Miliary Tuberculosis Induced by Intravesical Bacillus Calmette–Guérin Immunotherapy: A Rare Complication

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Abstract

A 52-year-old man who had undergone intravesical immunotherapy with BCG for transitional cell bladder carcinoma and who presented with malaise, dyspnea, non-productive cough and a reticulonodular interstitial pattern on the chest radiograph is presented. Transbronchial biopsy specimen revealed caseating granulomas. Although no growth was evident on tuberculosis culture of the specimens, the patient's condition improved with antituberculous antibiotics. The mechanism for BCG–induced granulomatous inflammation is poorly understood. In our case the presence of a caseating granulomata indicates a probable infectious cause of the pulmonary disease process. An attempt to identify the organism should be made in each case of pneumonitis complicating BCG therapy and antituberculous chemotheraphy should be considered. The use of corticosteroids in such cases is still controversial and requires further investigation.

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Key words: *miliary tuberculosis, BCG immunotherapy*

Introduction

Intravesical immunotherapy with bacillus Calmette-Guérin (BCG) against transitional cell cancer of the bladder is regarded as a safe and highly efficient regimen (1-3). Side effects and complications of such immunotherapy are usually local, self- limited and of a minor nature, but occasionally may result in severe and systemic manifestations (1-6). In the majority of cases, systemic toxicity is manifested by granulomatous inflammation involving multiple organs, which is culture negative and shows no organisms on mycobacterial stains (3,4,7,8). Pulmonary involvement is unusual, but when it does occur, it generally manifests itself as a bilateral intersititial pneumonitis (2,9,10). It is uncertain whether these systemic manifestations are due to dissemination of infection or due to hypersensitivity, and therefore mode of treatment remains controversial (3,4). Although some cases may regress without therapy, antituberculous chemotherapy with or without corticosteroids has been used in the majority of reported cases (3). In the present report, we describe caseating granulomas in the transbronchial biopsy tissue of a patient treated with intravesical BCG immunotherapy, a finding which improved promptly after antituberculosis therapy alone.

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Case Report

A 52 year-old man presented with a 2 months' history of dyspnea, malaise and nonproductive cough. He had been well until 6 months ago

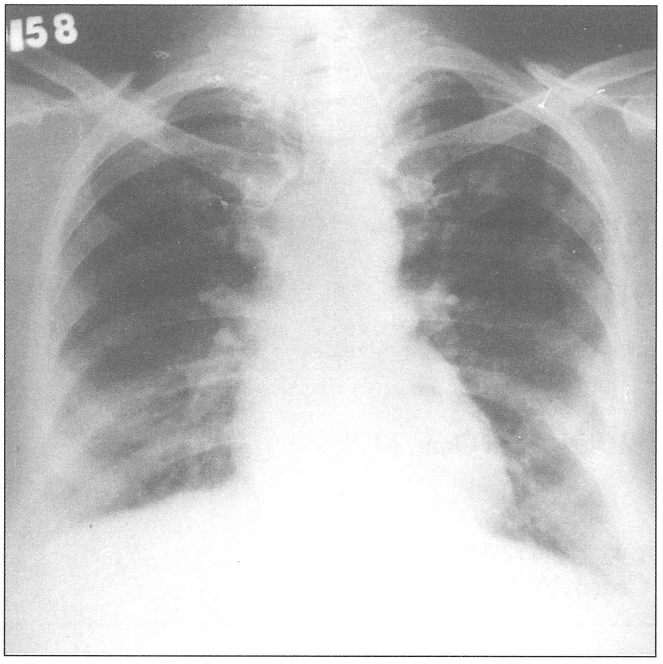

Figure 1. *Chest radiograph on admission.*

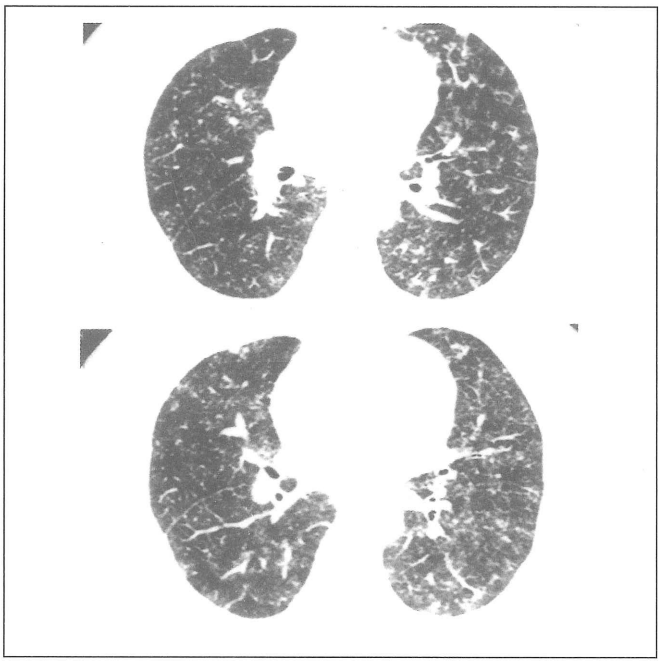

Figure 2. *HRCT scan on admission.*

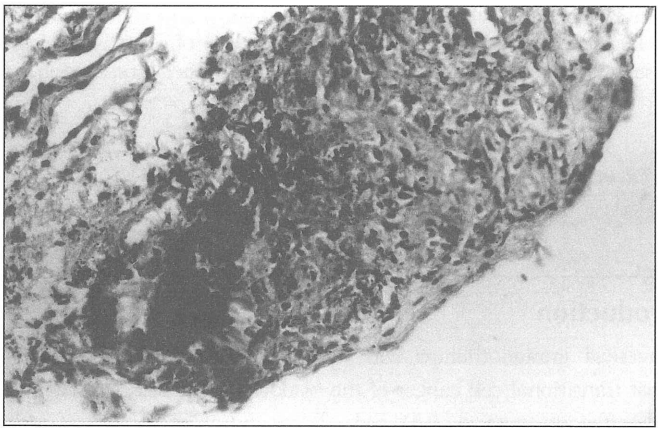

Figure 3. *Caseating granulomatous reaction seen in transbronchial biopsy. 400xHE.*

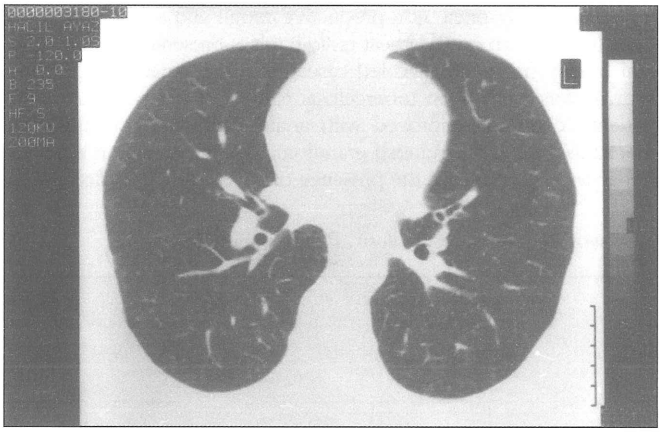

Figure 4. *Control HRCT scan.*

when he had been found to have transitional cell bladder carcinoma. He was operated on and was started on a regimen of weekly immunotherapy with intravesical BCG. for 6 consecutive weeks at the Inönü University Hospital. The first instillation was given intraoperatively.

On admission, exertional dyspnea and nonproductive cough with massive hematuria were noted. A chest radiograph revealed reticulonodular infiltrations (Fig 1).

Aside from massive hematuria, laboratory findings were normal. A chest computed tomography (CT) scan confirmed a miliary intersititial pattern with absence of hilar lymphadenopathy (Fig 2). A transbronchial biopsy specimen revealed granulomas with karyorrhexis, multinucleated giant cells and plasma cell infiltration (Fig 3). A five tuberculin unit (TU) intradermal skin test with purified protein derivative (PPD) resulted in 8 mm induration after 72 h. The patient was started on a regimen of isoniazid, rifampin, pyrazinamide and ethambutol. On the 10th day of therapy, the patient was free of cough and dyspnea. A control CT scan performed 1 month after the initiation therapy revealed a normal pattern (Fig 4). Pyrazinamid and ethambutol therapy was discontinued after 2 months, isoniazid and rifampin therapy was discontinued after 6 months. Treatment was uneventful and the patient is now free of pulmonary disease.

Discussion

BCG immunotherapy administered by intradermal, subcutaneous, intrapleural, intraperitoneal or intralesional injection has been used in the treatment of neoplastic disorders (1-3). Intravesical BCG was shown to be the most effective adjuvant treatment for superficial bladder cancer therapeutically and prophylactically (1-4). Complications of intravesical BCG

are usually minor and self limited, but severe toxic reactions may occur occasionally (1-4). Relationships between incidence of systemic side effects complicating BCG immunotherapy varies and route of administration or rate of intravesical instillation are still not well known (3,11). Incidence of pulmonary side effects after intravesical BCG therapy appears to be low. Miliary pneumonia was observed in about 0.5% of patients after BCG immunotherapy in the series reported by Paterson and Patel (12).

In this report of a patient who developed dyspnea and nonproductive cough during treatment with intravesical BCG for transitional cell bladder cancer, a chest radiogram revealed reticulonodular infiltrations and a transbronchial biopsy specimen revealed caseating granulomas. The patient had a marked and rapid improvement after treatment with antituberculous therapy.

The mechanisms underlying the systemic side effects of intravesical BCG immunotherapy are controversial. (2-4) To demonstrate dissemination of infection, a positive culture for mycobacteria from a distant site is required (3). Cultures positive for *M. tuberculosis* in patients with pulmonary complications after intravesical instillation of BCG immunotherapy has been reported in only five patients (1). On the other hand, granulomas have been detected in the liver, in the lungs and in bronchial lymph nodes following intravesical BCG instillation (2,3). Open lung biopsy specimens in 5 patients receiving BCG for immunotherapy of osteogenic sarcoma revealed granuloma formation in 4 (14). Hematogenous dissemination has also been confirmed to occur as a rare complication of immunisation with BCG (3,15). A hypersensitivity response to BCG has been suggested as an alternative mechanism underlying the systemic side effects of intravesical BCG immunotherapy, including pneumonitis (3,10,13). With the paucity of proven cases of BCG mycobacteremia, presence of granulomas in affected tissues and/or increased activated alveolar lymphocytes on bronchoalveolar lavage analysis has been suggested as supportive evidence for hypersensitivity (3,4,10,16). The hypersensitivity theory is supported by beneficial effects of corticosteroids in cases with total resolution of symptoms after receiving corticosteroid therapy only (4,10,17). It has been suggested that disseminated BCG infection is more likely to be the mechanism for the systemic complications of intravesical BCG in patients with cellular immunity defects while hypersensitivity is the more likely mechanism when cellular immunity is functioning (3,13).

In our patient, disseminated infection occurred in the presence of functioning cellular immunity. The majority of all reported systemic complications are associated with urethral trauma, suggesting more or less direct intravenous access of BCG (5,18,19). Although our patient had no record of traumatic instillation, he was given the first BCG immunotherapy intraoperatively. In a recent publication by Bohle *et al*, manipulation of the bladder during cystectomy was reported as another potential source for a bacteremic event (5). Intraoperative manipulation indeed may have been a relevant factor for a systemic spread also in our patient. At present there is no evidence to completely exclude the possibility that minor bacteremia may occur with each intravesical instillation of BCG even without traumatic catheterization or an open intracavitary lesion (1,5).

The patient we describe was given BCG immunotheraphy intraoperatively, was not immunocompromised and responded successfully to antituberculous chemotherapy alone. The transbronchial biopsy specimen revealed caseating granulomas and this provides another proof for the dissemination of the bacillus Calmette-Guérin as the mechanism underlying miliary pneumonitis complicating intravesical BCG immunotherapy.

In summary, the result of treatment in this patient suggest that treatment for BCG induced granulomatous pneumonitis should include antituberculous therapy, while the use of corticosteroids as a standard treatment is still controversial.

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