Reactive Arthritis after Intravesical Bacillus Calmette-Guerin Immunotherapy

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Intravesical Bacillus Calmette-Guerin instillation is used widely in the treatment of superficial transitional cell carcinoma of the urinary bladder to treat existing or residual tumors, prevent tumor recurrence and disease progression, and prolong survival. Intravesical Bacillus Calmette-Guerin presumably stimulates an immune response to the tumor and thus is associated with unique side effects, such as abacterial cystitis, hematuria, and distant infection. However, there have been few reports of reactive arthritis following intravesical immunotherapy. We present a case of typical reactive arthritis, which developed after Bacillus Calmette-Guerin instillation for superficial transitional cell carcinoma of the urinary bladder. **(Mid Taiwan J Med 2006;11:191-5)**

Key words

Bacillus Calmette-Guerin, transitional cell carcinoma, reactive arthritis

INTRODUCTION

Transitional cell carcinoma (TCC) is not an unusual disease in modern society. In the United States, it ranked the fourth most common cancer among men and the tenth among women in 2004 [1]. Transurethral resection of bladder tumor (TURBt) is the standard procedure for treatment of early-stage bladder cancer. The use of intravesical Bacillus Calmette-Guerin (BCG) immunotherapy for superficial bladder cancer has become commonplace since it was initially reported by Morales et al in 1976 [2]. Although long-term studies have documented that BCG immunotherapy decreases the progression rate, decreases the recurrence rate, reduces cystectomy and also improves survival [3,4], numerous side effects, such as transient abacterial cystitis, fever, hematuria, distant infection in the lungs, liver, prostate and epididymis, have been reported.

Reactive arthritis (ReA), one of the spondyloarthropathies, is an infection-related disease that occurs in a genetically predisposed individual and is characterized by an immune-mediated synovitis with intra-articular persistence of viable nonculturable bacteria and/or immunogenic bacterial antigens. We report an extremely rare case of ReA with onset after 6 intravesical BCG instillation treatments for superficial TCC of the urinary bladder.

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CASE REPORT

A 55-year-old woman underwent transurethral resection of bladder tumor in October 2002; multifocal TCC of the urinary

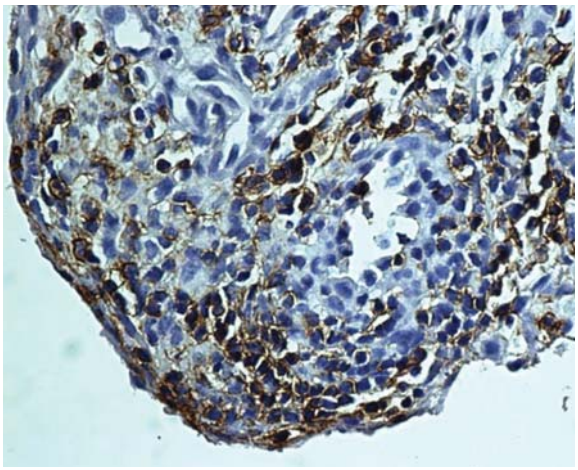

Fig. 1. Most lymphocytes stained positively for UCHL1 after immunohistochemistry (IHC) staining, indicating T-cell origin (400 ×).

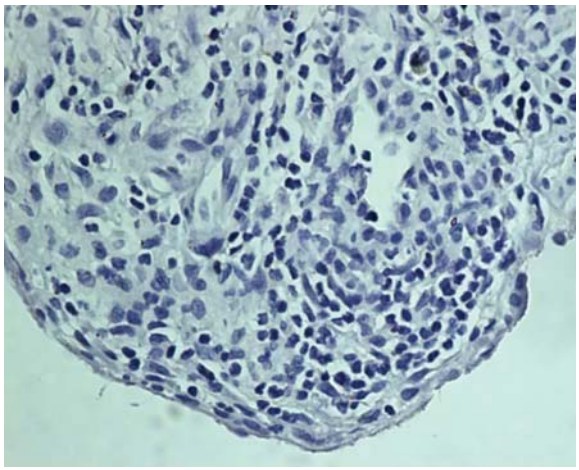

Fig. 2. A few lymphocytes stained positively for B-cell marker of L26 after IHC staining (400 ×).

bladder was diagnosed (T1G3 associated with carcinoma *in situ*). She was in a good health previously except for intermittent painless gross hematuria for 13 months before TURBt. Family history revealed that her mother had gouty arthritis. The patient received TURBt for two foci of papillary TCC in the urinary bladder followed by a 6-week course of once-weekly intravesical BCG instillations, which were started at the 25th postoperative day. Unfortunately, she developed painful swelling and a warm sensation in both ankles and the right knee joint followed by edema in both lower legs a few days after the sixth BCG installation.

Arthrocentesis of the right knee joint yielded 10 ml of turbid, deep yellowish synovial fluid; analysis of the fluid revealed a white blood count (WBC) of 10,250/cumm with 90% neutrophile. Blood tests showed C-reactive protein (CRP) 4.16 mg/dL, IgA 122 mg/dL, rheumatoid factor 2.9 U/mL, HLA B-27 negative and chlamydia IgM Ab 0.50. The synovium from the right knee was sent for mycobaterial culture and DNA probe PCR testing. The specimen was negative for acid-fast bacilli, and the synoivial mycobaterial culture yielded no growth of microorganisms after 90 days. However, the presence of mycobacterium bovis was detected using polymerase chain reaction-mediated direct DNA-sequencing analysis for pncA gene with a C-to-G residue change at nucleotide 169 [5]. Therefore, the diagnosis of BCG reactive arthritis, rather than BCG septic arthritis was confirmed.

Biopsy of the synovial membrane of the right knee joint revealed chronic inflammation and fibrinoid necrosis predominated with T-lymphocytes (Figs. 1, 2). Both quantitative sacroiliac scan and whole body bone scan were normal. After a series of studies, reactive arthritis related to intravesical BCG installation was diagnosed.

The patient received pulse therapy (methylprednisolone 500 mg via intravenous infusion once daily for 2 days) during the acute stage in January 2003. After the symptoms and signs subsided, she was discharged and nonsteroid anti-inflammatory drugs (NSAIDs) and prednisolone (10 mg p.o. t.i.d.) were prescribed to alleviate the pain in the right knee and both ankles. Subsequent follow-up at the outpatient department revealed that the arthritis pain was lessening gradually; therefore, prednisolone was tapered as symptoms subsided. The corticosteroid and NSAIDs were discontinued 11 months after onset of the reactive arthritis. She is now in complete remission and no recurrence was detected at 25-month follow-up.

DISCUSSION

Data suggest that the most effective agent currently available for the treatment of superficial bladder cancer is intravesical immunotherapy with BCG [6]; in fact, it is more effective than intravesical chemotherapeutic agents in eliminating existing papillary disease (a 60% response rate compared with 30% to 50% for thiotepa, doxorubicin, and mitomycin) [7]. However, intravesical BCG therapy may cause adverse effects, such as frequent urination, dysuria, hematuria, fever, malaise, granulomatous hepatitis, tuberculous epididymo-orchitis, prostatitis, skin rash, vertebral osteomyelitis, necrotizing pyelonephritis and polyarthritis [8]. According to a study by Resel Folkersma et al [9], the most common side effects after intravesical BCG therapy were local irritative symptoms (80%) and cystitis (22%). No ReA was reported in their study of 200 patients. In our experience, the incidence of ReA after intravesical immunotherapy is very rare.

ReA consists of sterile axial or peripheral articular inflammation,enthesitis, and extra-articular manifestations, like acute anterior uveitis. Exposure to specific bacterial antigens is usually the triggering factor. The long term prognosis is not as good as it was earlier believed. Two-thirds of patients develop prolonged joint discomfort, lower back pain, or enthesopathies after acute ReA, and 15% to 30% of them develop chronic symptoms. The therapeutic options for patients with the more severe forms of the disease are rather limited. However, if the triggering microorganism can be identified in the early inflammatory stage and specific antimicrobial agents are given in time, the severity of arthritis and overall treatment course can be diminished [10-12].

BCG is known to produce a T-cell mediated immune response that has been linked to antitumor activity in both humans and mice [13]. Mouly et al reported a case of remitting seronegative symmetrical synovitis with pitting edema following intravesical BCG instillation [14]. BCG instillation may have triggered active synovitis via local T-cell activation and a T-help-1 (Th-1)/Th-2 inflammatory profile. Clinically, our patient presented with seronegative oligoarthritis involving the knees and ankles with pitting edema over both lower legs after the sixth course of intravesical BCG therapy. Furthermore, the pathologic finding of the synovial membrane biopsy specimen proved T-lymphocyte predominant inflammation. However, after high dose steroid treatment, her arthritis subsided.

Clavel et al reported that ReA usually occurs 2 to 4 weeks after an infection and knees and ankles are the most common joints involved [11]. The medical treatment of BCG reactive arthritis varies from NSAIDs alone to NSAIDs plus corticosteroid, to corticosteroid alone or plus either isoniazid or rifampicin. The majority of patients experience a good recovery and only a small percentage of subjects present with a chronic disease process requiring long-term therapy [12].

Since early diagnosis enables early treatment and hence early recovery, ReA should be kept in mind when patients with a history of bladder cancer who have received bladder instillation with BCG present with arthritis. To date, however, there is still no good way to identify those who are at high risk of developing ReA, hepatitis, pyelonephritis or even sepsis before undergoing intravesical BCG instillation therapy. Therefore, the risk factors associated with complications from bladder BCG instillation need to be studied further.

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膀胱內卡介苗灌注免疫治療後誘發反應性關節炎

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卡介苗膀胱灌注廣泛地使用於表淺的膀胱移形上皮細胞癌病患，治療殘存的膀胱腫瘤，以避免腫瘤復發及惡化並提高存活率。此方式是藉由卡介苗誘發膀胱內的免疫反應以治療腫瘤，然此亦可能產生一些副作用，如無菌性膀胱炎、血尿及遠處感染等。目前文獻上有關膀胱內免疫治療誘發反應性關節炎的案例報告不多，因此筆者在此提出一個典型的個案，描述其診斷過程及治療結果。（中台灣醫誌 **2006;11:191-5**）

關鍵詞

卡介苗，移形上皮細胞癌，反應性關節炎

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