Case Report

Reactive Arthritis After the Intravesical Instillation of BCG

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A B S T R A C T

The intravesical instillation of bacillus Calmette-Guérin (BCG) is a widely used and efficacious procedure for treatment of intermediate to high-grade superficial bladder cancer. The occurrence of osteoarticular side effects is infrequent compared to the number of administrated doses, and reactive arthritis is included within these effects. We present the case of a 54 years old HLA-27 (+) male, who developed reactive arthritis featuring asymmetric oligoarthritis and dactylitis after the second intravesical BCG instillation, which was resolved with administration of Etorcixib and Isoniazid.

Introduction

Local immunotherapy by intravesical instillations of the Calmette-Guerin bacillus (BCG) has been used since 1976 in patients with intermediate and high grade superficial bladder carcinoma, its use being widespread at present and having proven safe and effective. Its antitumor activity is concentrated at the site of instillation, suggesting that the immunomodulatory activity is mainly local. However, this treatment is capable of inducing non-serious systemic side effects and self-limiting malaise and fever in up to 5% of patients. Osteoarticular side effects are rare, being described in 1%-5%, mainly joint pain and arthritis in 0.5%-1% of patients. We report the case of a patient who, after receiving 2 intravesical instillations of BCG for the treatment of bladder carcinoma, developed reactive arthritis (ReA).

Clinical Presentation

The case is a 54-year-old male, diagnosed in April 2010 with high grade superficial bladder carcinoma (stage pT1aG3), without systemic dissemination, treated with transurethral bladder resection and subsequently being programmed for the administration of 6 intravesical instillations of BCG with intervals of 15 days between June and August 2010.

After the second instillation, he began to show diffuse swelling and inflammatory pain of the second right toe compatible with dactylitis, and a few days presenting a similar episode on the third toe. The patient was referred to our service for evaluation and treatment.


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finger of his left hand. The right knee and left ankle were sub-
sequently swollen (Fig. 1). Coinciding with the joint manifesta-
tions, the patient developed fever (up 38.8 °C, without associated dys-
thermia), purulent urethral discharge and self-limiting diarrhea
during the first 2 days. He did not present eye inflammation or skin
lesions, and had no limitations or inflammatory signs of the axial
skeleton or entheses. The patient denied previous similar episodes
of arthritis, back pain or history of inflammatory or heel pain, but
had a family history of spondyloarthritides (a brother with ankylosing
spondylitis [AS]).

From the analytical point of view, he showed an increase of
acute phase reactants (C reactive protein 98.60 mg/l, erythrocyte
sedimentation rate 97 mm/l; first hour), with other tests resulting
normal, including blood chemistry, CBC, immunology (rheumatoid
factor, antinuclear antibody, complement and immunoglobulins)
and serology (Chlamydia, Salmonella, Yersinia, Brucella, human
immunodeficiency virus, hepatitis viruses B and C). The culture of
the urethral discharge was also negative. HLA typing revealed the
presence of A24/AX, B44, B27, BW4/BW4, DQ7 and DQ5.

The radiographs of hands, feet, ankles and knees showed only
soft tissue growth corresponding to arthritis without joint erosions,
but enthesophytes were identified on the Achilles tendon as well
as a bilateral right heel spur (Fig. 2). Sacroiliac X-rays and MRI
were normal. Doppler ultrasound detected signs of synovitis and
tenosynovitis of the second PIP flexor tendon of the third finger
of his left hand, second and third right metatarsophalangeal joints
and second left tibiotalar joint as well as the right knee, with no
increase in the power-Doppler signal.

Because of the temporal relationship between the intravesical
BCG instillation and the onset of dactylitis and the asymmetrical
oligoarthritis with urethritis, fever and HLA-B27 (+) with subclin-
ical enthesopathy, we established the diagnosis of ReA secondary
to BCG. The patient initially received low-dose corticosteroids (pred-
nisone 5 mg/day), without any improvement, so we associated
etoricoxib 90 mg/day and isoniazid 300 mg/day, with treatment
lasting up to 4 months, between October 2010 and February 2011,
achieving progressive control and complete disappearance of the
inflammatory joint signs in 3 months. After 6 months no joint
remission (or axial or peripheral) or other manifestations suggest-
ing active disease have been seen.

Discussion

The development of musculoskeletal side effects secondary to
intravesical BCG instillation for the treatment of bladder cancer
is very rare considering its wide distribution and the number of
patients under treatment, reducing its frequency to case reports
and small series.³ Tinazzi et al. conducted a systematic review of
48 articles that included 61 cases of autoimmune manifestations
related to the intravesical administration of BCG. They found joint
pain and/or arthritis in 64% of patients, Reiter’s syndrome in 24%,
arthritis and fever in 4%, peripheral arthritis in patients with AD in
4%, psoriatic arthritis in 2% and Sjögren’s syndrome in 2%.¹

ReA secondary to BCG usually occurs in men between 50 and
60 years of age, manifesting as asymmetric and additive arthritis,
normally found in knees, ankles and wrists, and fever associated
in more than half of cases.² Dactylitis,⁶ urethritis⁸ and uveitis⁷ have
also been described as part of this picture. Most often it devel-
ops late after the fourth or fifth instillation (although in our case it
appeared after the second). In complementary examinations there
is usually a moderate increase in acute phase reactants, joint fluid
has inflammatory characteristics with predominance of polymor-
phonuclear cells and mycobacteria cultures obtained from the joint
fluid, urine and blood are negative (thus excluding the possibility
of septic arthritis by BCG, which has also been described).³,⁵

The mechanism by which the instillation of BCG induces ReA is
not established. 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
(+).⁹ The autoimmune response induced by the administration
of BCG occurs more frequently in patients with HLA-B27 (+) (nearly
60% of reported cases) or B7 (+) (which shows strong affinity with
HLA-B27).¹

Most patients with secondary ReA respond favorably to com-
plete suspension of BCG treatment. The disease may become
chronic in a small percentage of cases and requires specific ther-
apy, with NSAIDs and corticosteroids used alone or in combination,
rarely requiring the association of immunosuppressants such as
methotrexate. In patients with an inadequate response to these

Fig. 1. Diffuse swelling of the second right toe (dactylitis) and arthritis of the left
ankle.

Fig. 2. Feet X rays showing (A) a heel spur on the right foot (arrow) and bilateral
Achilles enthesophytes (arrowheads).
treatments, as in our case, some authors suggest the addition of anti TB drug treatment. Although this approach is controversial, some chronic and refractory cases have been reported solved after treatment with isoniazid for 3 months.\textsuperscript{10,11}

Conclusions

The development of ReA following intravesical BCG immunotherapy in patients with bladder carcinoma is a rare event. However, we should consider this diagnosis when confronted with an osteoarticular clinical picture in patients treated with BCG. It is more common in patients with HLA B27 and B7, and generally has a self-limited course and a favorable prognosis.

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 they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of Interest

The authors have no disclosures to make.

References