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Case Report

Polyarthritis as a Complication of Intravesical Bacillus Calmette–Guerin Immunotherapy for Bladder Cancer

Ö. Onur and R. Çeliker

Department of Physical Medicine and Rehabilitation, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Abstract: Bacillus Calmette–Guerin (BCG) is the most effective agent currently available for the treatment of superficial bladder cancer. However, this form of treatment is associated with some complications, including arthritis. In this report, we present a 69-year-old woman who developed inflammatory polyarthritis following BCG treatment for superficial bladder cancer. The arthritis resolved following treatment with a non-steroidal anti-inflammatory drug and chloroquinine.

Keywords: BCG immunotherapy; Polyarthritis

Introduction

Instillation of Bacillus Calmette–Guerin (BCG) is now an accepted form of treatment for in-situ carcinoma and recurrent low-grade bladder carcinoma [1]. However, because the therapeutic mode of action involves an inflammatory reaction of the bladder, this treatment is associated with various local and systemic side-effects. Adverse effects of intravesical BCG immunotherapy have been reviewed by Lamm et al. [2,3]. In his series, most patients had local side-effects whereas serious systemic side-effects were quite rare. In 0.5% of patients, arthritis and arthralgia were reported. In this report, we describe a case of polyarthritis associated with intravesical BCG therapy for recurrent superficial bladder carcinoma.

Correspondence and offprint requests to: Reyhan Çeliker, MD, Department of Physical Medicine and Rehabilitation, Hacettepe University Hospital, 06100 Sıhhiye, Ankara, Turkey. Fax: 00 90 (312) 310 57 69.

Case Report

A 69-year-old woman was referred to our department with the complaints of pain and swelling of the wrists and fingers. She also had pain in her right hip. Eleven months previously, a superficial carcinoma of the bladder was removed by transurethral resection (TUR). However, 5 months after tumour resection, cystoscopy showed a recurrence of the tumour and a treatment regimen of intravesical BCG (Immucyst 81 mg-week) was started. BCG was instilled weekly for 6 weeks. Following the sixth and last treatment, she had painful swelling of the wrists and fingers, complained of morning stiffness lasting about 3–4 h. She had fever (38.3 °C) which was responsive to paracetamol 500 mg four times a day. She was anorexic and had severe malaise. Past medical history revealed that she had had diabetes mellitus for 7 years and was on oral antidiabetic treatment.

On physical examination, she had pain and limitation of motion of her shoulder, hip and elbow on the right side. The wrists, metacarpophalangeal joints and interphalangeal joints were swollen and tender on both sides. Laboratory examinations showed a slight leucocytosis with a white blood cell count of 11700/μl (normal range 3600–10000/μl) and a haemoglobin level of 11.2 g/dl (normal range 12-18 g/dl). All biochemical parameters other than fasting blood glucose (210 mg/dl, normal range 70–110 mg/dl), including liver function tests, blood urea nitrogen, creatinine and uric acid, were within the normal range. The erythrocyte sedimentation rate (ESR) was increased to 115 mm/h (normal range 0–20 mm/h) and C-reactive protein (CRP) was 185 mg/dl (normal range 0–0.8 mg/dl). Serum rheumatoid factor (RF) measured by the RF latex test, antinuclear antibody (ANA) and brucella agglutination tests were negative.

Serum immunoglobulin (IgA 219 mg/dl, normal range 60–330 mg/dl; IgG 1269 mg/dl, normal range 550–1900 mg/dl; IgM 107 mg-dL, normal range 45–145 mg/dl) and complement (C_3 130 mg/dl, normal range 90–180 mg/dl; C_4 33 mg/dl, normal range 10–40 mg/dl) concentrations were within the normal range. A routine urinary examination was normal and no bacterial growth was observed in a urine culture. There was no radiological abnormality of the affected joints. The chest radiograph was free of infiltrate and a tuberculin skin test (Intervax Biologicals, 0.05 U) was negative. Computed tomography of the lungs was also normal. A blood culture for acid-fast bacilli yielded no bacterial growth. Attempts to take a synovial aspirate for synovial fluid analysis and culture were unsuccessful because the involved joints were small and the amount of aspirate was inadequate.

Non-steroidal anti-inflammatory drug (acemetacin 500 mg twice a day) therapy was initiated; however, 2 weeks later no clinical and laboratory improvement was observed. She still had pain and morning stiffness. The ESR (110 mm/h, normal range 0–20 mm/h) and CRP (149 mg/dl, normal range 0–0.8 mg/dl) were still high and the haemoglobin level had decreased to 9.2 g/dl. A peripheral blood smear showed slight hypochromia with normal erythrocyte morphology. A routine urinary examination was normal and occult blood in the stool was negative. Serum iron (18 μg/dl, normal range 37–158 μg/dl) and iron-binding capacity (267 μg/dl, normal range 274–494 μg/dl) were below the normal range. This suggested that the anaemia was an anaemia of chronic inflammatory disease. For the persisting articular complaints, chloroquinine 250 mg daily was combined with acemetacin. At the end of 5 weeks of therapy, the patient had no more arthritis, and ESR (80 mm/h), CRP (40 mg/dl) and fasting blood glucose (156 mg/dl) levels began to decrease but were still above the normal limits. The haemoglobin level increased to 11.8 g/dl. She had another cystoscopy and biopsy of the bladder, which showed no tumour recurrence.

At the present time, 3 months later, the patient remains asymptomatic with no active inflammation of the joints. However, on physical examination there is still a residual synovial thickening and limitation of movement in the wrists and metacarpophalangeal joints. The ESR and CRP are still high (60 mm/h and 21 mg/dl, respectively). Therefore, we decided to continue the treatment with chloroquinine and acemetacin until the ESR and CRP return to normal values.

Discussion

A variety of complications from intravesical BCG therapy have been reported since its introduction for the management of superficial forms of bladder cancer. Lamm et al. [2,3] described complications of intravesical BCG therapy in 2602 patients treated in multiple centres of North America and Europe. Local complications account for the largest percentage of the cases with more than 90% of the patients experiencing dysuria and frequency. Major systemic complications, including pneumonitis, hepatitis and sepsis, are less frequently reported [3]. Among the systemic side-effects, low-grade fever and influenza-like symptoms are encountered most frequently. In his series, Lamm et al. reported arthralgia and arthritis on 0.5% of cases.

In this report, we present a case of polyarthritis, which is a rare complication of intravesical BCG immunotherapy. In the literature, there are only a few case reports describing arthritis and other musculoskeletal complications related to intravesical BCG therapy [4–10]. Arthritis after BCG therapy is usually symmetrical polyarthritis of the small joints, including the wrists, metacarpophalangeal and proximal interphalangeal joints, but may also involve larger joints on rare occasions [4,6,7]. Morning stiffness is a prominent feature of this type of arthritis. Patients are RF negative and synovial fluid analysis shows an increased neutrophil count [11]. Our patient had symmetrical polyarthritis of the wrists and small joints of the fingers. Morning stiffness was very troublesome for our patient. Polyarthritis was accompanied by constitutional symptoms such as low-grade fever, malaise and anorexia, which were suggestive of systemic involvement.

The pathophysiology of arthritic complications is questioned by many authors. It is claimed that arthritis is the result of a reactive immunogenic response that is essential for the therapeutic effect of BCG on the bladder cancer [7]. Some authors believe that a cross-reaction between the mycobacterium antigen present in BCG and a host articular antigen results in a clinical synovitis and produces a ‘human model’ of adjuvant arthritis of the rats [1,4,8]. This is supported by the absence of signs of infection in the synovial fluid aspirate and synovial biopsy specimens. Also, histological examinations and cytokine profiles show a neutrophilic dominance with increased concentrations of interleukin 8 (IL–8) and tumour necrosis factor alpha (TNF-α) in the beginning, which subsequently change to lymphoplasmocytoid synovitis with elevated IL–1 and TNF-α [12].

There is no consensus on the treatment protocol for arthritic complications of BCG treatment. Many believe that it is not necessary to discontinue BCG treatment. In patients who are at high risk for tumour recurrence or progression, prophylactic INH therapy may be necessary to prevent the development of severe arthritic complications that would necessitate the discontinuation of the BCG therapy [1]. However, some authors claim that antituberculosis treatment may diminish the antitumoral effects of BCG [13]. In the literature, most authors recommend the use of non-steroidal anti-inflammatory drugs to control the arthritic complications [4–7]. In our case, we combined choloroquinine with the non-steroidal anti-inflammatory drug and the patient responded well. However, further studies with such arthritides may help to establish the optimum treatment regimen. As immunotherapy with BCG vaccine becomes more commonly used, more cases of this new form of reactive

arthritis are likely to occur, so physicians should be aware of arthritic complications after intravesical BCG therapy.

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