

Reactive arthritis after application of intravesical BCG immunotherapy in bladder cancer

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KEY WORDS

bladder ► bladder cancer ► Bacille Calmette-Guerin immunotherapy ► reactive arthritis

ABSTRACT

BCG (Bacille Calmette-Guerin) immunotherapy remains successful supplementary therapy in some cases of bladder cancer (T1 G2-G3, Tis). Reactive arthritis is one of the rarely described complications after this kind of treatment. We present the case of the patient with knee and jumping arthritis which occurred after intravesical immunotherapy with BCG. In this paper we describe available diagnostic and treatment methods in the case of such a complication.

INTRODUCTION

BCG Immunotherapy (Bacille Calmette-Guerin) remains successful supplementary kind of treatment in some cases of bladder cancer: T1 G2-G3, Tis [1]. As a rule this kind of therapy is quite safe, 95% of treated do not experience any serious side effects.

Risk factors such as traumatic catheterization or coexisting bladder inflammation might be the reason of severe complication involving fatal cases of sepsis, one of the rare complications is arthritis. Tnazii et al. revealed 59 cases of this complication in the systematic review described in worldwide literature in 2006 [2, 3].

CASE REPORT

The 75 year old patient after administration of six series of intravesical BCG Oncotice because of the bladder cancer (T1 G2) was admitted to the internal ward because of the high temperature up to the 40°C having lasted for 10 days, swelling and pain of both, knee and ankle. The medical history did not reveal any other diseases and the patient did not take any drugs. Slightly raised temperature, joint pain had occurred after the infusion of the drug from the 3rd cycle. These ailments subsided after application of non-steroid anti-inflammatory tablets. The complaints had steadily worsened in subsequent cycles. High temperature up to 40°C and visible effusion in the knee and ankle had developed during the 6th cycle after the second day.

A medical examination did not manifest any other deviation apart from the swelling of the joints. Conducted blood tests revealed high level of inflammatory parameters: CRP 245 mg/l (N: 0-5 mg/l), OB 78 mm/h (N: 0-10 mm/h), averagely increased WBC 9.8 G/l (N: 3.8-10 G/l) out of which 81% were granulocytes. Urinary tests, apart from 4-6 leukocytes per field of vision, without any other abnormalities.

During puncture of knee joints, which was performed twice, about 70 ml of clear, yellow, inflammatory liquid without any crys-

tal structure was obtained. Such tests as: bacterial cultures, both mycobacterium culture and PCR test on genetic material of mycobacterium were negative. We took bacterial culture of blood and urine which did not disclose any additional information. There were no antibodies against antigens such as Mycobacterium tuberculosis. Blood tests for the presence of Varicella-Zoster Virus, Influenza Virus type A(H1N1), type A(H3N2), type B, *Yersinia enterocolitica*, *Toxoplasma gondii*, *Borrelia afzelii*, *Borrelia burgdorferi*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae*, which are the most common cause of post infectious reactive arthritis, were negative too. Also antibodies against ANA Hep-2 and rheumatic factor were not detected. Because the urosepsis was suspected antibiotics ceftazidime 6 g/day and ciprofloxacin 800 mg/day iv were applied, yet neither fever, nor the level of inflammatory parameters did not decrease.

Having excluded infection, it was acknowledged that reactive arthritis triggered by BCG immunotherapy was the reason for patient complaints. Methylprednisolone 32 mg/day and meloxicam 15 mg/day were applied and after 7 days a decrease in the level of CPR to 16.9 mg/l and swelling of the joints were observed. The amount of drugs was gradually reduced during the 4 weeks. The patient's complaints, the level of inflammatory parameters, and tests on presence of HLA B27 antigen were negative during the medical inspection after 3 months.

DISCUSSION

Reactive arthritis is an asymmetric arthritis of several joints, mainly lower limbs and tendons, quite often followed by an infection of alimentary canal or reproductive organs. It frequently coexists with painless erosion, blisters on the glans or the body of the penis, changes on the skin and mucous membranes, conjunctivitis, inflammation of the uvea. In the axial form, asymmetric sacroilitis and spondylitis may occur [4]. In the described case, apart from the symptoms of the arthritis, any other deviation was not discovered during the medical examination.

To begin with, infectious arthritis and crystal inflammation should be excluded in the differential diagnosis. Biochemical tests of joints fluid, lack of crystals and negative bacteriological culture permitted to exclude that suspicion. The next step in the diagnostic process should be to broaden on many other causes of reactive arthritis particularly infection of *Chlamydia trachomatis* which is responsible for 35-70% of all cases of reactive arthritis. In the end, the general BCG infection must be eliminated. Results of classical bacteriological culture aimed Mycobacterium are known after 4-5 weeks, but using radiometric system might shorten this period to 5-15 days. Measurement of antibodies against Mycobacterium antigens and more widely applied PCR might be useful in the quick diagnostic process. Applying these methods in the presented case permitted the exclusion of a BCG infection, and then confirmed it by bacteriological culture of urea, blood, and joint fluid. Tuberculinic reaction does not reckon, thus it does not differentiate between infection and diseases.

The mechanism of triggering inflammation changes in joints during BCG immunotherapy is barely recognized. Activation of the

immunological system is provoked by cooperation of many factors. Similarity of some mycobacterium antigens with synovial membrane, genetic factors, or HLA B27 antigen may be considered some among others. The presence of HLA B27 antigen increases the risk of reactive arthritis about 50 times and is a risk factor for transformation of severe arthritis into chronic disease [5].

To date, the methods of treatment for reactive arthritis after immunotherapy BCG remains unsolved. In the case of arthritis of the lower limb the limitation of movement, prevention of thrombotic disease, physiotherapy, and kinesiotherapy are recommended.

In the less severe cases only using non-steroidal anti-inflammatory drugs may be sufficient. Sometimes the addition of steroids with slowly reduced doses is necessary for a short period. Moreover, the latest reports show the effectiveness of chemoprevention of isoniazid, although the drug might lead into debility of immunological response toward cancerous cells [6]. If the symptoms of arthritis still remain after many months, the treatment of methotrexate should be considered.

CONCLUSIONS

The majority cases of reactive arthritis after BCG immunotherapy of bladder cancer run a mild course and abate spontaneously after stopping treatment. In some cases, a supply of steroids is necessary. Chemoprevention with isoniazid is controversial since it might lessen the immunological response against the cancer cell [6].

REFERENCES

1. Lamm DL, van der Meijden AP, Akaza H et al: *Intravesical chemotherapy and immunotherapy: How do we assess their effectiveness and what are their limitations and uses?* Int J Urol 1995; 21 (suppl 2): 23-35.
2. Koya MP, Simon MA, Soloway MS: *Complications of intravesical therapy for urothelial cancer of the bladder.* J Urol 2006; 175 (6): 2004-2010.
3. Tinazzi E, Ficarra V, Simeoni S et al: *Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review.* Rheumatol Int 2006; 26 (6): 481-488.
4. Kwiatkowska B: *Reaktywne zapalenie stawów (Reactive arthritis)* In: Szczekliki A (ed). *Choroby wewnętrzne, Medycyna Praktyczna, Kraków* 2006: 1715-1720.
5. Shoenfeld Y, Aron-Maor A, Tanai A, Ehrenfeld M: *BCG and autoimmunity: another two-edged sword.* J Autoimmun 2001; 16: 235-240.
6. De Boer LC, Steerenberg PA, van der Meijden PM et al: *Impaired immune response by isoniazid treatment during intravesical administration in the guinea pig.* J Urol 1992; 148 (5): 1577-1582.

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