BCG sepsis following inadvertent intravenous BCG administration for the treatment of bladder cancer can be effectively cured with anti-tuberculosis medications

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Abstract

Aim To the best of our knowledge we are presenting the very first case of inadvertent intravascular administration of BCG and its successful treatment with anti-tuberculosis medications on a patient with superficial bladder cancer.

Methods A search of the English literature (PubMed/Medline) was performed concerning inadvertent BCG administration for bladder cancer by using the key words.

Results The patient was admitted to our hospital with high fever and chills a few hours after intravascular BCG administration. Chest CT showed bilateral infiltration of the lungs. Patient was placed on anti-tuberculosis treatment including isoniazid, rifampycin, ethambutol and methylprednisolone initially; and this treatment was adjusted according to his clinical course and liver function tests. By the end of the 4th week of hospitalisation patient was responded well with normalisation of his clinical status, liver function tests and a normal chest X-ray. Thereafter, he was discharged home on isoniazid, ethambutol for 6 months, streptomycin, cycloserine-C and ofloxacin for 2 months, methylprednisolone which was stopped eventually after dose reduction. On follow-up at 6th month after discharge from the hospital, he was fully recovered with normal chest X-ray and blood tests.

Conclusions Development of severe sepsis is inevitable following inadvertent intravascular BCG administration. Therefore, urologists should warn and inform not only their patients and families but also healthcare workers such as nurses regarding the route of administration of the BCG treatment for bladder cancer. Our experience also proved that such a serious complication can be successfully treated if promptly acted.

Intravesical BCG administration applied to prevent recurrence and progression of superficial bladder cancer is associated with many side effects and disseminated BCG infection is a rare but severe complication. Herein, we presented and discussed the history, clinical features, treatment and outcome of our patient who developed Mycobacterium bovis (M. bovis) sepsis following inadvertent bacillus Calmette-Guérin (BCG) administration through intravenous route for the treatment of bladder cancer.

Case report

A 51-year-old male patient had a transurethral resection of papillary multiple bladder tumours (TUR-BT) and 40-mg of single dose intravesical mitomycin-C. Intravesical
BCG instillations were recommended for his pT1G3 transitional cell carcinoma (TCC). Unfortunately however, 81 mg of BCG (ImmuCyst®) was given intravenously at another hospital.

A flulike illness with nausea, fatigue, cough, shortness of breath and fever occurred hours after inadvertent intravenous BCG administration. The following day, his symptoms worsened and the patient was re-admitted to our hospital.

Respiratory sounds were weak on auscultation with palpable hepatomegaly, disseminated skin eruptions (abdomen and chest). Blood pressure was 90/60 mmHg, pulse rate was between 85–120/minute and body temperature was 38.1°C.

Complete blood count (CBC) and serum biochemistry values of the patient were presented in Table 1. Urine microscopy revealed white blood cells. Urine and blood cultures including *M. bovis* were all negative.

**Table 1. Laboratory values during the course of treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal values</th>
<th>On Admission</th>
<th>Hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mmol/L)</td>
<td>2.5–9.2</td>
<td>21.8</td>
<td>16.1–5.4</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>53–114.9</td>
<td>282.9</td>
<td>70.7–88.4</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>136–145</td>
<td>137</td>
<td>135–137</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>3.5–5.1</td>
<td>3.6</td>
<td>3.5–4.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>98–107</td>
<td>137</td>
<td>137–108</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.2–2.5</td>
<td>1.5</td>
<td>1.6–2.3</td>
</tr>
<tr>
<td>AST (U/mL)</td>
<td>8–34</td>
<td>445</td>
<td>202–158</td>
</tr>
<tr>
<td>ALT (U/mL)</td>
<td>10–49</td>
<td>324</td>
<td>147–130</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.4–4.8</td>
<td>3.0</td>
<td>2.9–2.2</td>
</tr>
<tr>
<td>Bilirubin (direct) (µmol/L)</td>
<td>0.0–3.4</td>
<td>–</td>
<td>111–35.9</td>
</tr>
<tr>
<td>Bilirubin (total) (µmol/L)</td>
<td>≤17.1</td>
<td>–</td>
<td>133–104</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>0–190</td>
<td>721</td>
<td>485–930</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>13.5–18</td>
<td>13.2</td>
<td>11.4–11.6</td>
</tr>
<tr>
<td>Hematocrit (Proportion of 1.0)</td>
<td>0.42–0.50</td>
<td>0.38</td>
<td>0.33–0.33</td>
</tr>
<tr>
<td>Platelet (×10^9/L)</td>
<td>170–450</td>
<td>47.7</td>
<td>10.5–106</td>
</tr>
</tbody>
</table>

Note: Bold italic values correspond to elevated serum levels. BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.

Abdominopelvic ultrasound revealed hepatomegaly. Chest computerised tomography (CT) demonstrated bilateral pleural effusions and infiltrations (Figure 1).

Patient was placed on isoniazid (1×300 mg/day, PO), rifampin (2×300 mg/day, PO), ethambutol (500 mg/day, PO, 3 times a week) and methylprednisolone 40 mg/day. On the 4th-day of hospitalisation lamivudine (100 mg, 1×1, PO) was initiated for his elevated hepatitis-B-DNA and steroid therapy. On the 3rd-day of hospitalisation, due to the elevated liver function tests, thrombocytopenia and leucopenia, rifampin dose was tapered down to 450 mg/day.

After the normalisation of renal function tests (6th day of hospitalisation), streptomycin (1 gr/day, IM) was initiated. At the end of the second week, due to the presence of dyspnoea, vomiting, fever and worsening of the chest X-ray, rifampin was...
stopped due to the highly elevated serum liver enzymes and cycloserine-C (250 mg, 1×300/day, PO) and ofloxacin (2×400 mg/day, PO) were initiated.

**Figure 1. Thorax computed tomography (CT) scan of the patient on the first week of hospitalisation showing bilateral septal infiltrations with groundglass appearance**

Supportive treatment including human albumin for hypoalbuminemia, thrombocyte suspensions for thrombocytopenia and fresh frozen plasma to prevent coagulation disorders were also given.

Clinical condition improved by the end of 4th-week and discharged home on isoniazid (300 mg, 1×1, PO), ethambutol (500 mg, 1×2, PO) for 6-months, streptomycin (1 gr, 1×1, IM, for 1 month), cycloserine-C (250 mg, 1×3, PO) and ofloxacin (200 mg, 2×2, PO) for 2 months, methylprednisolone (32 mg/day) and dose reduced by 4 mg every 4 days and eventually stopped. On follow-up at 6th month after discharge from the hospital, he was fully recovered with normal chest X-ray and blood tests (Table 1).

**Discussion**

Intravesical BCG instillations for the treatment of superficial bladder cancer are frequently associated with side effects. More serious complications include pneumonitis, hepatitis, sepsis and even death.\(^1,2\)

In the English literature (Pubmed/Medline), only 2 case reports exist related with inadvertent “intramuscular” injection of BCG.\(^3,4\) However, in our patient BCG was inadvertently administered intravenously.
In cases with intramuscular (IM) injections, severe and prolonged local reactions developed.\textsuperscript{3,4} Former was inadvertent intramuscular injection of BCG-vaccine into an already tuberculin-sensitive individual.\textsuperscript{3} However, latter was a 60-year-old male with bladder TCC. Following intramuscular administration, systemic symptoms including fever and headache developed with normal chest X-ray who was treated with anti-tuberculosis drugs successfully.\textsuperscript{4}

Rare cases of disseminated \textit{M. bovis} infection in patients with bladder cancer following intravesical BCG instillation have been reported.\textsuperscript{5–10} Although some authors proposed “hypersensitivity” as a cause of symptoms due to the presence of \textit{M. bovis} antigens in the presence of histologic noncaseating granulomas with negative cultures in addition to rapidity and completeness of the response to short term (6 weeks) of therapy\textsuperscript{9,11–14} others debated that these granulomatous lesions might result due to hematogenous spread of BCG bacteria.\textsuperscript{5}

Gonzalez et al classified the clinical course of BCG-related disease occurring after intravesical instillation as early and late presentation diseases in their literature review.\textsuperscript{9} They suggested rapid and complete response to therapy resulting from host immunity that becomes effective when the treatment is initiated for relatively low-grade virulence \textit{M. bovis}.\textsuperscript{9} They summarised the clinical courses of 20 patients who developed early-presentation disseminated BCG infection or hypersensitivity.

In our patient, due to the presence of chest CT and X-ray findings (Figure 1), elevated serum liver enzymes, elevated BUN/creatinine, hepatomegaly and thrombocytopenia we assumed our patient had pneumonitis, hepatitis, bone marrow involvement and renal failure. Gonzalez et al reported that miliary pattern or interstitial infiltrates was present on chest X-rays in almost half of the patients whereas in some patients chest X-rays were within normal limits.\textsuperscript{9} Gonzalez et al reported the interval between the first instillation and the onset of symptoms as between <1 hour and 22 weeks.\textsuperscript{9}

In our patient, symptoms occurred few hours after intravenous BCG administration. Although Gonzalez et al obtained tissue biopsies (liver, lung, bone marrow), no granuloma was detected in some biopsies in their series. Similarly, \textit{M. bovis} was only detected in 25\% of the urine and blood samples in these patients. A variety of stains could be used however none might detect any microorganisms.\textsuperscript{5} We did not take any tissue biopsies for microscopic investigation from our patient. Urine and blood cultures for \textit{M. bovis} were negative. Factors affecting the culture results depend on the number of microorganisms present, handling of the biopsied tissues, culture technique and the need for highly sensitive and specific molecular techniques in order to isolate the mycobacteria.\textsuperscript{9}

Late presentation disease has been also suggested after intravesical BCG instillation with a mean interval between instillation of BCG and onset of symptoms reported to be 15.7 months.\textsuperscript{9} These patients seem to have a tendency of developing disease particularly localised to the genitourinary tract without systemic symptoms or affect sites such as the spine or bones.\textsuperscript{6,9} Generally, laboratory or radiographic findings are normal.\textsuperscript{9} Therefore, long term close follow-up has been recommended to our patient.

The recommended treatment for disseminated BCG disease includes a combination of antituberculous medications with the exception of pyrazinamide, to which BCG is resistant.\textsuperscript{5,9} The following agents are used in different combinations for the treatment...
of symptoms in these patients: isoniazid, rifampin, ethambutol, streptomycin, erythromycin, levofloxacin, ofloxacin, cycloserine, steroids and plasmapheresis.\textsuperscript{5–10} The length of the treatment may be as short as two weeks in cases of mild symptoms or as long as 6 to 9 months for severe disseminated disease.\textsuperscript{5}

Addition of corticosteroids to the antituberculous therapy is also suggested in severe cases in preventing hypersensitivity reaction.\textsuperscript{5} Inclusion of antibiotics such as ofloxacin have also been suggested for the treatment of disseminated BCG infection in order to decrease the incidence of moderate to severe adverse events with BCG immunotherapy.\textsuperscript{15} Gonzalez et al reported that out of 20 patients with disseminated BCG infection, 15 patients (75\%) recovered whereas in 5 patients (25\%) died despite therapy.\textsuperscript{9} Therefore, the risk of death is very high in patients with BCG sepsis.

Recent research and studies have suggested some new agents and drugs which might be used in the treatment of disseminated tuberculosis. Tumour necrosis factor (TNF) has been suggested to play an important role in the regulation of chronic inflammatory diseases particularly in the host immune system against tuberculosis. Infliximab and etanercept are antagonists of TNF and have been suggested to inhibit TNF thereby used in the treatment of disseminated tuberculosis which warrants further research.\textsuperscript{16}

Recently, it has been shown that Rifacinna\textsuperscript{®} provides excellent in vitro activity against \textit{Mycobacterium tuberculosis} and \textit{Mycobacterium avium} complex (MAC) strains. Single daily dose of 10 mg/kg was demonstrated to provide complete eradication of mycobacteria in experimental generalised tuberculosis with good tolerability and safety profile.\textsuperscript{17} The efficacy of the presently used BCG vaccine against active tuberculosis in adults has been challenged and recently new live and attenuated strains of \textit{M. tuberculosis}, improved recombinant BCG strains and subunit vaccines have been tested in preclinical animal models with promising results.\textsuperscript{18}

In conclusion, due to the intravenously administration of BCG, we regard our case as BCG sepsis with multiorgan involvement. With prompt and proper treatment recovery is possible. Healthcare personnel and patients should be clearly informed about how to administer BCG when they decide to receive such treatment. They should re-admit in case systematic symptoms develop even after proper instillations.

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References:


