

Pulmonary disease following intravesical BCG treatment

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Abstract

The potentially toxic nature of intravesical BCG is illustrated by two patients who developed profound systemic illness with fever, rash, basal crackles, and bilateral shadowing on the chest radiograph after treatment.

Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis* that has been used in the treatment of malignant disease for over 20 years and for the treatment of bladder cancer since 1976.¹ Major complications of this treatment are infrequent.² We report two cases of systemic illness with pulmonary manifestations after treatment with intravesical BCG.

Case reports

CASE 1

A 67 year old man with in situ transitional cell carcinoma of the bladder was treated with suspensions of 120 mg of BCG in 60 ml of saline instilled into the bladder at weekly intervals. The initial full blood count, liver enzymes, and chest radiograph were normal.

Immediately after the fourth treatment he developed fever and urinary symptoms. Urine analysis showed numerous white cells and bacteria but cultures were negative. One month later he complained of intermittent fever, and a 4.5 kg weight loss.

Fever, bilateral basal inspiratory crackles, numerous small (<5 mm) erythematous macules with haemorrhagic centres on his back and a few petechial lesions on his shins were noted. Pancytopenia was present with a haemoglobin concentration of 11.5 g/dl, white cell count of $3.8 \times 10^9/l$, and platelet count of $14 \times 10^9/l$. Alkaline phosphatase, aspartate transaminase, alanine transaminase and γ glutamyl transferase were two to three times normal. Diffuse bilateral microreticulonodular shadowing was noted on his chest radiograph. A gallium scan showed a 4+ diffuse lung uptake bilaterally with an enlarged spleen indicated by increased uptake. Bronchoalveolar lavage revealed 30% neutrophils, 15% lymphocytes, and 55% alveolar macrophages. Blood, urine, sputum, lavage fluid and bone marrow cultures were negative. Bone marrow biopsy showed non-caseating granulomas.

The patient was diagnosed as having disseminated BCG and was started on isoniazid 300 mg and rifampin 600 mg daily on his sixth day in hospital. His fever resolved and he was clinically improved by the eighth day of treatment (about six weeks after his last course of intravesical BCG). After one month of treatment his haemoglobin was 12.7 g/dl and the white cell count, platelet count, liver enzymes, and chest radiograph had returned to normal.

CASE 2

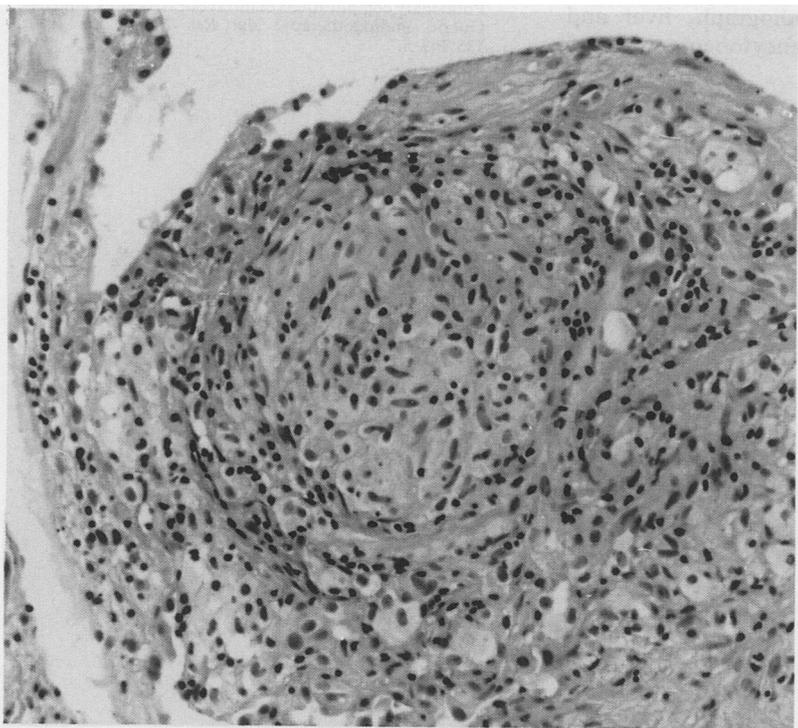
A 75 year old man was treated with intravesical BCG (120 mg of BCG in 60 ml of saline) for transitional cell carcinoma of the bladder. After his third monthly treatment he presented with a seven day history of cough and fever and increasing dyspnoea for one day. He was febrile and he had bilateral basal inspiratory crackles and palpable purpuric skin lesions 3-4 mm in diameter over the thorax. A full blood count showed mild leucocytosis. Alkaline phosphatase activities were mildly increased. A chest radiograph showed bilateral interstitial infiltrates. Granulomas were seen on transbronchial lung biopsy. Skin biopsy showed erythema multiforme; neither granulomas nor acid fast bacilli were seen.

Intensive care was needed because of hypoxaemic respiratory failure five days after admission to hospital. Isoniazid 300 mg daily, rifampin 600 mg daily, and prednisone 60 mg daily were started on the day of his transfer. On the 14th day an open lung biopsy was performed because of increasing hypoxaemia and progressive radiographic infiltrates. Diffuse alveolar damage (acute and organising) and granulomatous inflammation were noted (figure). No acid fast bacilli were seen and cultures were negative for mycobacteria. Viral studies, blood cultures, and serological tests for atypical organisms gave negative results.

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Section of an open lung biopsy specimen showing non-caseating granuloma and alveolar lining cell hyperplasia with mild chronic inflammatory cell infiltration in the adjacent pulmonary parenchyma. (Haematoxylin and eosin.)

Isoniazid was replaced with ethambutol 1 g daily because of increased liver enzyme activities. The patient required a prolonged course of mechanical ventilation, which was complicated by a pneumothorax. Clinical improvement in his respiratory condition did not occur until about seven weeks after the start of antituberculous treatment. The chest radiograph and liver enzyme activities gradually returned to normal. The patient was discharged home about 19 weeks after admission to hospital.

Discussion

Intravesical BCG has been used successfully in the treatment of bladder tumours since 1976,^{1,3} skin test reactivity being useful in predicting a response to treatment.⁴ Intravesical BCG is regarded as a fairly benign treatment, which is well tolerated with infrequent major side effects. Minor complications such as irritative bladder symptoms and fever are most frequent and usually resolve without specific treatment.² In 1278 treated patients cystitis occurred in 91%, fever of over 103°F in 3.9%, granulomatous prostatitis in 1.3%, pneumonitis or hepatitis in 0.9%, rash in 0.4%, epididymo-orchitis in 0.2%, hypotension in 0.1%, and cytopenia in 0.1%.² Fever usually occurred after at least six treatments. Two cases of granulomatous hepatitis and localised pneumonitis following intravesical BCG occurred in 91 patients.⁵ One patient also had a mild leucopenia ($3.7 \times 10^9/l$). Recently three cases of bilateral interstitial pneumonitis secondary to intravesicular BCG without evidence of granulomatous inflammation of the lung were reported.⁶

The first case in this report, with a miliary pattern on the chest radiograph, liver and spleen disease, and pancytopenia with a

granulomatous bone marrow, showed more widespread dissemination than previously reported from intravesical BCG. The pattern of granulomatous inflammation suggests haematogenous spread, though a hypersensitivity reaction cannot be excluded.⁶ Our second case shows for the first time granulomatous inflammation of the lung with diffuse lung injury, in keeping with the adult respiratory distress syndrome. As mycobacteria were not identified either by acid fast stains or cultures, we cannot firmly determine the mechanism of this process.

Although infrequent, the cases presented and others that have been reported indicate that intravesical BCG may result in appreciable toxicity. Such complications appear to be responsive to standard antituberculous treatment with or without the addition of corticosteroids.^{2,5,6}

It has been proposed that severe systemic complications may be prevented by prophylactic isoniazid given for three days with each BCG treatment.⁵ This hypothesis has not been formally tested and it is not known whether prophylactic isoniazid might interfere with the antitumour effect of intravesical BCG.

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