Case Report

BCG pneumonitis with a miliary radiological pattern complicating intravesical BCG immunotherapy

Evangelia Fouka[1], Nikolaos Angelis[2], Penelope Stefanopoulou[1], Nikolaos Galanis[3]

[1]Pneumonologist,
[2]Trainee Pneumonologist,
[3]Pneumonologist, Coordinating Director
1st Pulmonary Clinic, General Regional Hospital "G. Papanikolaou". Thessaloniki

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Correspondence to:
Evangelia Fouka, General Regional Hospital "G. Papanikolaou", Exochi 57010, Thessaloniki,
Tel.: 2313 307249
E-mail: evafouka@gmail.com,

SUMMARY. The case is described of a 42 year-old male who presented with fever, haematuria, hypoxaemia, impaired liver function and a miliary pattern on chest X-ray while receiving intravesical BCG treatment for superficial bladder cancer. Initiation of antituberculous therapy resulted in rapid amelioration of the symptoms and the X-ray findings, and the patient left hospital in a good general state of health. Although *M. bovis* was not isolated from samples of sputum, bronchioalveolar lavage fluid (BALF) or bronchial biopsy tissue, the prompt response to antituberculous therapy suggests an infectious aetiology due to microbial dissemination. *Pneumon 2010, 23(4):388-391.*

INTRODUCTION

Bacillus Calmette-Guèrin (BCG), an attenuated strain of *Mycobacterium bovis*, has been used intravesically for the treatment of superficial bladder cancer since 1976[1]. BCG is generally well tolerated, with usually mild local side effects. Systemic reactions are uncommon; it is uncertain whether they represent dissemination of infection or a secondary hypersensitivity reaction[2]. The case is presented of pneumonitis with a miliary radiological pattern complicating BCG intravesical immunotherapy, in which the diagnosis was based on clinical suspicion and radiological findings.

CASE REPORT

A 42 year-old man was being treated with weekly intravesical BCG (BCG-medac©) instillations after transurethral resection of a grade II carcinoma of the bladder. Within hours of the third instillation, he complained of fever, malaise, dysuria and haematuria. He was administered isoniazid, 300mg per day, by his urologist and after five days the symptoms of cystitis disappeared but the fever remained. The patient was admitted to a regional hospital where chest X-ray revealed a diffuse miliary pattern (Figure 1). Rifampin 600mg,

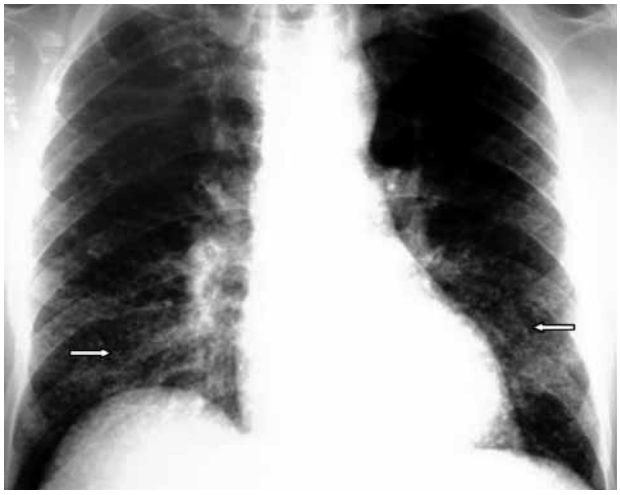

FIGURE 1. Chest radiograph at presentation demonstrates small 2- to 3-mm nodules in both lung fields consistent with a miliary pattern of spread (arrows).

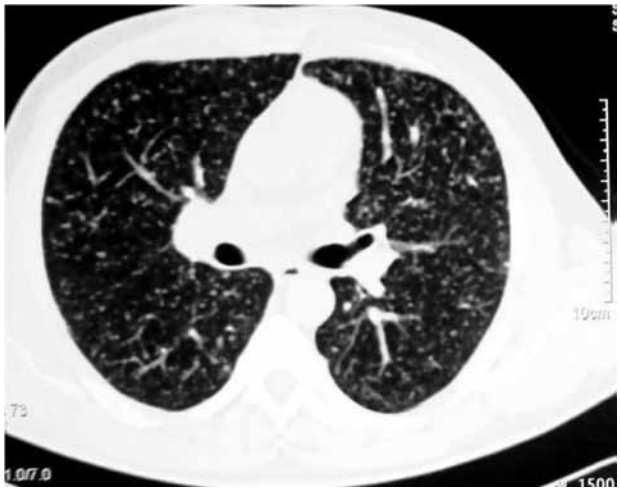

FIGURE 2. HRCT scan obtained at level slightly inferior to tracheal bifurcation showing numerous small nodules, randomly distributed and absence of hilar lymphadenopathy.

ethambutol 25mg/Kg, imipenem/cilastatin 500+500mg three times daily and amikacin 15mg/kg twice daily were added to his treatment and he was referred to the pulmonary clinic. On admission he manifested high fever (>39ºC), tachypnoea (24 breaths/min), tachycardia (110 beats/min), and a nonproductive cough with bilateral basal inspiratory crackles. Arterial blood gas analysis showed PaCO2 of 35mm Hg and PaO_2 of 60 mm Hg on ambient air. His medical history did not reveal exposure to tuberculosis or other concomitant disease. The full blood count was normal but the liver enzymes were mildly elevated, with ALP 220 IU/L, AST 65 IU/L, ALT 56 IU/L and γ-GT 570 IU/L. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were high, 38mm and 8.89 mg/dl respectively. Sputum smears and urine and blood cultures were negative for both common bacteria and acid-fast bacilli. A tuberculin intradermal skin test produced 35mm induration. The chest high resolution computed tomography (HRCT) scan demonstrated bilateral small diffuse nodules, evenly and randomly distributed, and the absence of hilar lymphadenopathy (Figure 2). Abdominal ultrasound (US) and CT scan revealed no abnormal findings. The patient underwent bronchoscopy, and the bronchioalveolar lavage fluid (BALF) and bronchial biopsy samples were negative for *M.bovis* on polymerase chain reaction (PCR) examination and culture. The bronchial biopsy did not reveal either epithelioid granulomas or signs of malignancy.

The patient was treated for presumed disseminated BCG infection with isoniazid 300mg, rifampin 600mg, ethambutol 25mg/Kg and streptomycin 15mg/Kg per day for 2 months, followed by a two-drug regimen of isoniazid 300mg and rifampin 600mg for 4 months. His clinical status improved, with rapid resolution of his symptoms, gradual improvement in liver function and fall of CRP to normal within 15 days. Examination at 3 months revealed normal liver function, ESR and chest X-ray (Figure 3). No recurrence of bladder cancer or symptoms of BCG infection were detected after one year of close follow-up.

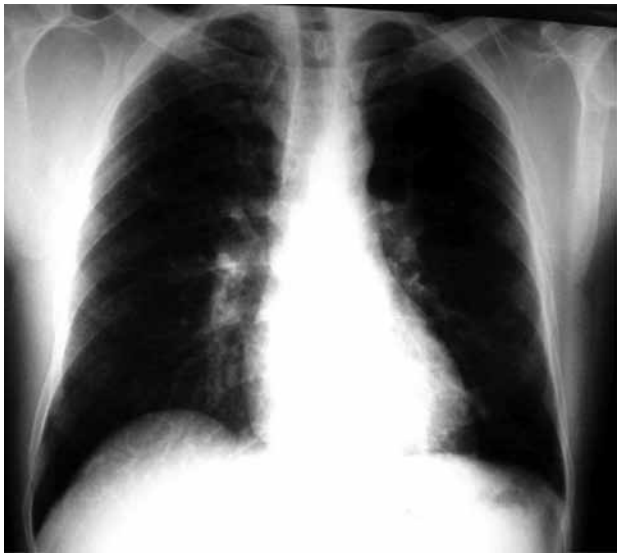

FIGURE 3. Chest radiograph at 3 months showing no signs of residual disease.

DISCUSSION

BCG instillation is an effective treatment for superficial and in situ carcinoma of the bladder, resulting in complete eradication of residual malignant cells and prolonged protection from tumour recurrence in 70% of patients[3]. BCG is thought to elicit a local T-helper/inducer immune response, with persistence of inflammatory cytokines such as IL-2, INF-γ and IL-12 within the so-called BCG-induced granulomas. The effector cells involved are activated natural killer (NK) cells, known to selectively kill malignant targets. Multiple cytokines can also be detected in the serum, indicating some degree of systemic response[4].

BCG immunotherapy is regarded as fairly benign, with side effects, when present, being usually mild and well tolerated. Cystitis, defined as urinary frequency, dysuria and macroscopic haematuria, is the commonest (90%) complication. It typically occurs after the third instillation and is related to the local inflammatory response. Systemic manifestations such as fever, pneumonitis, hepatitis, rash, arthritis, granulomatous prostatitis and sepsis occur in less than 3% of patients[5]. Risk factors include traumatic bladder biopsy or catheterization, simultaneous cystitis, use of immunosuppressive agents and diseases such as HIV and diabetes[6]. The mechanism of systemic complications remains incompletely understood; it is uncertain whether they represent dissemination of infection or a secondary hypersensitivity reaction[7].

Pneumonitis with a miliary radiological pattern is an unusual (0.7%) complication of BCG immunotherapy, usually co-existing with granulomatous hepatitis[5]. Reports of isolation of *M. bovis* from the sputum, blood and transbronchial biopsies, and identification of non-caseating granulomas in the lungs, liver or bone marrow suggest mycobacterial dissemination[8-11]. However, a hypersensitivity reaction cannot be excluded, since acid fast stains, PCR studies and cultures are often negative and a profound clinical response has been noted with the administration of corticosteroids[12,13]. "Miliary-like" radiographic patterns are indicative, but they may be absent during the initial course of the disease, and they occur with both disseminated infection and hypersensitivity phenomena[7]. In contrast, small pulmonary nodules, randomly distributed in relation to secondary lobular structures may be an early HRCT finding suggestive of miliary tuberculosis[14,15]. Thus, HRCT scan may be helpful if radiography is normal or inconclusive.

Current recommendations[16] are that patients with fever or bladder irritation should be initially treated symptomatically, with standard painkillers and antispasmodics. If symptoms do not subside within 48 hours, complementary investigations, including urine cultures, are recommended, and isoniazid 300 mg per day should be prescribed for 15 days. The BCG dose should be reduced if symptoms increase after subsequent instillations. Granulomatous prostatitis or epididymitis require therapy with isoniazid and rifampicin for 3 months. For pulmonary and other systemic manifestations, such as granulomatous nephritis and abscesses, hepatitis and osteomylitis, the recommended therapy is early administration of isoniazid, rifampin and ethambutol, to be continued for 6 months. Pyrazinamide is contraindicated, as all forms of *M.bovis* are resistant. In case of severe life-threatening systemic reactions, corticosteroids should be added urgently, since infection and hypersensitivity cannot be differentiated. Intravenous antibiotics such as ampicillin and gentamycin should be given to cover the possibility of bacterial sepsis. BCG should be discontinued and its permanent avoidance must be considered in severe cases.

In the case described here, although *M. bovis* was not isolated, several findings suggest dissemination rather than a hypersensitivity reaction as the underlying pathogenetic mechanism: The symptoms developed within hours of BCG instillation; Chest X-ray and HRCT revealed a miliary pattern, consistent with pulmonary spread of *M. bovis*[14,15]. The patient was cured while receiving antituberculous treatment only, demonstrating prompt and significant clinical improvement without the need for urgent adjunctive corticosteroid administration, according to data cited above[16]. Since recovery he has been closely monitored for signs of severe complications that could be attributed to a hypersensitivity reaction or bacterial sepsis. Cystoscopy after tumour resection did not reveal signs of residual cancer, so it can be presumed that neither traumatic catheterization nor localized failure of the bladder mucosal integrity during BCG instillation could have possibly resulted in rapid dissemination of viable mycobacteria. The patient denied any history of previous exposure to tuberculosis and was not obviously immunocompromised, thus repeated BCG therapy resulted in immunization, as indicated by the positive tuberculin test. Preexisting delayed-type hypersensitivity aimed at prompt control of infection but did not eventually prevent the development of systemic manifestations due to organism virulence.

In conclusion, BCG pneumonitis should be suspected in any patient who presents with persistent fever and a diffuse miliary radiological pattern after intravesical BCG

instillations for bladder cancer. Antituberculous agents should be initiated as soon as possible, with the addition of corticosteroids in serious cases.

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