



Reiter's Syndrome after Intravesical *Bacillus Calmette-Guérin* Therapy for Bladder Cancer

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Intravesical urinary bladder instillation of *Bacillus calmette-guérin* is a widely used and well-established treatment for superficial transitional cell carcinoma. The mechanism of action of this mode of treatment is probably non-specific immunostimulation. Although clinically very effective, this method is associated with a variety of adverse effects, including fever, granulomatous hepatitis and prostatitis, rash, pneumonitis, orchiepididymitis and even sepsis [1]. Arthritic involvement is uncommon and the clinical triad of Reiter's syndrome rare [2,3]. We report a case of Reiter's syndrome following BCG with an unusually prolonged clinical course.

Case Description

A 65-year-old man was admitted with fever of 38°C, painful red and swollen right elbow, left ankle, and second proximal right phalanx, redness and burning sensation in both eyes, and painful and swollen glans penis. He had a history of hypertension treated with calcium channel blockers, diabetes mellitus type 2 treated with sulfonylurea agents, and stable anginal syndrome. Two years before admission, following macroscopic hematuria, TCC of the renal pelvis was found and left ureteronephrectomy was performed.

BCG = *Bacillus calmette-guérin*
TCC = transitional cell carcinoma

Recently, due to *in situ* recurrence of TCC, treatment with intravesical BCG was started. A week before admission he completed his fifth weekly BCG instillation. Physical examination revealed bilateral conjunctivitis, acute arthritic signs with marked limitation of movements in the affected joints, ulcerations around the glans penis (circinate balanitis), tender prostate and urethral purulent discharge obtained by prostatic massage. Basic laboratory tests revealed elevated erythrocyte sedimentation rate of 110/hour, normocytic normochromic anemia (hemoglobin 12.1 g/dl), leukocytes 10,000/mm³ and platelets 321,000/mm³. Uric acid levels, rheumatoid factor, anti-nuclear factor, anti-DNA, and C3 and C4 were all normal. HLA typing was B27 positive. Gram stain of urethral discharge disclosed gram-positive cocci. Blood, urine, and urethral discharge cultures were all sterile, and no mycobacterium was found. PPD skin test elicited a 2.5 mm induration. Ultrasound-Doppler studies of the femoropopliteal veins did not detect any thrombus. Bone scan showed hyperabsorption in the left ankle.

Two weeks of combined treatment with naproxen, tetracyclin, and ofloxacin did not improve his condition. Prednisone, 30 mg qd, was then initiated, with marked amelioration of the extra-articular symptoms but with persistence of arthritis for more than 3 months despite increments in corticosteroid dose in combination with sev-

eral non-steroidal anti-inflammatory drugs. A partial response was noticed only after 4 months of therapy. The NSAIDs were stopped after 2 months due to deterioration of renal function, which resolved subsequently. Residual arthritis was still present a year after initiation of steroid treatment.

Comment

Since 1976, intravesical instillation of BCG has been shown to be an effective treatment for transitional cell carcinoma of the urinary bladder. Ninety-five percent of patients tolerate the treatment without any serious side effects [1]. Most of the side effects such as malaise, hematuria, low grade fever, and cystitis are of short duration. Few adverse effects, however, are serious or life-threatening. In a series of 2,602 patients treated with various BCG substances, 2.9% had high fever (>39°C), 1% hematuria, 0.9% granulomatous prostatitis, 0.7% pneumonitis and hepatitis, 0.5% arthritis or arthralgia, 0.4% epididymitis, 0.4% sepsis, 0.3% rash, 0.3% constricted bladder, 0.1% renal abscess and 0.1% cytopenia [1].

Reactive arthritis after BCG treatment, as noted previously, is a rare phenomenon with an incidence of 0.5% in treated patients. It usually occurs 1 to 5 months after the first injection, and sometimes a few days after the first or second injection. It can be potentiated

NSAIDs = non-steroidal anti-inflammatory drugs

by another instillation. The usual clinical signs are polyarthritis of the small joints, including the wrist, metacarpophalangeal, proximal interphalangeal joints as well as the knees [2]. Radiographs of the affected joints are usually normal. Laboratory data show nonspecific signs of inflammation like elevated ESR, C-reactive protein and mild anemia. The intra-articular fluid shows inflammation but no infection, and the synovial membrane biopsy usually reveals nonspecific inflammation. Clinical improvement can be detected within a few days to several months [2]. Reiter's syndrome, a subgroup of reactive polyarthritis, is a very rare complication of BCG therapy and we found only four cases reported in the literature [3]. HLA-B27 is highly prevalent in patients with BCG-induced arthritis [2], and in all the reported cases of Reiter's syndrome [3].

The mechanism of action of BCG-induced arthritis is not clear. The most plausible model is based on studies of adjuvant arthritis. In this rat model, cross-antigenicity was shown between *Mycobacterium tuberculosis* antigens and proteoglycans purified from cartilage [4]. In urothelium biopsies from

patients shortly after BCG treatment, the immunohistochemical profile showed strong expression of HLA-DR molecules on the surface of the urothelial cells, which persisted for several months after therapy [5]. These findings suggest proliferation of CD4 T cell clone, specific for an antigen shared by cartilage proteoglycan and the mycobacterium bacillus after BCG instillation. This proliferation could be caused by penetrance of some bacteria or bacterial products into the blood circulation through the vascularized tumor. The antigen triggers the T cell clone to proliferate and "attack" the joints, especially in susceptible subpopulations with specific HLA types like HLA-B27.

Our patient exhibited most of the typical symptoms of Reiter's syndrome. He had polyarthritis, conjunctivitis, balanitis and urethritis. The outcome was less favorable, with resistance to NSAIDs and with slow and gradual response to steroids.

Although the incidence of BCG-induced reactive arthritis and Reiter's syndrome is low, and there are no data on the risk of HLA-B27 positive carriers for developing this complication, clinicians and rheumatologists should be alert to arthritic symptoms

following BCG therapy, especially in individuals with known HLA-B27 typing. In such cases, treatment must be stopped immediately.

References

1. Lamm DL, Van Der Meijden ADP.M, Morales A, Brosman SA, Catalona WJ, Herr HW, Soloway MS, Steg A, Debruyne FMJ. Incidence and treatment of Bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596-600.
2. Belmatoug N, Levy-Djebbour S, Appelboom T, De Gennes C, Peltier AP, Meyer O, Kahn MF, Carbon C. Polyarthritis in 4 patients treated with intravesical BCG therapy for carcinoma of the bladder. *Rev Rhum Ed Fr* 1993; 60:162-6.
3. Pancaldi P, Van Linthoudt D, Alborino D, Haefliger JM, Ott H. Reiter's syndrome after intravesical Bacillus Calmette-Guerin treatment for superficial bladder carcinoma. *Br J Rheumatol* 1993;32(12):1096-8.
4. van Eden W, Holoshitz J, Nevo Z, Frenkel A, Klajman A, Cohen IR. Arthritis induced by a T-lymphocyte clone that respond to Mycobacterium tuberculosis and to cartilage proteoglycans. *Proc Natl Acad Sci USA* 1985;82(15): 5117-20.
5. Prescott S, James K, Busuttill A, Hargreave TB, Chisholm GD, Smyth JF. HLA-DR expression by high grade superficial bladder cancer treated with BCG. 1989; *Br J Urol* 63(3):264-9.

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