

CASE REPORT

Complications of misuse of Bacillus Calmette-Guerin

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Abstract: Intravesical BCG is a good treatment choice for vesical carcinomas. Nevertheless, it can also become a mortal toxin when applied in a wrong way. The application routes of the prescribed drug should be rigorously described to patients and detailed instructions regarding the ways of application such as intravesical application should be given to the persons taking this medicine (Ref. 9). Full Text in free PDF www.bmj.sk.
Key words: Bacillus Calmette–Guerin, toxin, vesical carcinomas.

Bacillus Calmette–Guerin (BCG) is a live attenuated vaccine prepared from *Mycobacterium bovis* strain. The intravesical BCG has been used in the treatment of superficial vesical carcinoma as well as in prevention of its recurrence since 1970 (1). This application is generally regarded as reliable, but very frequently, it can cause minor side effects such as cystitis, dysuria, hematuria and fever. It is also known that intravesical BCG application can sometimes cause localized activations such as prostatitis, retroperitoneal abscesses as well as systemic activations such as hepatitis, pneumonia, mycotic vascular infections, acute renal failure, rhabdomyolysis, and multi-organ dysfunction (2).

We present here a case with tuberculous sepsis, rhabdomyolysis, acute renal failure, disseminated intravascular coagulopathy (DIC), and multi-organ dysfunction. These complications developed as a result of erroneously carried out route of administration of BCG, namely intravenous instead of intravesical application after transurethral resection due to vesical carcinoma. No such case is available in literature.

Case

A 51-year-old male patient was admitted to our emergency department due to a cold, chill, nausea, vomiting and syncope that took place twice within eight hours and lasted for approximately five minutes. Upon arrival at the emergency department, the patient was conscious, looked ill, his blood pressure was 85/55 mmHg, heart rate was 132 beats/min and his body temperature was 38.5 °C. Upon auscultation of the lungs, the respiratory sounds were equally normal on both sides. His heart sounds were rhythmic, with no additional sounds or murmurs. Electrocardiography (ECG) showed

normal sinus rhythm. His neurological examination revealed no pathology. Laboratory examinations revealed values as follows: blood urea nitrogen (BUN): 164 mg/dL, creatine: 5.3 mg/dL, aspartate aminotransferase (AST): 304 U/L, alanine aminotransferase (ALT): 251 U/L, Creatine kinase (CK): 5621 U/L, CK-MB: 127 U/L, hemoglobin: 15.3 g/dL; white blood cells (WBC): 8 940/mm³, thrombocytes: 64700 K/uL, activated partial thromboplastin time (aPTT): 80.4 sec, prothrombin time (PT): 22.4 sec, INR: 2.4, D-Dimer: 9937.28 ng/mL, Arterial blood gas analysis yielded values as follows: pH: 7.44, PCO₂: 25.9 mmHg, PO₂: 81.7 mmHg, sPO₂: 96.4 %, HCO₃⁻: 17.6 mmol/L. Posteroanterior chest x-ray and computerized thorax tomography yielded normal findings. Abdominal ultrasonography was interpreted as normal. In his computerized cerebral tomography minimal cerebral oedema was observed.

From the case history we learned that the patient had been treated with transurethral resection (TUR) due to vesical cancer in January 2009 and prescribed intravesical BCG (Immucyst®) was to be applied on February 22. It was found out that this prescribed drug had been accidentally applied intravenously at a healthcare unit while his complaints started in half an hour following the application of medicine. The patient was hospitalized with the diagnosis of rhabdomyolysis, acute renal failure, DIC and tuberculous sepsis that developed due to the erroneously chosen route of drug application. The patient was followed up and medical supportive treatment was administered. On the 23rd day, he was discharged as completely recovered.

Discussion

As BCG is a form of live attenuated vaccine prepared from *Mycobacterium bovis* microorganism, it is used as an efficient method in the treatment of low degrees of cancer or *in situ* carcinoma of vesical surface. Especially when it is applied after transurethral resection, it is reported to hinder the muscle invasion and to decrease recurrences (3). The details of local immune response and local anti-carcinogenic activity of intravesical BCG in uroepithelial tissue have not been well defined so far. The possible mechanism of effects includes lymphocytic activation, den-

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dritic cells and natural killer cells. It is estimated that BCG forms a local immune response resulting in death of tumor cells (4).

Upon intravesical BCG application, the local and systemic complications develop in less than 5 % of patients. The most frequently encountered side effect of BCG application is represented by fever, which is generally of low grade, i.e. rarely exceeding 38.5 °C. The degree of fever is dependent on BCG and increased immune response. Granulomatous prostatitis, epididymitis and retroperitoneal abscesses are the most commonly known local side effects. The systemic complications are less frequent, however more serious. They include granulomatous hepatitis, pneumonia, mycotic vascular infections, osteomyelitis, acute renal failure, sepsis and multi-organ failure (3).

In the present case, we conclude that the complications developed following the intravenous application of BCG, which should have been applied intravesically. Acute renal failure was one of them. While the patient's renal tests had been originally normal, the laboratory tests carried out at the emergency department revealed BUN and creatine values amounting to 164 mg/dL and 5.3 mg/dL, respectively. Literature provides a limited number of cases with acute renal failure developed following intravesical BCG application. According to available information, renal failure occurs as a result of mesenchymal glomerulonephritis, epithelioid granuloma formation and interstitial nephritis depending on the bacteria or bacterial proteins' hematogenous expansion brought about by vesical perforation or excessive tumor resection depending on the urinary tract's traumatic resonances (1, 5). In our case, the application was intravenous and acute renal failure developed as a result of the latter way of application.

Noncaseating granulomatous hepatitis is another systemic complication reported to be developing during BCG treatment. Instead of BCG expansion, it is the developed hypersensitivity that is reported to be a factor responsible for hepatitis. A moderate level of fever and an increase in liver enzymes are the most important factors in this clinical view (2, 6). The levels of AST and ALT amounted to 304 U/L and 251 U/L, respectively, while the body temperature was 38.5 °C. The existing clinical and laboratory data make us think that hepatitis was induced by BCG.

Other systemic complications revealed in our case included rhabdomyolysis and DIC. BUN and creatine values increasing with the increase in CK values show rhabdomyolysis. Armstrong has also reported two cases including rhabdomyolysis and metastatic infection developed following intravesical BCG application (7). The severe metabolic and electrolyte imbalance, acute renal failure and DIC are the important complications of rhabdomyolysis. DIC can also develop depending on various drugs and toxins. In our case, the increase in PT, aPTT and D-Dimer values, together with a decrease in thrombocytes explain the DIC panel.

Serious sepsis and multi-organ failures are very rarely encountered life-threatening complications of intravesical BCG treatment (8). In our case, in addition to the known infection source, the symptoms of high fever and tachycardia comply with sepsis. There were various organ dysfunctions (liver, kidney) accompanied with metabolic acidosis and hypotension. These findings can be interpreted as serious sepsis (9).

In the present case, some of the observed systemic complications can also be observed after intravesical BCG application. These complications develop as a direct result of hematogenous spread of intravesically applied bacteria or proteins. However, in our patient, the drug was given intravenously. Therefore, the intravenous BCG application consequently caused more substantial and more serious complications when compared to intravesical application.

Conclusion

Intravesical BCG is a good treatment choice for vesical carcinomas. Nevertheless, it can also become a mortal toxin when applied in a wrong way. The application routes of the prescribed drug should be rigorously described to patients and detailed instructions regarding the ways of application such as intravesical application should be given to the persons taking this medicine.

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