 - D1), he presented to the outpatient clinic complaining of persistent fever and increased sudoresis for 2 weeks, after the 12th BCG instillation; he denied any other symptoms. The physical examination was unremarkable, apart from being slightly more disoriented than usual. The analytic panel revealed an elevated C reactive protein, elevated liver enzymes with normal bilirubin; elevated creatinine (see **Table 1**) and mild leucocyturia (89 cells/μL) without any other urinary changes. On abdominal ultrasonography, an enlarged liver with heterogenic parenchyma was noted, suggesting acute hepatitis.

He was admitted to our hospital, a urine culture for mycobacteria was collected, and he began oral levofloxacin (500 mg id). His clinical condition deteriorated, and on D6 he was admitted to the Infectious Diseases Intensive Care Unit (ID-ICU) due to dyspnoea and oxygen desaturation (86% on pulse oximetry) which did not resolve with oxygen supplementation. He presented tachypnea (36 cpm), tachycardia (106 bpm), poor distal

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Table 1. Patients evolution before and during ID-ICU admission.

Paramater (units)	Day 1	Day 6	Day 10	Day 15	Day 20	Day 25
Haemoglobin (g/dL)	11.8	9.9	9.6	8.8	7.0	9.0
Leukocytes ($\times 10^6$/L)	6.180	17.540	7.030	4.900	4.300	5.960
Neutrophils (%)	60.8	83.7	74.8	57.6	60.2	64.4
Platelets ($\times 10^9$/L)	112	133	13	47	114	223
C Reactive Protein (mg/L)	135.4	139.9	188.7	40.5	56.7	52
Creatinine (mg/dL)	1.63	1.20	1.60	1.63	1.01	0.82
ALT (IU/L)	198	334	80	23	26	28
Total/Conjugated Bilirrubin (mg/dL)	0.71/0.34	1.61/1.00	7.80/5.05	4.11/2.29	2.21/1.04	2.17/0.92
aPTT/PT (sec)	-/-	50.2/17.3	54/15.3	32.9/13.8	33.3/12	-
pO2/FiO2 ratio	-	53	131	223	224	200
Lactate (mmol/L)	-	6.59	2.56	2.43	1.67	1.92
Comments	Levo	ID-ICU admission Added RIF, INH, ETB	Added steroids Stop RIF	-	PRBC transfusion Stop amminergic support	Discharged from ID-ICU

ALT—alanine aminotransferase; aPTT—activated partial thromboplastin time; ETB—ethambutol; ID-ICU—Infectious Diseases Intensive Care Unit; INH—isoniazid; PRBC—1 unit of packed red blood cells; PT—prothrombin time; RIF—rifampicin.

perfusion signs and bilateral crackles on lung auscultation. The chest roentgenography revealed bilateral and diffuse patchy infiltration, suggestive of ARDS. The arterial blood gases analysis showed a pO2/FiO2 ratio of 122, along with respiratory alkalosis and hyperlactatemia (3.74 mmol/L). Orotracheal intubation was needed and mechanical ventilation started. Despite fluid therapy, vasopressor support was required. Apart for norepinephrine, dobutamine was added due to severely depressed left ventricular function noted on transthoracic echocardiography. Besides the septic shock, he had cardiovascular, respiratory, renal, liver, and haematological dysfunction. Blood, urine and endotracheal aspirate were collected for both bacteria and mycobacteria cultures and he was started on intravenous therapy with isoniazid (300 mg id), rifampicin (600 mg id), levofloxacin (750 mg id) and oral ethambutol (1200 mg id) for systemic BCG infection; intravenous ceftriaxone (2 g id) was added to widen antibacterial coverage, since levofloxacin was apparently insufficient to restrain an eventual bacterial infection.

Over the next days, deterioration of cardiovascular, hepatic, renal and hematologic dysfunctions was observed. On D10, rifampicin was suspended due to hepatotoxicity and steroids (2 mg/kg daily prednisolone equivalent) were started; ceftriaxone was suspended after all bacteriologic cultures were known to be negative. Subsequently, the patient progressively improved, with vasopressor support being withheld on D19; successful extubation was accomplished on D20. He was transferred from the ID-ICU on D25, and was finally discharged home on D36, maintaining oral therapy with isoniazid, ethambutol and levofloxacin (same dosages). Corticosteroids were stopped after tapering.

Acid-fast auramine stain exams of urine, blood and respiratory samples were negative. *Mycobacterium tuberculosis* complex DNA detection exam was also negative. The broth cultures of blood, endotracheal aspirate and urine (with Middlebrook medium and monitored by BD Bactec™ 9000 MB and BD Bactec™ MGIT™ 960 systems) were negative.

3. Discussion

Mycobacterium bovis was isolated in 1902 by the French veterinarian and microbiologist Edmond Nocard [1]. Bacillus Calmette-Guérin (BCG) is a low-virulence mycobacteria originated from successive cultures of *M. bovis*, resulting from the combined efforts done of Albert Calmette and his assistant Camille Guérin [1]. This strain was initially used to vaccinate cattle to prevent tuberculosis and later was successfully used in humans. Nowadays, it is implemented in many countries with a high incidence of tuberculosis, mainly in the setting of routine newborn immunization.

Apart from vaccination, BCG is also widely used in the treatment of bladder cancer. The intravesical instillation of BCG appears to stimulate significantly the immune response, inducing the production of large amounts of cytokines that draw cytotoxic activity by natural killer cells and cytotoxic cells against transitional cancer cells,

diminishing the probability of recidivant or invasive neoplasia [2].

Intravesical administration of BCG can be associated with several complications. These may be local or systemic and occur early or late on the course of BCG treatment. The majority of patients experience local symptoms (such as dysuria and frequency) within two hours of BCG instillation, which may be accompanied by low-grade fever and malaise. Like in the case reported, these symptoms usually resolve within 48 hours and may be more frequent in patients who have previously received intravesical instillations [3]. Some authors suggest that the occurrence of low fever and cystitis after intravesical instillation may be signs of a good therapeutic response [4]. However, local complications can occur, and there are reports of granulomatous ulceration of the glans penis, prostatitis, epididymitis, ureteral obstruction, bladder contracture and renal abscess [5].

In the majority of the intravesical BCG sepsis cases, symptoms developed only after several instillations. However, in a case described by Frey *et al*. [6], septic shock developed rapidly after the first BCG intravesical instillation in a 31-year old patient not previously immunized with BCG. In the present case, the patient was on BCG treatment for a year. After the last instillation (without any known local trauma associated) he presented with persisting fever for 2 weeks, which alerted the clinicians for a possible complication.

BCG-related sepsis diagnosis is frequently challenging since symptoms are indistinct from other sepsis causes: patients often develop high fever, chills, hypotension, disorientation, disseminated intravascular coagulation, respiratory insufficiency, jaundice and leucopenia. Lamm *et al*. [4] have suggested that fever or shivering during or shortly after BCG intravesical instillation may be predictive for the risk of developing a severe infection.

This patient had no lower urinary tract symptoms, but there was mild leucocyturia; persistent fever was the only sign of possible disseminated infection, but the seemingly benign clinical appearance led to assumption of local complication, and so he began the treatment with levofloxacin. This proved to be rather insufficient, since he subsequently developed septic shock with multiple organ dysfunction.

Although BCG instillations contain live attenuated mycobacteria, the likelihood that BCG can be isolated through culture is affected by many factors, including the number of organisms present (which, in turn, reflects the ability of the immune system to control infection), the handling of the samples, and culture technique [7]. As happened in the case described, there is no direct proof of infection by *M. bovis* in almost a third of cases of serious complications [8]. In BCG disseminated infection or sepsis, both the tuberculin skin test and the interferon gamma release assay (IGRA) can be positive, although IGRA performance for detection of active disease has not been fully evaluated and should not be part of the routine diagnostic approach for *M. bovis* infection suspicion [9]. Staining of specimens for acid-fast bacilli, cultures and PCR testing for mycobacterial DNA should be performed in any patient with suspected disseminated BCG infection, even though all of these procedures can be negative in some cases. However, it is important to note that nucleic acid hybridization probe assays cannot be used to distinguish among members of the *M. tuberculosis* complex directly from samples, since they lack sensitivity. So the identification of mycobacteria through these techniques relies on the cultural isolation of *M. bovis* [9].

There are no controlled studies that determined the optimal therapy of intravesical BCG-related sepsis. In a clinically suspected case of BCG related complication, some studies recommend immediate start of fluoroquinolone therapy, since this treatment is effective against both BCG and Gram-negative urinary pathogens [10]. Like *M. bovis*, BCG is susceptible to most of the antituberculous drugs, apart from pyrazinamide and cycloserine [11]. Isoniazid (300 mg id) and rifampicin (600 mg id) are usually recommended for 6 - 9 months [12,13].

Additionally to antituberculous therapy, some human and animal studies have suggested potentially beneficial effect of corticosteroid use in the treatment of severe cases of disseminated BCG infection [12-17]. The mechanism related to this beneficial effect may be related to the possible hypersensitivity reaction developed during BCG treatment [2,12]. In the case reported, standard treatment for septic shock was started, and the antituberculous scheme was broadened; nevertheless, the patient's status deteriorated during the next 4 days. Steroid use in septic shock (of any aetiology) as long been controversial, but in this case it was only after steroid therapy introduction that the patient slowly (yet steadily) improved. We started with 2 mg/kg/daily prednisolone equivalent, tapering the dose to half every 3 - 4 days until suspension after 23 days. It's rather tempting to attribute the initial improvement of this patient to the anti-inflammatory effect of steroids. Yet, mixed outcomes and recognized side-effects associated with steroids lead to uncertainties concerning its recommendation. Besides, there have been descriptions of clinical aggravation after steroid suspension [13]. Although potentially helpful in some cases of septic shock, steroid therapy in the setting of BCG sepsis remains debatable. With the increasing development of anti-inflammatory therapies (especially monoclonal antibodies), perhaps new and tailored-made therapies could have beneficial impact on this rare yet potentially fatal complication.

Since optimal therapy is still uncertain, measures to prevent infection by BCG are of paramount importance.

These include deferral of BCG instillation in patients with difficult bladder catheterizations, cystitis, or persistent haematuria following transurethral resection of the bladder tumour [13]. Furthermore, BCG intravesical instillations should be permanently suspended in patients who develop infectious complications requiring antituberculous therapy. Drug prophylaxis has also been tested. Isoniazid (either 300 mg id, or concurrent administration with intravesical instillation of BCG) showed no efficacy in preventing BCG related complications and suggested contributing to lesser efficacy of BCG instillation treatment, since live organisms seem to be required for the instillation's immunological effect [18,19]. Ofloxacin administered after each BCG instillation reduced the incidence of severe local reactions and the need for antituberculous therapy; a recent study using prulifloxacin reported similar findings [20]. Somehow, this strategy doesn't seem to affect the efficacy of BCG anti-neoplasic treatment. Yet, present data is not sufficient for a clear recommendation about drug prophylaxis.

4. Conclusion

BCG-induced sepsis after intravesical instillation for bladder cancer is a rare complication. Pathophysiology remains largely unknown, but BCG's low virulence suggests that an immunological hipersensitivity reaction probably plays a role. In severe cases, high-dose steroids could be added to antituberculous therapy and the cornerstone of BCG-induced sepsis. Measures to prevent BCG infection should be strictly observed.

REFERENCES

[1] U. V. A. Silva, L. S. Viana, P. T. O. Castro, R. Almeida and R. S. P. daSilva, "Fatal Sepsis after Intravesical Instillation of BCG—Case Report," *Rev Bras Ter Intensiva*, Vol. 23, No. 1, 2011, pp. 104-107. http://dx.doi.org/10.1590/S0103-507X2011000100016

[2] S. Brandau and H. Suttmann, "Thirty Years of BCG Immunotherapy for Non-Muscle Invasive Bladder Cancer: A Success Story with Room for Improvement," *Biomed Pharmaceuticals*, Vol. 61, No. 6, 2007, pp. 299-305. http://dx.doi.org/10.1016/j.biopha.2007.05.004

[3] M. J. Barza, J. H. Blum and F. M. Graeme-Cook, "A 57-Year-Old Man with Fever and Jaundice after Intravesical Instillation of Bacille Calmette-Guérin for Bladder Cancer," *The New England Journal of Medicine*, Vol. 339, No. 12, 1998, p. 831.

[4] D. L. Lamm, "Efficacy and Safety of Bacille Calmette-Guérin Immunotherapy in Superficial Bladder Cancer," *Clinical Infectious Diseases*, Vol. 31, No. S3, 2000, pp. S86-S90. http://dx.doi.org/10.1086/314064

[5] C. French, L. Hickey and D. Bell, "Caseating Granulomas on the Glans Penis as a Complication of Bacille Calmette-Guérin Intravesical Therapy," *Reviews in Urology*, Vol. 3, No. 1, 2001, pp. 36-39.

[6] H. M. Frey, "Septic Shock in a 3l-Year-Old Male with a Superficial Bladder Tumor," *Clinical Infectious Diseases*, Vol. 2, No. 4, 1998, pp. 226-229. http://dx.doi.org/10.1016/S1201-9712(98)90058-3

[7] O. Gonzalez, D. Musher, I. Brar, S. Furgeson, M. Boktour, E. Septimus, R. Hamill and E. Graviss, "Spectrum of Bacille Calmette-Guérin (BCG) Infection after Intravesical BCG Immunotherapy," *Clinical Infectious Diseases*, Vol. 36, No. 2, 2003, pp. 140-148. http://dx.doi.org/10.1086/344908

[8] F. Saint, L. Salomon, R. Quintela, A. Cicco, C. C. Abbou and D. K. Chopin, "Classification, Facteurs Favorisants, Prévention et Traitement des Effets Indésirables Associés au Bacille de Calmette-Guérin dans le Traitement des Tumeurs Superficielles de Vessie," *Annales of Urology*, Vol. 36, No. 2, 2002, pp. 120-131. http://dx.doi.org/10.1016/S0003-4401(01)00085-7

[9] E. Talbot, C. F. von Reyn and E. L. Baron, "*Mycobacterium Bovis*," 2013. http/www.uptodate.com/contents/mycobacterium-bovis

[10] C. Durek, A. Jurczok, H. Werner, D. Jocham and A. Bohle, "Optimal Treatment of Systemic Bacillus Calmette-Guerin Infection: Investigations in an Animal Model," *Journal of Urology*, Vol. 168, No. 2, 2002, pp. 826-831. http://dx.doi.org/10.1016/S0022-5347(05)64751-9

[11] C. Durek, S. Rüsch-Gerdes, D. Jocham and A. Böhle, "Sensitivity of BCG to Modern Antibiotics," *European Urology*, Vol. 37, No. S1, 2000, p. s21. http://dx.doi.org/10.1159/000052378

[12] S. C. Koukol, J. I. DeHaven, D. R. Riggs and D. L. Lamm, "Drug Therapy of Bacillus Calmette-Guérin Sepsis," *Urological Research*, Vol. 22, No. 6, 1995, pp. 373-376. http://dx.doi.org/10.1007/BF00296878

[13] M. Elkabani, J. N. Greene, A. L. Vincent, S. Van Hook and R. L. Sandin, "Disseminated *Mycobacterium bovis* after Intravesicular Bacillus Calmette-Guérin Treatments for Bladder Cancer," *Cancer Contact*, Vol. 7, No. 5, 2000, pp. 476-481.

[14] R. Wittes, L. Klotz and U. Kosecka, "Severe Bacillus Calmette-Guérin Cystitis Responds to Systemic Steroids When Antituberculous Drugs and Local Steroids Fail," *Journal of Urology*, Vol. 161, No. 5, 1999, p. 1568. http://dx.doi.org/10.1016/S0022-5347(05)68961-6

[15] A. Steg, C. Leleu, B. Debré, *et al*., "Systemic Bacillus Calmette-Guérin Infection in Patients Treated by Intravesical BCG Therapy for Superficial Bladder Cancer," *Progress in Clinical and Biological Research*, Vol. 310, No. 1, 1989, p. 325.

[16] J. I. DeHaven, C. Traynellis, D. R. Riggs, E. Ting and D. L. Lamm, "Antibiotic and Steroid Therapy of Massive Systemic Bacillus Calmette-Guérin Toxicity," *Journal of Urology*, Vol. 147, No. 3, 1992, pp. 738-742.

[17] D. L. Lamm, "Complications of Bacillus Calmette-Guérin Immunotherapy," *Urologic Clinics of North America*, Vol. 19, No. 3, 1992, pp. 565-572.

[18] Y. Durán, F. Santos, D. Serentill, P. Montaperto, P. Valencia and C. Solé, "Tuberculosis Miliar in a Patient Treated with Intravesical Instillations of Bacillus Calmette-Guérin," *Med Intensiva*, Vol. 30, No. 3, 2006, pp. 116-

119. http://dx.doi.org/10.1016/S0210-5691(06)74485-0

[19] A. P. van der Meijden, M. Brausi, V. Zambon, W. Kirkels, C. de Balincourt and R. Sylvester, "Intravesical Instillation of Epirubicin, Bacillus Calmette-Guérin and Bacillus Calmette-Guérin plus Isoniazid for Intermediate and High Risk Ta, T1 Papillary Carcinoma of the Bladder: A European Organization for Research and Treatment of Cancer Genito-Urinary Group Randomized Phase III Trial," *Journal of Urology*, Vol. 166, No. 2, 2001, p. 476. http://dx.doi.org/10.1016/S0022-5347(05)65966-6

[20] R. Damiano, M. De Sio, G. Quarto, *et al*., "Short-Term Administration of Prulifloxacin in Patients with Nonmuscle-Invasive Bladder Cancer: An Effective Option for the Prevention of Bacillus Calmette-Guérin-Induced Toxicity?" *BJU International*, 2009, Vol. 104, p. 633. http://dx.doi.org/10.1111/j.1464-410X.2009.08469.x