Case Report

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Reactive arthritis following Bacillus Calmette-Guérin immunotherapy

Bacillus Calmette-Guérin (BCG) is a vaccine derived from attenuated strains of *Mycobacterium bovis*. *Mycobacterium bovis* BCG-based therapy is considered an effective alternative for bladder carcinoma *in situ* when exclusive transurethral resection is inadequate. Among the complications associated with therapy, there are few reports in the literature on reactive arthritis. We report the case of a 56-year-old woman who develops predominantly peripheral spondyloarthritis, following instillation of BCG, as preventive treatment of relapse onset high-grade urothelial carcinoma after surgical resection.

Keywords: arthritis • BCG vaccine • *Mycobacterium bovis* • reactive • spondylarthritis • urinary bladder neoplasms

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Background

Bladder cancer is the fourth leading cause of malignancy among men, following prostate, lung and colorectal cancer, and the tenth among women [1,2]. Approximately, 70% of patients diagnosed with this disease have organ-confined disease [3]. Bacillus Calmette-Guérin (BCG) is a vaccine derived from attenuated strains of *Mycobacterium bovis*. In 1976 [4], Morales made the first description of the antitumor effects of intravesical application. Today, it is considered one of the most effective therapies available for bladder cancer *in situ* when exclusive transurethral resection is inadequate [5]. Tumor regression following BCG immunotherapy correlates with positive conversion of purified protein derivative test and the development of antibodies against BCG, suggesting that its effectiveness is a result of cell-mediated immunity [6]. BCG immunotherapy is well tolerated, and adverse effects occur in approximately 5% of patients and are usually mild and transient, including: malaise (14%), fever (25%), dysuria/hematuria (23%), frequency and urinary urgency (71%). Other complications, such as epididymitis, renal abscess, pneumonitis, sepsis, psoas abscess, osteomyelitis and reactive arthritis, are rarer [7,8].

Reactive arthritis occurs between 0.5 and 1% of bladder cancer patients treated with intravesical BCG [7]; mainly these subjects are positive for HLA-B27 allele, seronegative for rheumatoid factor and antinuclear antibodies, and have a transient course, rarely chronic, and respond to treatment with anti-inflammatory drugs (NSAIDs), glucocorticoids, anti-tuberculosis (TB) drugs and/or discontinuation of immunotherapy [9,10].

We herein report the case of a female patient who presented symptoms and clinical signs of reactive arthritis at 3 weeks after the last administration of intravesical BCG immunotherapy.

Case report

A 56-year-old woman, without personal or family history of relevant diseases, had past medical history of high-grade papillary urothelial carcinoma, with involvement of mucosa diagnosed in November, 2011. The patient underwent surgical resection of the tumor, followed by series of intravesical BCG instillations in 2012. She received six weekly instillations for 6 weeks; 3 months later, she received

Future Medicine part of fsg

weekly instillations for 3 weeks; 3 weeks after the last application of BCG, without previous episodes of joint involvement, she featured left Achilles tendinitis and dactylitis in the fourth left toe and second right toe, followed by third right metacarpophalangeal arthritis with morning stiffness less than 30 min (Figure 1).

The patient received NSAIDs (celecoxib 200 mg daily) for 5 days, with no improvement. Laboratory tests were conducted and reported: a negative rheumatoid factor and antinuclear antibodies by indirect immunofluorescence, elevated C-reactive protein, and negative HLA-B27 antigen. Other laboratory values, both at the onset and during evolution, are presented in Table 1.

Initial diagnosis/assessment

Reactive arthritis diagnosis was performed. Due to the poor response to initial treatment, etofenamate 1 g daily administered intramuscularly for 5 days and etoricoxib 120 mg daily for 7 days were added, with persistent symptoms.

Treatment, management, outcome & implications

She was referred to rheumatology service in January 2013, which decided to add sulfasalazine 500 mg every 12 h and topical piroxicam, with evolution towards improvement during the following weeks of treatment. In February 2013, the patient attends control, documenting decreased acute phase reactants and improvement in symptoms (Figure 2 & Table 1).

Discussion

Mycobacterium tuberculosis infections have been widely associated with autoimmune phenomena. Similarly, they have been related with various musculoskeletal manifestations, as Poncet's disease (described by this author in 1893), characterized by aseptic inflammatory polyarthritis in patients with active TB [3,4,6]. This complication can be seen as much as 6% and not only associated to *Mycobaterium tuberculosis*, but also *Mycobacterium avium intracelulare* and BCG [4]. In the review of the literature, there have been reported less than 50 cases of reactive arthritis secondary to intravesical BCG application, one of them in our country [4].

BCG is the live attenuated *Mycobacterium bovis* vaccine after several subcultures [11–16]; it currently has some therapeutic uses, including vaccination and bladder instillation for the management of superficial bladder carcinoma [17]. This effect is explained by a dual immune response: cellular immunity mediated primarily by T cells, and humoral immunity [1,4,17].

After intravesical instillation, BCG binds with the urothelium and triggers a local immune response, initially induced by macrophages, and subsequently CD4 lymphocytes, which induces a cytokine release (IFN-γ, TNF-α, IL-1, IL-2, IL-6, IL-8 and IL-10), upon a toxic response on tumor cells [4,7].

HLA class II antigens are expressed in the urothelium and persist for several months [7]. Such antigens stimulate CD4 T lymphocytes locally, and can also enhance a distant immune response mediated by CD8 T lymphocytes in peripheral blood and synovial fluid [1,18], especially in patients with positive HLA-B27 allele [4,7,8,10,11], which has been identified in approximately 60% of subjects with the disease [19], considering it as a susceptibility factor. There have also been found patients with HLA-DR3 and DR4 alleles, considered as individuals with an exaggerated response to the

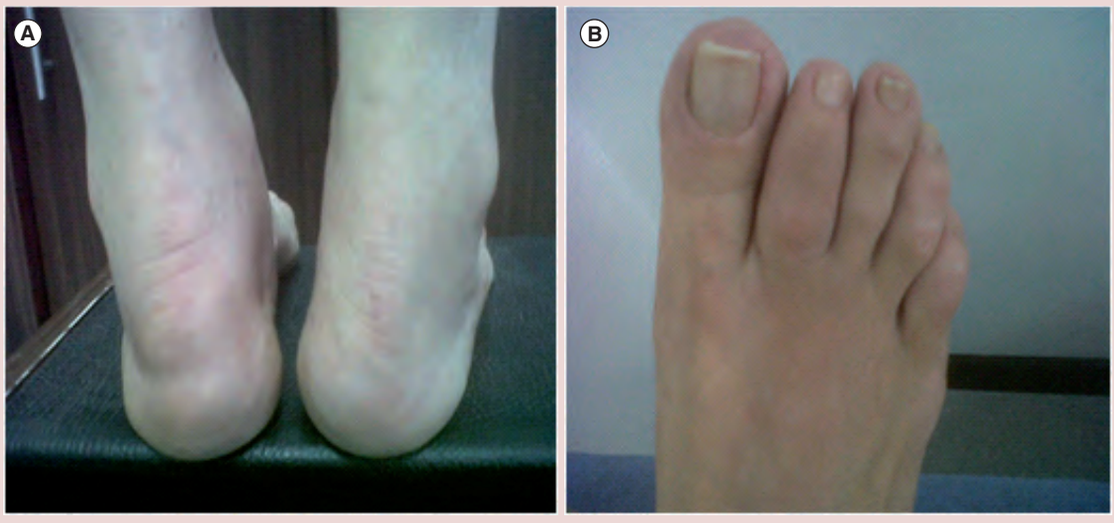

Figure 1. Patient with left Achilles tendinitis and dactylitis in the fourth left toe and second right toe.

Table 1. Laboratory tests.

Parameters	December 2012	February 2013
Hemoglobin (g/dl)	14.3	13.3
Hematocrit (%)	40.3	39.5
Leucocytes (cells/µl)	9500	6780
Neutrophils (%)	69.9	61.8
Lymphocytes (%)	21.4	25.1
Platelets (cells/µl)	258.200	285.500
C-reactive protein (mg/dl)	1.4	0.7
Erythro-sedimentation rate (mm/h)	70	33
Urine test	Normal	Normal

presence of mycobacterial antigens [10]. These antigens confer specific clinical features: HLA -DR3 carriers develop a symmetrical polyarthritis [10], whereas HLA-B27 positive individuals usually develop asymmetrical polyarthritis [10].

The mechanism through which articular cartilage is affected at distance [4,8,14] is unknown; however, some hypotheses have been proposed, including: an arthritogenic peptide, and antigen migration from mycobacteria to joints [10,17]. The former suggests the presence of a common antigen between mycobacteria and articular cartilage. This molecule was described by Buchs *et al.*, who characterized it as 65-kDa heat shock protein present in mycobacteria [4,13,14,17,18], *Chlamydia* spp., and *Borrelia burgdorferi*. It has been established that this antigen shares up to 50% of amino acid residues with its human counterpart, 60-kDa heat shock protein [15], leading to cross-reaction with

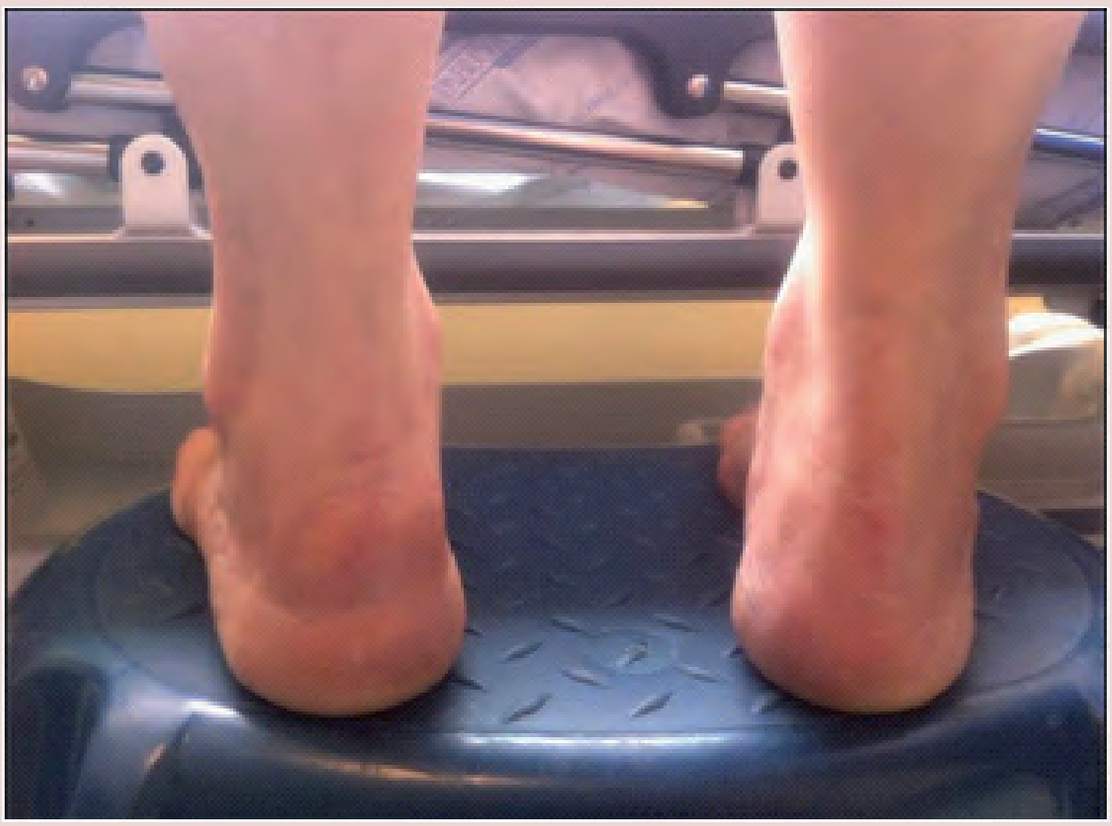

Figure 2. Improvement of Achilles tendinitis after treatment with sulfasalazine and topical piroxicam.

proteoglycans [8], favoring a reaction mediated by T lymphocytes that perpetuates the inflammatory effect. This mechanism is known as constitutive molecular mimicry [7]. The other hypothesis suggests a local bacterial infection, which is manifested slowly or as a response to mycobacterial antigens present in the joint cavity. The latter theory is based on the detection of DNA and RNA from organisms in the synovial fluid of patients with BCG reactive arthritis [10,17,19]. The first theory is the most widely accepted today.

The prevalence of reactive arthritis secondary to intravesical BCG instillation is estimated between 0.5 and 1%. However, these data are extracted from individual reviews of the literature, but not from population-based estimates [4]; furthermore, considering the hundreds of patients who have received BCG instillations worldwide, this prevalence may be underestimated.

Several adverse effects have been documented and associated with BCG administration; local effects, such as cystitis due to local aseptic inflammation (60–80% of patients), whose evolution is usually spontaneous 2–4 days after the instillation. Locoregional effects, as symptomatic granulomatous prostatitis (0.2–4% of cases) and epididymitis have also been described. Other symptoms, such as fever and/or nausea, are described in 25–50% of cases. Systemic manifestations, including pneumonia and liver disease, have also been reported [13]. After a detailed literature review available, BCGitis is not reported in previous case reports and systematic reviews.

In a retrospective study of 2602 patients with use of BCG, the complication rate was less than 5%. It was found that 3% of the subjects had fever, 1% hematuria and erythema, 0.9% granulomatous prostatitis, 0.7% pneumonitis and hepatitis, 0.5% arthralgia, 0.3% epididymitis and urethral obstruction, 0.2% bladder contraction, and 0.1% renal abscess and bone marrow toxicity [2,4]. Most patients with reactive arthritis following BCG instillation showed symmetrical synovitis of small joints of the hands, which resolved spontaneously after a few weeks. In these cases, they found mononuclear cell infiltration without the formation of granulomas in the synovial membrane [2].

Many features suggest a resemblance with reactive arthritis, including: the time of occurrence after antigen exposure, asymmetrical distribution of arthritis, predominant engagement of lower limbs, the presence of ocular abnormalities (conjunctivitis or uveitis), appropriate response to NSAIDs, and high prevalence of HLA-B27 [14]. Usually, the laboratory findings and studies are nonspecific, such as cytochemical and histological analysis of synovial fluid, where BCG is undetectable [12].

Although it was previously mentioned that polyarthritis is more common than oligoarthritis after intravesical BCG therapy, the patient featured asymmetrical oligoarthritis.

Raheem *et al.* published, in 2012, a review of the literature, identifying 42 case reports and four review articles, from January 1986 until January, 2011. After applying exclusion criteria, a total of 23 case reports and four review articles were analyzed, including a total of 40 patients (80% male and 20% female). Polyarthritis (68%) and fever (58%) were the most common symptoms, followed by monoarthritis (13%). Knees (41%), ankles (26%) and wrists (19%) were the most commonly involved joints, yet there was also joint affection in temporomandibular, shoulder, elbow, metacarpophalangeal, interphalangeal, chest wall, hip, metatarsophalangeal and sacroiliac joints (the latter in 3% of cases). While the onset of symptoms occurred along induction therapy, most patients developed symptoms after the fourth infusion of BCG (25%). They documented, additionally, positivity in acute phase reactants in 100% of patients (C-reactive protein, erythrocyte sedimentation rate or leukocytosis). Finally, mycobacterial agents were not confirmed in the synovial fluid cultures, nor positive test results for rheumatoid factor; HLA-B27 was positive in 62% of individuals. Extra-articular involvement was represented by conjunctivitis (38%), uveitis (8%), and urethritis (20%) [7].

Regarding treatment, BCG therapy was discontinued in all subjects, 40% received further monotherapy (25% NSAIDs, 8% glucocorticoids, and 7% anti-TB drugs); the remaining 60% was managed with combination therapy (NSAIDs, glucocorticoids and anti-TB drugs: 20%; NSAIDs and glucocorticoids: 20%; anti-TB drugs: 12%; NSAIDs and intra-articular injection of glucocorticoids: 5%; NSAIDs and chloroquine: 2%). One of these patients required the addition of sulfasalazine to achieve control of symptoms [7]. Other immunosuppressive agentes, such as methotrexate and cyclophosphamide, have been used with variable responses.

Most patients have a good response to treatment, probably due to the removal of the offending agent (BCG immunotherapy). Only a small proportion of subjects had a chronic course, potentially related to their genetic predisposition.

Table 2 highlights the main characteristics of previous studies of reactive arthritis following intravesical BCG therapy. Unfortunately, the vast majority are case reports enrolling one patient each, with obvious methodological limitations. The two systematic reviews included agreed in the concepts of the low frequency of reactive arthritis following BCG vaccine and the rapid response to anti-inflammatory agents.

Table 2. Previous studies regarding reactive arthritis following Bacillus Calmette-Guérin instillation.

Author	n	Methodology	Ref.
Tizzani *et al.*	48	Systematic review	[1]
Valenzuela-Suárez *et al.*	1	Case report	[2]
Rueda *et al.*	1	Case report	[4]
Manzini *et al.*	1	Case report	[5]
Hogarth *et al.*	1	Case report	[6]
Raheem *et al.*	27	Systematic review	[7]
Henares-García *et al.*	1	Case report	[8]
Nesher *et al.*	1	Case report	[10]
Mas *et al.*	1	Case report	[11]
Devlin *et al.*	1	Case report	[12]
Miranda *et al.*	2	Case report	[13]
Tinazzi *et al.*	1	Case report	[15]
Tektonidou *et al.*	1	Case report	[16]
Macía-Villa *et al.*	1	Case report	[18]

Conclusion

The presence of oligo- or poly-arthritis in patients treated with intravesical BCG infusions should do suspect the possibility of reactive arthritis.

Future perspective

Physicians involved in the care of patients with bladder cancer should be alert for the development of chronic arthritis and spondylarthritis after intravesical instillation of BCG.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent

For this case report, the authors had the approval of the Ethic Committee of Hospital Pablo Tobon Uribe in Medellín, Colombia. They obtained verbal informed consent of the patient and included all the proceedings to maintain patient anonymity.

Executive summary

Background

- Bacillus Calmette-Guérin (BCG) is a vaccine derived from attenuated strains of *Mycobacterium bovis*. It is considered one of the most effective therapies available for bladder cancer *in situ* (CIS) when exclusive transurethral resection is inadequate. Reactive arthritis occurs between 0.5 and 1% of bladder cancer patients treated with intravesical BCG; mainly these subjects are positive for HLA-B27 allele, and have a transient course, responding to treatment with anti-inflammatory drugs.

Case report

- A 56-year-old woman, had past medical history of high-grade papillary urothelial carcinoma, with involvement of mucosa diagnosed in November 2011. The patient underwent surgical resection of the tumor, followed by series of intravesical BCG instillations (from March to November 2012). Three weeks after the last application of BCG, she featured left Achilles tendinitis and dactylitis in the fourth left toe and second right toe, followed by third right metacarpophalangeal arthritis. Reactive arthritis diagnosis was performed. There was no response to NSAIDs, and sulfasalazine 500 mg every 12 h was added. In February 2013, the patient attends control, documenting decreased acute-phase reactants and improvement in symptoms.

Discussion

- The mechanism through which articular cartilage is affected at distance after BCG instillation is unknown; two hypotheses have been proposed: arthritogenic peptide, and antigen migration from mycobacteria to joints.

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• of interest; •• of considerable interest

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•• **This is a systematic review in MEDLINE in order to analyze the frequency of this clinical complication, its pathogenesis and outcome. A total of 48 papers were included.**

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• **This is a well-designed experiment which investigated the pathogenic mechanism of reactive arthritis after instillation of Bacillus Calmette-Guérin. Through flow cytometry, they analyzed the phenotype and T-cell receptor expression of peripheral blood and synovial fluid T cells in a patient who developed reactive arthritis following intravesical Bacillus Calmette-Guérin immunotherapy for bladder cancer.**