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

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Day 1</th>
<th>Day 6</th>
<th>Day 10</th>
<th>Day 15</th>
<th>Day 20</th>
<th>Day 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.8</td>
<td>9.9</td>
<td>9.6</td>
<td>8.8</td>
<td>7.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Leukocytes (×10^6/L)</td>
<td>6.180</td>
<td>17.540</td>
<td>7.030</td>
<td>4.900</td>
<td>4.300</td>
<td>5.960</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>60.8</td>
<td>83.7</td>
<td>74.8</td>
<td>57.6</td>
<td>60.2</td>
<td>64.4</td>
</tr>
<tr>
<td>Platelets (×10^9/L)</td>
<td>112</td>
<td>133</td>
<td>13</td>
<td>47</td>
<td>114</td>
<td>223</td>
</tr>
<tr>
<td>C Reactive Protein (mg/L)</td>
<td>135.4</td>
<td>139.9</td>
<td>188.7</td>
<td>40.5</td>
<td>56.7</td>
<td>52</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.63</td>
<td>1.20</td>
<td>1.60</td>
<td>1.63</td>
<td>1.01</td>
<td>0.82</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>198</td>
<td>334</td>
<td>80</td>
<td>23</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Total/Conjugated Bilirubin (mg/dL)</td>
<td>0.71/0.34</td>
<td>1.61/1.00</td>
<td>7.80/5.05</td>
<td>4.11/2.29</td>
<td>2.21/1.04</td>
<td>2.17/0.92</td>
</tr>
<tr>
<td>aPTT/PT (sec)</td>
<td>-</td>
<td>50.2/17.3</td>
<td>54/15.3</td>
<td>32.9/13.8</td>
<td>33.3/12</td>
<td>-</td>
</tr>
<tr>
<td>pO2/FiO2 ratio</td>
<td>-</td>
<td>6.59</td>
<td>2.56</td>
<td>2.43</td>
<td>1.67</td>
<td>1.92</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>-</td>
<td>6.59</td>
<td>-</td>
<td>2.56</td>
<td>2.43</td>
<td>1.67</td>
</tr>
</tbody>
</table>

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 from 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 neo-
plasia [2].

Intravesical administration of BCG can be associated with several complications. These may be local or sys-
temic and occur early or late on the course of BCG treat-
ment. The majority of patients experience local symp-
toms (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 con-
tracture and renal abscess [5].

In the majority of the intravesical BCG sepsis cases, symp-
toms developed only after several instillations. How-
ever, in a case described by Frey et al. [6], septic shock
developed rapidly after the first BCG intravesical instil-
lation 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, dis-
orientation, disseminated intravascular coagulation, res-
piratory insufficiency, jaundice and leucopenia. Lamm et
al. [4] have suggested that fever or shivering during or
shortly after BCG intravesical instillation may be predic-
tive 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 seem-
ingly 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 sep-
sis, both the tuberculin skin test and the interferon gam-
ma 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 di-
agnostic 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 infec-
tion, even though all of these procedures can be negative
in some cases. However, it is important to note that nu-
cleic acid hybridization probe assays cannot be used to
distinguish among members of the M. tuberculosis com-
plex directly from samples, since they lack sensitivity. So
the identification of mycobacteria through these techni-
ques relies on the cultural isolation of M. bovis [9].

There are no controlled studies that determined the op-
timal therapy of intravesical BCG-related sepsis. In a cli-
nically 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]. Iso-
niazid (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 me-
chanism 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 antituber-
culous 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 introd-
uction that the patient slowly (yet steadily) improved. We
started with 2 mg/kg/daily prednisolone equivalent, tape-
ring 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 ef-
fect 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 suspen-
sion [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 anti-
bodies), 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-neoplastic 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 hypersensitivity 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.

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