Systemic granulomatous disease and syndrome of inappropriate antidiuretic hormone

Introduction

Bacillus Calmette–Guérin (BCG) is a routinely used vaccine for prevention of tuberculosis and it has also been recently used for the treatment of bladder cancer. This article reports a case of a patient who developed systemic granulomatous disease along with syndrome of inappropriate antidiuretic hormone following intravesical BCG use.

Discussion

BCG is a live attenuated vaccine that has been mainly used for the prevention of tuberculosis worldwide over the last century (Mooren et al, 2000). It is derived from *Mycobacterium bovis* which stimulates hypersensitivity to *M. tuberculosis*.

In addition to its primary role, intravesical instillation of BCG is very successful for the treatment of superficial bladder carcinoma, recurrent low grader bladder carcinoma and carcinoma in situ. The treatment usually comprises 6-weekly doses of BCG instilled into the bladder followed by further doses at 3, 6, 12, 18 and 24 months after the initial treatment. Although the mechanism of action is not fully understood, the general consensus is that intravesical BCG works by elaborating helper T-cell cytokines leading to a localized immune response that helps to destroy neoplastic cells (Smith et al, 1999).

Adverse effects of BCG use in the treatment of bladder carcinoma are rare and were found to be less than 5% in a retrospective analysis of nearly 2600 patients, with haematuria being the most common side effect occurring in about 1% of patients (Lamm, 2000). Sepsis caused by BCG infection and immune-mediated pneumonitis was also noted in 0.5% of patients. A Cochrane review of 585 patients from six different trials concluded that the main side effects of intravesical BCG were cystitis, haematuria, urinary

Figure 1. Chest X-ray showing some nodular changes bilaterally.

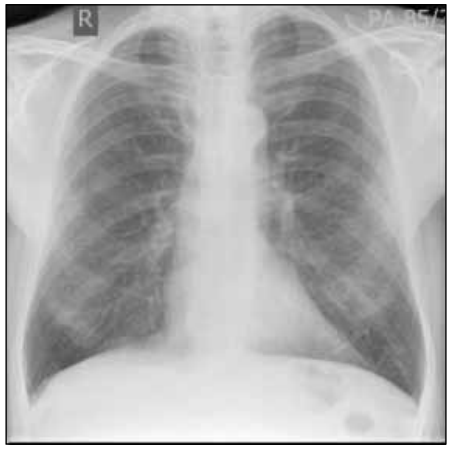
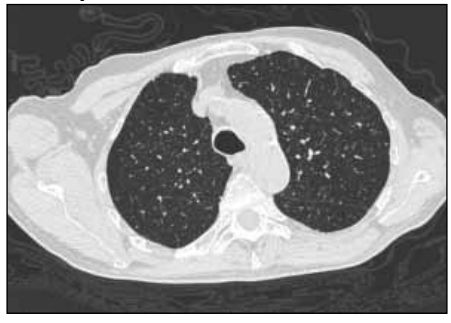


Figure 2. High resolution computed tomography scan showing bilateral miliary nodules suggestive of miliary tuberculosis.



Case Report

A 71-year-old man was admitted with generalized tiredness, mild confusion and low-grade pyrexia following the fourth cycle of intravesical bacillus Calmette–Guérin instillation for the treatment of superficial bladder carcinoma. These symptoms were accompanied by some weight loss which was difficult to quantify. His past medical history included type 1 diabetes mellitus, chronic obstructive pulmonary disease and prostatic hyperplasia. He was a smoker and consumed a moderate amount of alcohol. Physical examination was unremarkable with the exception of confusion (abbreviated mental test score 7/10). Initial investigations showed low serum sodium of 122 mmol/litre with normal potassium, renal and thyroid functions. His liver functions were abnormal with aspartate transferase of 76 IU/litre and alkaline phosphatase 286 U/litre. Chest X-ray showed bilateral non-specific reticular changes suggestive of infection. Two sets of blood cultures showed no growth after 72 hours. Urine tests for legionella and pneumococcal antigen were negative.

Computed tomography of the brain revealed deep white matter changes suggestive of small vessel disease. On further investigations urine osmolality was 546 mOsm/kg, serum osmolality 256 mOsm/kg, urine sodium 61 mmol/litre and the short Synacthen test was normal, confirming the diagnosis of syndrome of inappropriate antidiuretic hormone. After fluid restriction to 1 litre per day his sodium level started to improve slowly, but the patient's condition continued to deteriorate with ongoing low-grade pyrexia, confusion and lethargy.

A repeat chest X-ray 5 days later (*Figure 1*) showed multiple small non-calcified nodules in both lungs raising the possibility of miliary tuberculosis. This was confirmed on high resolution computed tomography scan of the chest (*Figure 2*) as presence of bilateral diffuse miliary shadowing in keeping with a diagnosis of miliary tuberculosis. In view of his confusion, CSF examination was done to rule out CNS involvement, but this was normal. No endobronchial lesions were identified on bronchoscopy and bronchial washings were sent for analysis and cultures. The patient was started on anti-tuberculous treatment (isoniazid, rifampicin and ethambutol) as well as steroids and pyridoxine. Unfortunately, the patient suffered a cardiac arrest and died a week after starting the treatment. Cultures of bronchial lavage and CSF did not grow any mycobacterium. On post-mortem examination he was found to have multiple small whitish nodules in both lungs, with caseating granulomata, central areas of necrosis and multinucleated giant cells microscopically.

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frequency and fever. Systemic granulomatous disease was not mentioned and no deaths were reported in this review (Shelley et al, 2000).

Systemic granulomatous disease with and without viable mycobacteria has been reported in the literature (Thompson and Cumming, 1990; McParland et al, 1992; Mooren et al, 2000; Shelley et al, 2000) but the authors have not found any case reports with co-existing syndrome of inappropriate antidiuretic hormone. The pathophysiology of systemic disease following intravesical BCG instillation is not entirely clear. The presence of viable mycobacteria, especially *M. bovis*, in many body tissues including lungs, liver and bone marrow has been reported, suggesting that it is an infectious complication of BCG occurring as a result of leakage of mycobacteria into lymphatics and blood stream through a disrupted urothelium.

In patients with systemic disease, where no mycobacterium can be isolated, immune-mediated hypersensitivity may be responsible and treatment with steroids and tuberculosis drugs may be needed. Concomitant treatment with isoniazid in patients undergoing BCG immunotherapy for bladder cancer has been unsuccessful in preventing systemic disease (Thompson and Cumming, 1990).

Radiological investigations including computed tomography of the chest and abdomen should be considered in suspected patients and specimens from the suspected body tissue and fluids should be sent for mycobacterial staining, cultures and polymerase chain reaction (Mignon et al, 2002). Empirical treatment can be started in high-risk patients after liaison with the local tuberculosis specialist team. The mainstay of treatment for these patients is anti-tuberculous drugs including rifampicin, isoniazid and ethambutol along with glucocorticoids. As most of the cases are caused by *M. bovis*, which is typically resistant to pyrazinamide, the latter is not routinely used in treatment (Proctor et al, 1993; Durek et al, 2000).

Conclusions

Intravesical BCG is a safe treatment for superficial bladder carcinoma and serious adverse effects are rare. It is important to monitor these patients closely to identify systemic complications early and if these arise close liaison with the local tuberculosis specialist team is essential to initiate appropriate investigations and treatment. As there is some evidence to suggest that patients with disrupted urothelium, i.e. those with recurrent cystitis and gross haematuria, could be at a greater risk of developing systemic disease, it may be prudent to defer the BCG immunotherapy to allow the urothelium to heal (Elakabani et al, 2000). **BJHM**

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