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CASE REPORT

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Reiter's syndrome following intravesical bacille bilié de Calmette–Guérin treatment for superficial bladder carcinoma: report of six cases

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Abstract We report the cases of six patients who developed acute Reiter's syndrome following intravesical bacille bilié de Calmette–Guérin (BCG) immunotherapy for superficial bladder cancer. After the third to eighth BCG intravesical injection, the patients developed conjunctivitis, aseptic urethritis, and polyarthritis consistent with a diagnosis of Reiter's syndrome. HLA-B27 antigen was negative in five of the patients examined. Two of the patients responded to nonsteroidal anti-inflammatory drugs for polyarthritis, and the other four responded to steroids (prednisolone 5–10 mg/day). The frequent use of intracavitary BCG may increase the incidence of BCG-induced Reiter's syndrome. Further analysis of the relationship between HLA-B and -DR alleles and arthritis should shed light on the mechanism of BCG-induced Reiter's syndrome.

Key words Bladder carcinoma · Intravesical bacille bilié de Calmette–Guérin (BCG) · Reiter's syndrome · Therapy

Introduction

Intravesical bacille bilié de Calmette–Guérin (BCG) immunotherapy is an effective treatment for superficial bladder cancer and carcinoma in situ.[1] The most common adverse effects are persistent fever, malaise, and irritable urination. Arthralgia and arthritis are reported to occur in 0.5% of patients treated with intravesical BCG.[2] We report six cases of BCG-induced Reiter's syndrome, discuss the possible pathogenesis, and review the literature.

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Case reports

Patient 1

A 79-year-old man with a history of pulmonary tuberculosis at 18 years of age was admitted to the hospital because of persisting macrohematuria. Endoscopic examination revealed a superficial bladder carcinoma, which was confirmed histopathologically to be a transitional cell carcinoma (Grade 2), stage T1N0M0 according to the TNM classification. The bladder carcinoma was removed by endoscopic resection, which was followed by four courses of weekly intravesical BCG therapy to prevent a relapse of the bladder cancer. After each BCG injection, the patient reported self-limiting fever and ureteral pain for a few days. Five days after the fourth injection, he developed bilateral conjunctivitis (Fig. 1a), and 7 days later he developed soft tissue swelling and effusions in the right shoulder joint, and both wrists and knees (Fig. 1b), bilateral first metacarpophalangeal (MCP) joints (Fig. 1c), and the left ankle (Fig. 1d).

Hematological investigations showed leukocytosis of 9100/mm^3, increased erythrocyte sedimentation rate (ESR) of 106 mm/h, and high C-reactive protein (CRP) of 11.3 mg/dl. Blood chemistry was within normal limits. Antinuclear antibody (ANA) was positive at 1:1280, with a speckled pattern. Anti-DNA antibody, anti-Sm antibody, anti-RNP antibody, anti-SS-A antibody, and anti-SS-B antibody were negative. Rheumatoid factor (RF) and HLA-B27 antigen were negative (HLA B46, B61), and DR4 and 8 were positive. A tuberculin test was positive at 12 mm in diameter. A chest X-ray was normal, and an X-ray of the knees revealed the presence of bilateral joint effusion. Thirty-five millilitres of yellowish-white synovial fluid (SF) was aspirated from the right knee. The SF was aseptic and the leukocyte count was normal. Urinary and blood cultures were negative. Serological tests for *Chlamidia trachomatis* were negative, and PCR for *Chlamidia trachomatis* was also negative. An ophthalmological examination confirmed the presence of bilateral conjunctivitis.

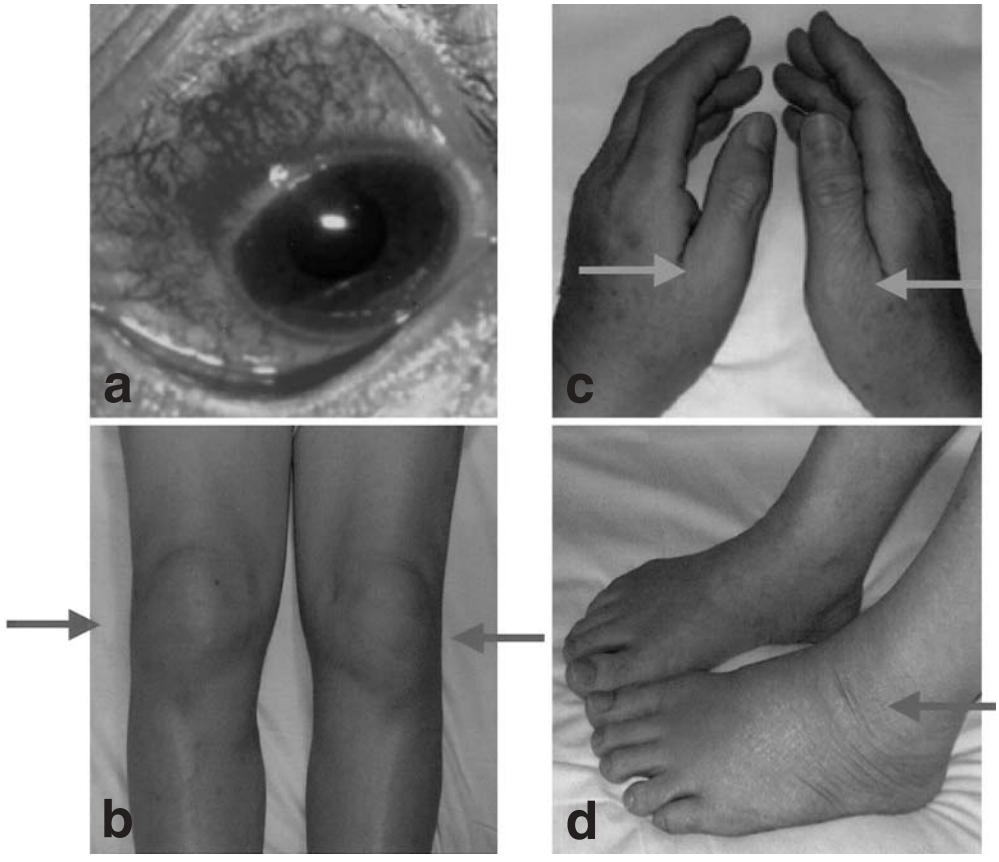

Fig. 1. **a** Bilateral conjunctivitis after intravesical bacillus Calmette–Guérin (BCG) therapy. **b** Swelling of the knee joints. **c** Swelling of bilateral first metacarpophalangeal joints. **d** Swelling of the left foot

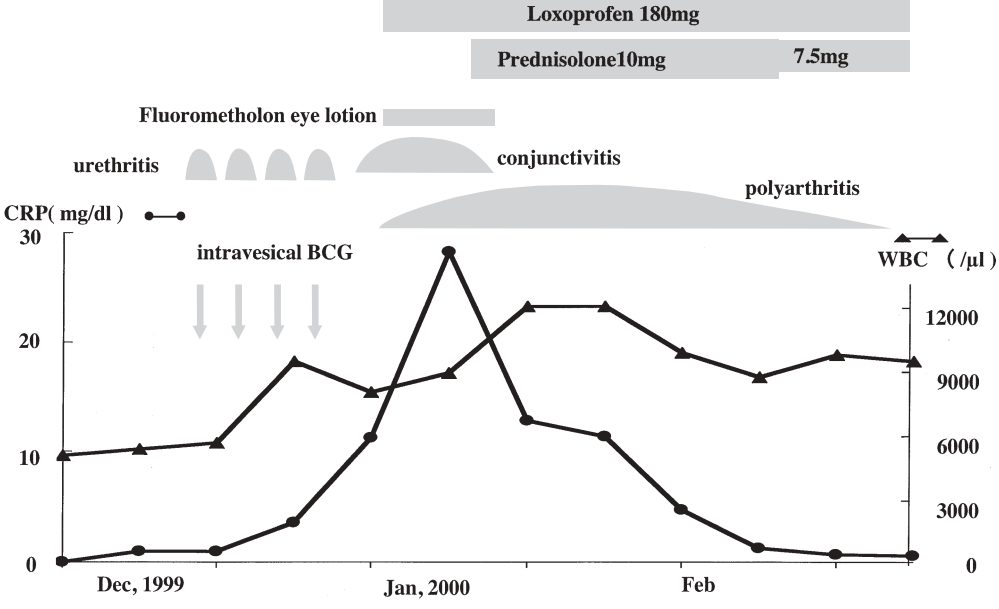

Fig. 2. The clinical course of patient 1. *CRP*, C-reactive protein

The diagnosis established was Reiter's syndrome based on polyarthritis, aseptic urethritis, and conjunctivitis. Discontinuation of the intravesical BCG resulted in a complete recovery from urethritis in 7 days. Bilateral conjunctivitis was treated with steroidal eye ointment for a few days, resulting in complete recovery. However, the administration of loxoprofen (180 mg/day) failed to resolve the arthritis. Oral prednisolone at 10 mg/day was started (Fig. 2). However, the polyarthritis and serological inflammatory findings gradually resolved to normal within about 2 months. The patient has remained asymptomatic, without any joint symptoms or medication, during the last 2 years of follow-up.

Patient 2

A 54-year-old man was diagnosed with a recurrence of transitional cell carcinoma of the bladder. After the second intravesical injection of BCG, he developed ureteral pain for a day. Two days after the fourth injection, he presented with arthritis affecting both knees, and 6 days later presented with bilateral conjunctivitis. Laboratory tests showed increased ESR (56 mm/h) and CRP (11.5 mg/dl). Blood chemistry was normal. ANA and RF were negative. HLA-B27 was negative, but HLA-DR was not checked. Blood and urine cultures were negative. Treatment with etodolac (400 mg/day) caused liver dysfunction. The patient was then switched to prednisolone at 5 mg/day, which resulted in an improvement in his symptoms. Prednisolone was discontinued after 2 months, and he remains asymptomatic 1 year later.

Patient 3

A 58-year-old woman was diagnosed with a recurrence of transitional cell carcinoma of the bladder. One day after the third injection of BCG intravesically, she developed hematuria and ureteral pain, followed by arthritis of the costotransverse and left fourth metatarsophalangeal (MTP) joints at 10 days, and bilateral conjunctivitis at 17 days. Laboratory tests showed increased ESR of 82 mm/h, and increased CRP of 1.8 mg/dl. Blood chemistry was normal. ANA and RF were negative. HLA-B27 was negative (HLA B39, B61), but HLA-DR was not checked. Blood and urine cultures were negative. Discontinuation of the intravesical BCG resulted in a complete recovery from urethritis in a few days. Bilateral conjunctivitis was treated with pranoprofen eye ointment for 5 days, resulting in a complete recovery. The joint symptoms disappeared after 2 months of etodolac treatment (400 mg/day). The patient remains asymptomatic 1 year later.

Patient 4

A 68-year-old woman was diagnosed with a recurrence of transitional cell carcinoma of the bladder. One day after the second intravesical injection of BCG, she developed pollakiuria and ureteric pain. Two days after the fifth BCG injection, she presented with arthritis of the ribs and both knees, and bilateral conjunctivitis. After the sixth BCG injection, the joint symptoms had disappeared, but the ureteric pain persisted after the eighth BCG injection. ESR, CRP, and blood chemistry were normal. ANA, RF, and HLA-B and HLA-DR were not checked. Blood and urine cultures were negative. Bilateral conjunctivitis was treated with steroidal eye ointment for a few days, resulting in a complete recovery. The administration of loxoprofen (120 mg/day) resulted in a gradual improvement in the ureteric pain, which disappeared after 23 months of loxoprofen treatment.

Patient 5

A 47-year-old man was diagnosed with a recurrence of transitional cell carcinoma of the bladder. One day after the sixth intravesical injection of BCG, he complained of ureteric pain, and 5 days after the eighth BCG injection he developed arthritis of the ribs and bilateral conjunctivitis. Eleven days later, he developed arthritis of the right wrist, knee, and foot. Laboratory tests showed high ESR (48 mm/h) and CRP (1.2 mg/dl). Blood chemistry was normal. ANA and RF were negative. HLA-B27 was negative (HLA B61, B70), but HLA-DR was not checked. Blood and urine cultures were negative. Treatment with diclofenac (75 mg/day) resulted in liver dysfunction. He was then treated with prednisolone at 5 mg/day, which resulted in an improvement in his symptoms. One year later, prednisolone was discontinued. He has remained asymptomatic during the last 6 months of follow-up.

Patient 6

A 42-year-old man was diagnosed with a recurrence of transitional cell carcinoma of the bladder. One day after the fourth intravesical injection of BCG, he developed ureteric colic. Four days after the sixth BCG injection, he presented with arthritis of the right knee, the right second proximal interphalangeal (PIP) joint and the left fourth PIP joint, and bilateral conjunctivitis. One day after the seventh BCG injection, he presented with arthritis of the left knee. Laboratory tests showed an increased CRP of 3.8 mg/dl. Blood chemistry was normal. ANA and RF were negative. HLA-B27 was negative (HLA B46, B52), but HLA-DR was not checked. Fifty millilitres of yellowish-white SF was aspirated from the left knee. The SF was aseptic and his leukocyte count was normal. Blood and urine cultures were negative. The administration of diclofenac (75 mg/day) provided only partial relief. Daily treatment with sulfasalazine at 1000 mg caused severe headache. He was then switched to prednisolone at 5 mg/day, which resulted in an improvement in his symptoms. Five months later, prednisolone was discontinued. He has remained asymptomatic during the last 6 months of follow-up.

Discussion

Most patients with synovitis occurring after intravesical BCG immunotherapy show the infiltration of mononuclear cells without granulomas in their synovial membrane.[3] Immunohistochemical studies, after intravesical BCG therapy, of serial bladder biopsies from patients with bladder carcinoma in situ have shown a large number of infiltrating mononuclear cells, consisting mainly of CD4+ T cells and macrophages, into the bladder. The antitumoral effect of BCG is thought to be mediated by T cell immunity. Although the antitumoral effect of BCG injection is considered to be limited to the urinary bladder, systemic reactions,

Table 1. The clinical characteristics of patients with Reiter's syndrome following intravesical BCG therapy

Case number	Age/sex	No. of BCG therapies	Arthritis	HLA-B27	Therapy	Reference
1	74/M	6	Knees, ankle	−	NSAID	9
2	64/F	4	Elbow, wrist, MCPs, PIPs, knee	+	NSAID + PSL + INH + RFP	10
3	35/F	5	Wrist, MCP, knee	−	NSAID	11
4	68/M	6	Knee	?	INH	12
5	71/F	4	MCP, knee	+	NSAID + PSL + INH	13
6	65/M	5	Elbow, PIP, ankle	+	NSAID + PSL	14
Present case	79/M	4	Shoulder, wrists, MCPs, knees	−	NSAID + PSL	
Present case	54/M	4	Knee	−	PSL	
Present case	58/F	3	Rib, MTP	−	NSAID	
Present case	68/F	5	Rib, knees	?	NSAID	
Present case	47/M	8	Wrist, MCP, knee	−	PSL	
Present case	42/M	6	Knee, PIPs	−	PSL	

BCG, bacillus Calmette–Guérin; MCP, metacarpophalangeal joints; MTP, metatarsophalangeal joints; PIP, proximal interphalangeal joints; PSL, prednisolone; NSAID, nonsteroidal anti-inflammatory drug; INH, isoniazid; RFP, refampicin

such as polyarthritis and conjunctivitis, may be induced. One possible mechanism for this condition is molecular mimicry between BCG and chondrocytes or conjunctiva, which is considered to be important in adjuvant arthritis[4] and Poncet's disease.[5] Adjuvant arthritis is induced in animals by the inoculation of a mycobacterium suspension (Freund). Similarly, Poncet's disease is characterized by an aseptic polyarthritis in association with *Mycobacterium tuberculosis* infection. T cell clones specific for *M. tuberculosis* established from rats with adjuvant arthritis are strongly arthritogenic,[6] suggesting the existence of a cross-reaction between some T cell antigens in human cartilage and *M. tuberculosis*.[7] One of the T cell antigens in the synovial fluid of patients with chronic inflammatory arthritis is a heat-shock protein (HSP) derived from *Mycobacterium bovis*.[8] A relationship between HSP and HSP-specific cytotoxic T cells has been implicated as the possible mechanism of inflammatory responses in patients with Reiter's syndrome.

A Medline search for the period between 1990 and 2002 showed reports of 36 patients with reactive arthritis and 6 patients with Reiter's syndrome that occurred subsequent to intracavitary BCG administration[9–14] (Table 1). Reiter's syndrome was diagnosed based on polyarthritis, aseptic urethritis, and conjunctivitis. These six patients developed asymmetrical arthritis, especially in the knee joints, after four to six doses of BCG immunotherapy. Reiter's syndrome occurred in 6 (7.6%) of 79 patients who received intravesical BCG immunotherapy in our hospital in the 13 years from 1989 to 2002 (Table 2). Three of 10 patients (2 patients were unknown) with BCG-induced Reiter's syndrome were HLA-B27-positive. It is possible that a restricted T cell epitope specific for the HLA-B27 molecule may induce arthrogenic T cells. However, this is not likely in our five patients, because they were negative for the HLA-B27 antigen. Other HLA-B antigens might induce arthrogenic T cells because three of our patients were HLA-B61-positive, two were HLA-B46 positive, and one was HLA-B39-positive. HLA-B39 and B27 recognize an overlapping peptide.[15]

Table 2. Laboratory tests of patients with Reiter's syndrome following intravesical BCG therapy

Case number	Age/sex	CRP (mg/dl)	ESR (mm/h)	ANA	RF
Case 1	79/M	11.3	106	+	−
Case 2	54/M	11.5	56	−	−
Case 3	58/F	1.8	82	−	−
Case 4	68/F	<0.3	ND	ND	ND
Case 5	47/M	1.2	48	−	−
Case 6	42/M	3.8	ND	−	−

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor; ND, not done

Our six patients developed Reiter's syndrome after intravesical BCG immunotherapy. Bilateral conjunctivitis and urinary complaints accompanied the occurrence of arthritis. Disorders such as connective tissue disease, septic or microcrystalline arthritis, arthritis secondary to other infectious agents, and seronegative spondyloarthropathy were ruled out by clinical and laboratory findings. Two of our patients responded to treatment with nonsteroidal anti-inflammatory drugs (NSAID), and the other four required steroids. A review of previously reported cases showed that six patients had also had good prognosis and responded favorably to NSAIDs, NSAIDs plus steroids, or antituberculous drugs.

The frequent use of intracavitary BCG may increase the incidence of BCG-induced Reiter's syndrome in the future. The prophylactic administration of isoniazid can prevent adverse effects after BCG therapy, but animal studies[16] suggest that prophylactic antituberculous drug therapy can reduce the antitumor effect as well as the immune response. Immunological studies are needed to determine the underlying pathogenic mechanism(s) of arthritis and conjunctivitis, and to search for an effective treatment or prevention of adverse events after intracavitary BCG immunotherapy.

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