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Reactive Arthritis – A Rare Complication of Intravesical BCG Instillation

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ABSTRACT

Reactive arthritis (ReA) with the classic triad of arthritis, conjunctivitis and urethritis, previously termed Reiter's syndrome, is a systemic illness, usually induced by genitourinary or gastrointestinal infections. However, it can be a rare complication of intravesical Bacillus Calmette-Guérin instillation (iBCG), a therapy prepared from attenuated strains of *Mycobacterium bovis*, a common and effective treatment for carcinoma in situ of the bladder (CisB). We report a case of a patient with CisB who developed ReA after iBCG. The symptoms resolved completely with corticosteroids. iBCG was stopped with no recurrence of carcinoma within 2 years.

LEARNING POINTS

- ReA is an aseptic arthritis, usually triggered by genitourinary or gastrointestinal infections, generally in individuals positive for HLA-B27.
- Septic arthritis and microcrystalline arthritis can mimic ReA and they must be ruled out with arthrocentesis.
- ReA may be considered as a complication in patients under iBCG.

KEYWORDS

Reactive arthritis, intravesical Bacillus Calmette-Guérin, carcinoma in situ of the bladder

CASE DESCRIPTION

A 69-year-old man presented with fever; bilateral, asymmetric and painful arthritis of interphalangeal, tibiotarsal and knee joints, with great functional disability and no relief with opioids; bilateral conjunctivitis and scrotum and glans redness, suggestive of urethritis. No recent gastrointestinal symptoms were reported. He had a pacemaker and a history of endovascular abdominal aortic aneurysm repair, a coronary stent medicated with acetylsalicylic acid, C4-C5 arthroplasty, recurrent gout medicated daily with allopurinol and colchicine and carcinoma in situ of the bladder (CisB) under intravesical Bacillus Calmette-Guérin instillation (iBCG). The fifth iBCG was carried out five days before the beginning of symptoms.

Laboratory tests showed high serum uric acid (10.8 mg/dl) and high levels of inflammation (sedimentation rate 100 mm/h, C-reactive protein 42.2 mg/dl), while PSA was slightly increased (4.71 mg/dl) and urinalysis was normal.

The patient was maintained on colchicine and antibiotic therapy (AB) was started with ceftriaxone later altered to piperacillin/tazobactam and vancomycin due to persistence of fever, no clinical improvement and increased C-reactive protein.

Diagnostic arthrocentesis was performed. The synovial fluid had normal levels of uric acid and no microcrystals. Cell count was not possible but the Gram stain was negative for bacteria and Ziehl-Neelsen staining did not reveal acid-fast bacilli. Microcrystalline arthritis was excluded and septic arthritis was less probable, especially after negative cultures for joint fluid (bacteria, mycobacteria and fungi).

With no improvement of arthritis, prednisolone was started with some pain relief and no fever 24 hours later. Inflammatory tests were normal 1 week later.

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Blood and urine cultures (bacteria, mycobacteria and fungi), HIV, hepatitis B and C virus and DNA of *Mycobacterium tuberculosis* bacilli in blood were negative, as were serology tests for *Shigella*, *Mycoplasma*, pneumococcus, *Campylobacter*, *Salmonella*, parvovirus, *Chlamydia* and *Yersinia*. HLA-B27 was positive but other immunological tests (antinuclear antibodies, complement levels and rheumatoid factor) were normal.

Due to the presence of medical devices, AB was maintained during the aetiological investigation. Transoesophageal echocardiography was performed to exclude endocarditis as well as thoracic-abdominal-pelvic CT, which excluded infectious foci.

The patient was under physical rehabilitation, and despite slow clinical improvement, corticosteroids were progressively reduced with complete resolution of arthritis 1 year later. iBCG was not restarted without evidence of CisB during 2 years of follow-up.

DISCUSSION

Reactive arthritis (ReA) is an autoimmune condition that classically develops 4 weeks after genitourinary infections, especially with Chlamydia trachomatis, or gastrointestinal infections by *Shigella*, *Salmonella* and *Campylobacter*. These microorganism triggers can reach the joints, although they are not found at sites of arthritis[1].

The diagnosis is based on medical history and clinical examination, with a high index of suspicion when the triad of asymmetric arthritis involving large joints in a lower extremity, noninfectious urethritis and conjunctivitis is present.

Despite no specific laboratory or radiological test that can confirm the diagnosis, joint fluid analysis is imperative in order to rule out septic and/or microcrystalline arthritis. With aseptic joint fluid, the diagnosis of ReA was more evident. HLA-B27 is usually positive but it is not a diagnostic tool. However, it may be helpful for supporting the diagnosis in patients with joint-restricted symptoms and to evaluate the severity and chronicity of arthritis [2].

After the negative results for the most common causes of ReA, iBCG as the cause was strongly supported by medical history.

iBCG can cause mild arthralgias but ReA is a very rare, severe adverse effect (incidence of 0.5–1%)[2]. The number (mean of 5.8) and the time between the instillation and the onset of symptoms (median 5.0)[2] are not correlated with the severity and prognosis of disease[3]. Two clinical patterns have been identified and associated with other musculoskeletal complaints (enthesitis, tendinitis, bursitis and dactylitis). The most common form is a symmetric or asymmetric polyarthritis, involving either small-large and upper-lower joints and the less common form, an asymmetric mono-oligoarthritis affecting the large joints of lower limbs. Urethritis and conjunctivitis may occur weeks before the arthritis [3].

Therapeutic strategies are not well established but include discontinuation of iBCG since a worsening of the arthritis was reported in 83.3% of cases that continued the treatment[2] and therapy for symptomatic relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used and the first-line monotherapy. Corticosteroids have been proposed, especially in cases of NSAID failure, but they also give a favourable outcome without recurrence and generally cause a shorter course of arthritis[2]. We preferred corticosteroids because of the patient's history of coronary artery disease. Most cases achieve resolution of symptoms within 6 months[2] but rarely they may progress to chronic disease. In these cases, methotrexate can be indicated and it was considered in our patient. However, the clinical improvement was gradually favourable, whereby we opted to maintain only corticosteroids. In severe cases, isoniazid or rifampicin have been proposed but this remains controversial, since they could lead to a decrease in the efficacy of iBCG on CisB[4].

ReA induced by iBCG is an exclusion diagnosis but should be considered in patients under this therapy. We add this case to the small number of previously described cases, increasing the number of alternative, though rarer, causes of ReA.

REFERENCES

1. García-Kutzbach A, Chacón-Súchite J, García-Ferrer H, Iraheta I. Reactive arthritis: update 2018. *Clin Rheumatol* 2018;**37**(4):869–874.
2. Bernini L, Manzini CU, Giuggioli D, Sebastiani M, Ferri C. Reactive arthritis induced by intravesical BCG therapy for bladder cancer: our clinical experience and systematic review of the literature. *Autoimmun Rev* 2013;**12**(12):1150–1159.
3. Nakagawa T, Shigehara K, Naito R, Yaegashi H, Nakashima K, Iijima M, et al. Reiter's syndrome following intravesical Bacillus Calmette-Guerin therapy for bladder carcinoma: a report of five cases. *Int Cancer Conf J* 2018;**7**(4):148–151.
4. Ben Abdelghani K, Fazaa A, Souabni L, Zakraoui L. Reactive arthritis induced by intravesical BCG therapy for bladder cancer. *BMJ Case Rep* 2014;2014:bcr2013202741.