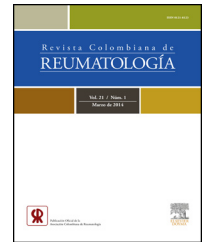




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Case Report

**Acute oligoarthritis following BCG treatment for urinary bladder cancer: A case report**



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ABSTRACT

Intravesical instillation of Calmette-Guérin bacillus (BCG) is an effective and safe treatment for superficial bladder cancer. The reactive arthritis is a rare osteoarticular side-effect following intravesical BCG immunotherapy.

The case is presented of a 65-year-old male, who developed reactive asymmetric oligoarthritis after the sixth BCG instillation, which was resolved with administration of non-steroidal anti-inflammatory drugs and discontinuation of intravesical instillation.

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**Oligoartritis aguda tras tratamiento con BCG en paciente con neoplasia de vejiga: reporte de caso**

RESUMEN

La instalación del bacilo de Calmette-Guérin es un tratamiento seguro y eficaz para el cáncer superficial de vejiga. La aparición de artritis tras su administración es un raro efecto secundario.

Presentamos el caso clínico de un varón de 65 años que desarrolló oligoartritis asimétrica después de la sexta instalación del bacilo de Calmette-Guérin, que fue resuelta tras el cese del tratamiento y la administración de antiinflamatorios no esteroideos.

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## Introduction

Local immunotherapy by intravesical instillation of Calmette-Guérin bacillus has been used since 1976 in patients with superficial bladder carcinoma. The good results obtained with this therapy increased their use and in the same way, their complications. Osteoarticular side effects are rare, being described in 1–5%, mainly pain joints and arthritis.

We report the case of a male patient who, after receiving 6 intravesical instillations of BCG for the treatment of bladder cancer, developed reactive oligoarthritis.

## Case report

Our case is a 65-year-old male diagnosed with superficial bladder cancer early 2014, with no evidence of dissemination, which was initially treated with transurethral bladder resection followed by weekly intravesical BCG immunotherapy for 6 weeks.

One week after the last instillation on June 2014, he was admitted to the hospital after complaining of malaise, pyrexia of 38 °C without associated dysthermia, inflammatory pain and swelling in his knees and feet. The physical examination revealed arthritis of the right ankle and both tarsus and knees, and dactylitis of the fifth finger of his right foot.

He did not present digestive symptoms, eye inflammation, urethral discharge or skin lesions, and had no limitation of the axial skeleton. The patient denied similar previous episodes and family history.

Initial laboratory evaluation showed an increase of acute phase reactants (C reactive protein 218 mg/dL with normal references 0–5 mg/dL, and erythrocyte sedimentation rate of 96 mm/1st hour). Blood chemistry and CBC were normal. Immunology, including complement and immunoglobulins, and serology (Chlamydia, Yersinia, Brucella, Parvovirus, Legionella, Mycoplasma) were also negatives. HLA-B27 was negative. Two series of blood cultures, the urine culture and stool culture were sterile. Examination of joint fluid drawn from the right ankle showed a turbid effusion with complete bacteriological analysis, including mycobacteria, was always sterile. The chest X-ray was normal. Doppler ultrasound detected signs of tenosynovitis and sinovitis in the right ankle. The patient was treated with indomethacin for 3 weeks at 100 mg/day. At present, and after 1 year without therapy, the patient remains asymptomatic with no joint signs and normal acute phase reactants.

## Discussion

The use of immunotherapy with intravesical instillations of BCG to prevent recurrence of superficial bladder tumors is widespread, as it has proven to be the most effective treatment.<sup>1</sup> The most common side effects are local, such as increased urinary frequency, cystitis and hematuria. The development of musculoskeletal side effects is uncommon, being the most common presentation in the form of joint pain, which occur in up to 0.5% of patients.<sup>2</sup> Arthritis is a very exceptional systemic effect and there are few cases reported in the

literature. It usually occurs in men between 50 and 60 years of age and the knee joint is the most frequently affected, followed by the ankles and wrists, with asymmetric presentation. Fever is associated in more than a half of cases. Most often it develops late after the fourth or fifth instillation.<sup>3</sup> The sacroiliac involvement usually occurs in about 14% of patients suffering from arthritis.<sup>4</sup> Ocular involvement in the form of conjunctivitis or uveitis occur in about 41% of cases.<sup>5</sup> And urethritis is also described.<sup>4,6</sup> The laboratory tests show non-specific signs of inflammation such as elevated erythrocyte sedimentation rate and C reactive protein.<sup>3–5</sup> Joint fluid has inflammatory characteristics with predominance of polymorphonuclear cells, and mycobacterial culture is negative in the joint fluid, blood and urine.

The mechanism by which the instillation of BCG induces reactive arthritis is not well established. Immunotherapy with intravesical BCG has no direct effect on the tumor cell. It has been shown that antitumor action concentrates specifically at the site of instillation, suggesting a local immune mechanism responsible for the therapeutic effect of BCG. Instillations with BCG induce granulocyte migration in the bladder wall, followed by mononuclear cells, mainly T lymphocytes CD4<sup>+</sup>. Following administration of BCG, urothelial cells expressing HLA-DR class II that they persist after several months of immunotherapy.<sup>4,7</sup> Also it has been suggested that molecular mimicry could be a cause, because the heat shock protein HSP65 of mycobacteria shares homology with a human cartilage proteoglycan, and also presents cross-reactivity with the haplotypes of HLA-DR1, DR3 and DR4, stimulating the secretion of cytokines and activation of CD8<sup>+</sup>.<sup>3,6–8</sup> The high prevalence of HLA B27 among affected supports the latter possibility.

The proposed in most publications treatment involves cessation of immunotherapy with administration of NSAIDs alone or in combination with low dose of glucocorticoids.<sup>3,9</sup> In patients with an inadequate response to these treatments or severe arthritis, some authors suggest the addition of immunosuppressor as methotrexate or anti-TB drug as isoniazid during 3 months, with mixed results.<sup>10,11</sup> There are still doubts about whether immunotherapy restart after resolution of the joint as there are reported cases with clinical recurrence after rechallenge with BCG instillations.

Although the frequency of reactive arthritis post-intravesical BCG is rare, we should not downplay as this can be really disabling. We should consider this diagnosis when confronted with an osteoarticular clinical picture in patients treated with BCG.

## Conflict of interest

All authors declare not present any conflict of interest or have received any funding to carry out this work.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this investigation.

**Confidentiality of data.** The authors declare that no patient data appears in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appears in this article.

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