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Review

Reactive arthritis induced by intravesical BCG therapy for bladder cancer: our clinical experience and systematic review of the literature

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ABSTRACT

Objective: Intravesical instillation of BCG (ivBCG) is an effective and safe immunotherapy of bladder carcinoma but it may have, as side effect, a reactive arthritis (ReA). The authors describe 5 cases observed during their own clinical experience along with the updated review of the literature on this topic.
Methods: Seventy-three papers were present in the world literature, each reporting almost 1 case for a total of 112 patients. However, the review focused on 61 papers, selected on the basis of reporting suitable for a correct clinical evaluation; thus, a total of 89 patients, including the cases observed in our clinic, were carefully analyzed.
Results: Among the 89 patients identified 73 were males and 16 females. Europe is the geographical area with the higher number of reports, namely 80.6% of the papers including 74.2% of the patients. The Mediterranean area accounts for 62.9% of the papers and 59.6% of the cases. The symptoms of ReA appeared after a mean number of instillations of 5.8. Polyarthritis was present in 55.1%, oligoarthritis in 37.0% and monoarthritis in 7.9%. Polyarthritis was symmetric in 51.0% and asymmetric in 49.0% of the cases; oligoarthritis was symmetric in 33.3% and asymmetric in 66.7% of the cases. Overall, an asymmetric distribution of arthritis was present in 59.6%. Knee and ankle were the joints most frequently involved. The antigen HLA B27 was positive in 42.6%. The synovial fluid analysis was defined as flogistic–aseptic in 71.9% of the patients. Arthritis was recovered within 6 months in 93.2% of the cases and in 70.5% of the patients within the first two months. NSAIDs and corticosteroids, alone or in conjunction with other drugs, are used in 65.1% and in 40.4% of the cases, respectively. The clinical features of ivBCG ReA are compared with ReA from other triggering agents, from which it differs for some clinical aspects and overlaps for others.
Conclusions: Compared with a previous report, this review allows to modify some figures of this topic as a reduced prevalence of polyarthritis (from 70% to 55.1%) and of spinal and sacroiliac involvement; polyarthritis remains the more frequent clinical pattern of ivBCG ReA that, however, is characterized by rather asymmetrical distribution and involvement of the large joints of lower limbs. A definite linkage to HLA B27 is present, although without prognostic value. Moreover, arthritis is aseptic, has a latency time from antigen exposure, and is associated with extra-articular features as commonly observed in ReA from other triggering agents. Arthritis is usually benign and rarely develops into a chronic form. NSAIDs and/or corticosteroids are largely effective. Noteworthy, the overall clinical picture of arthritis triggered by ivBCG emerging from this updated review is comparable to that of ReA from other bacterial agents.

Contents

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1. Introduction

The clinical connections between tuberculosis and rheumatologic diseases are well known and recently reviewed [1]. Among the clinical associations, the immuno-mediated effects of Bacillus Calmette–Guerin (BCG), a live attenuated vaccine resulting from attenuated strains of *Mycobacterium bovis*, which is widely used for vaccination and as immunotherapy to treat some neoplasms, are included. Rheumatic adverse events of BCG vaccination are exceedingly rare and specifically an aseptic polyarthritis is probably the result of a chance association [2]. A symmetric polyarthritis, mainly involving the hands and the wrists, was reported in ten of 159 patients (6.3%) with cancer treated with intradermal BCG [3]. Intravesical instillation of BCG (ivBCG) is an effective and safe immunotherapy used worldwide to treat and prevent the recurrency of urinary bladder cancer [4], although the mechanisms of action remain to be fully clarified: BCG acts not by directly killing the neoplastic cells but rather by stimulating the inflammatory response and the local cytokine production. The anti-neoplastic effect of BCG seems to be confined in the site of administration (bladder) where, after subsequent instillations, large amounts of several cytokines (IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, IL-18, interferon (IFN)-γ, TNF-α) are documented. Indeed, in association with a local, early, granulocytic and macrophagic response other immune cell types are recruited including $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and dendritic cells [5]. Antigen-specific CD4 and CD8 T cells have been found in the synovial fluid and synovial tissue of patients with reactive arthritis (ReA) and, as first step, a CD4 T-cell response at the site of inflammation stimulated and maintained by the bacterial components occurs; at a later time the effects of the CD8 T cells also appear. The Th1 cytokine response (IFN-γ, IL-2, IL-12), essential for the removal of the bacteria related to ReA, is not effective thus producing a predominance of Th2 response (IL-4 and IL-10) that keeps the bacteria in the joints alive. The hypothesis that HLA B27 may act as restriction molecule for antigenic peptides from bacterial proteins, that would be presented to and cross-recognized by cytotoxic $CD8^+$ T lymphocytes, supports the possibility that the inflammatory process is maintained even after the elimination of the bacteria [6]. The mechanism most likely invoked is the so-called molecular mimicry suggested by the shared homology between mycobacterial heat-shock protein HSP65 and cartilage proteoglycan link protein. Thus, the bacteria or bacterial antigens spreading from the bladder to the circulation may induce a systemic immuno-mediated response having the joints as target, particularly in subjects genetically predisposed as those positive for HLA B27 antigen [7].

Among the systemic side effects of ivBCG, described since 1985, "arthritis and arthralgia" are reported with variable prevalence (0.5% [8]–8.3% [9]), "persistent arthritis" in 1.7% [10], "arthralgia" in 28.1% [11], "arthritis" in 3.6% [12], and "musculoskeletal adverse reactions" in 3.2% [13] of the patients. This fluctuation may be due to the different numbers of patients in the various series and/or to a more or less complete assessment of the specific rheumatic features. Forty-three patients with aseptic arthritis following ivBCG have been recently reviewed [14] and the results were compared with a sample of reactive arthritis (ReA) pointing out some clinical differences from the classical pattern of ReA. Another review article [7] on ReA following BCG immunotherapy for urinary bladder carcinoma, selected 49 related papers reporting 59 patients at least 10 of them without detailed clinical data; the analysis was mainly focused on the immuno-mediated mechanisms of ReA. Arthritis following ivBCG is sometimes, but not always, defined as ReA and so classified [6,15–17]: it is known as the triggering microbial agent, arthritis is often described as an asymmetric oligoarthritis prevalent at large joints of the lower limbs, is a sterile synovitis, and has a frequent linkage with HLA B27. Extra-skeletal symptoms (ocular, cutaneous, urogenital) and inflammation of tendons, bursae and enthesis are not rarely reported.

We described here five of our cases of patients with inflammatory arthritis secondary to ivBCG given for carcinoma of the bladder and, at the same time, presented the results of the systematic review of the literature concerning ivBCG and arthritis.

2. Case reports

2.1. Case 1

A 75-year-old man underwent transurethral resection of papillary carcinoma of the bladder (transitional cell, grade 1) in April 2003. One month later he was treated with six weekly instillations of ivBCG. Seven days after the last injection he complained of pain, swelling and stiffness at the 2° and 3° metacarpophalangeal joints and at the 5° proximal interphalangeal joint of the right hand; he had also painful swelling to the right elbow and left knee. He was referred to the rheumatology outpatient clinic after 15 days and on examination the feature of asymmetric polyarthritis with mild effusion in the left knee was confirmed. He had no clinical symptoms related to gastrointestinal and/or genitourinary tract. Laboratory findings showed marked elevation of ESR (87 mm/h) and CRP (12.9, normal range: 0.32–0.5); rheumatoid factor, ANA, anti-ENA, and anti-DNA antibodies were negative and C3–C4 range in normal levels; other routine laboratory tests for blood cell count, liver and kidney function were normal. His major histocompatibility complex haplotypes were A2, A3, and B18. X-rays of the affected joints were normal and the chest roentgenogram showed findings of COPD. He was treated with indomethacin 150 mg/day with a rapid improvement of articular pain and swelling and 8 days after the signs of polyarthritis fully disappeared with consistent reduction of ESR (35) and CRP (1). Indomethacin was gradually tapered and discontinued after 15 days from the onset. The program with BCG immunotherapy was subsequently continued with further four endovesical injections without any kind of complications. At the follow-up, in January 2006, he was asymptomatic for articular complains and for any other features relating to ReA.

2.2. Case 2

Our case 2 patient is a 64-year-old white man. In April 2007, vesical neoformations, from polypus degeneration, were discovered and