The Recovery of an intravesical BCG-induced arthritis after RITUXIMAB treatment

Nejla El amri[1], Héla Zeglaoui[1], Salma Hmila[1], dhouha khalifa[1], Sadok Lataoui[1], Khadija Baccouche[1], and Elyes Bouajina[1]

[1]Farhat Hached University Hospital of Sousse

July 24, 2021

Abstract

BCG intra-vesical instillation is the standard of care for superficial bladder cancer at high risk of relapse and progression. Yet, this treatment can cause dysimmune complications. Osteoarticular manifestations related to BCG therapy are rare and frequently mild. We report a rare case of a severe form successfully treated with Rituximab.

The Recovery of an intravesical BCG-induced arthritis after RITUXIMAB treatment

Abstract

BCG intra-vesical instillation is the standard of care for superficial bladder cancer at high risk of relapse and progression. Yet, this treatment can cause dysimmune complications. Osteoarticular manifestations related to BCG therapy are rare and frequently mild.

We report a rare case of a severe form successfully treated with Rituximab.

Keywords

Intravesical BCG, Reactive arthritis, Rituximab, Adverse effect

Key clinical message

BCG therapy is frequently used in bladder cancer. Osteoarticular manifestations induced by this therapy are very rare and usually mild. We describe first time use of Rituximab in this severe case of polyarthitis resistant to conventional treatments.

Introduction

BCG intra-vesical instillation is the standard of care for superficial bladder cancer [1, 2]. Yet,

it may expose to osteoarticular problems due to immune dysfunction. These complications

concern 0.5 to 1 % of all treated patients [3].

To date, a hundred reported cases have been published. We report the case of a severe

arthritis following BCG intra-vesical instillation successfully treated with Rituximab (RTX).

Case report

A 61-year old male was treated for a non-muscle invasive bladder carcinoma with intra-vesical

BCG-instillation following the endoscopic resection of the tumor. Two weeks after treatment

onset, he presented with high fever, polyarthritis affecting small and large joints (shoulders, elbows, wrists, knees, metacarpals and interphalangeal joints).

Laboratory tests revealed a high erythrocyte sedimentation rate (90 mm/h) and elevated C-reactive protein of 120 mg/l. The Synovial fluid aspiration revealed an inflammatory formula but the fluid was aseptic. Blood cultures and bacteriological examination of the urine did not isolate any germs. The prostate specific antigen test and serum lactate dehydrogenase were within normal range. CT scan of the chest, abdomen and pelvis showed a homogeneous splenomegaly but no tumoral lesions or profound adenomegaly were found. Thus, paraneoplastic arthritis and hematological malignancies were unlikely.

Work up for auto immune disorders came out negative (Rheumatoid factor, antinuclear antibodies and anti-cyclic citrullinated peptide antibodies).

Hands, midfoot, and painful joints' radiographs showed no abnormalities.

Echocardiography was normal and ruled out endocarditis.

The diagnosis of BCG-induced arthritis was suspected. Thus, immunotherapy was discontinued. The patient was at first treated with non-steroidal anti-inflammatory drugs (NSAIDs). However, due to the absence of improvement of his symptoms we decided to put him on a three-day pulse of methylprednisolone followed by prednisone at a high dosage.

By that time, we obtained an improvement of the arthritis that did not last long as the patient relapsed and developed an acute anterior uveitis on dose degression.

Given that the patient was dependent to corticosteroids, he was put on methotrexate but he developed a cytolytic hepatitis 7 days after treatment onset so it was interrupted. In view of this severe form of reactive arthritis, a biological treatment was attempted. Since TNF alpha inhibitors were contraindicated regarding our patient's history of bladder cancer, RTX was the treatment of choice. He recieved 1 gram the first day followed by 1 gram 15 days later. The disease took quickly a favorable course as the patient reported a spectacular improvement of his pain, quality of sleep and morning stiffness. In total, he received 2 cures of RTX. Hence, a long term clinical and biological remission over a period of 5 years was obtained and all treatments were then suspended.

DISCUSSION

BCG immunotherapy is the intravesical instillation of a bovine tuberculosis bacillus, "Mycobacterium bovis", of reduced virulence. This therapy demonstrated its efficiency in the treatment of superficial bladder carcinoma and it's the standard treatment for patients at high risk of relapse and progression of the disease [1, 2, 4]. Yet it may expose to several local (aseptic cystitis, granulomatous prostatitis and epydidimitis) and general (lung, liver or joint infection) complications and dysimmune reactions [3, 5, 6].

The incidence of osteoarticular complications is estimated to be 0.5 to 1% [3, 7].

Osteoarticular aseptic manifestations are assimilated to reactive arthritis [8, 9]. They occur after exposure to infectious agents especially in patients with genetic susceptibility. They are due to an inappropriate immune reaction caused by a repeated antigenic stimulation. It could be explained by an antibody-crossed-reaction between a component of the mycobacterial cell wall (heat shock-protein) and its human analogous form, and also with cartilage proteoglycans [10]. The pattern of the joint involvement is variable. It usually presents as a polyarthritis or polyarthralgia in 70% of the time, oligoarthritis in 27% of the cases and as monoarthritis in about 30% of the cases. The most affected joints are the knees, the ankles, the wrists, frequently associated with metacarpal and midfoot involvement. Sacroilac joints are affected in only 14% of the cases [5, 7, 9]. Therefore, this form of reactive arthritis differs from those secondary to gastrointestinal or genital infections which present as a monoarhtritis or oligoarthritis affecting mainly large joints of the lower

limbs. Furthermore, the involvement of the spine and sacroiliac joints tend to occur less frequently. Dactylitis and inflammation of the Achilles tendon can, as well be observed. Our patient presented a severe form of polyarthritis affecting small and large joints masquerading as rheumatoid arthritis [11]. The most common extra-articular manifestations reported include fever in 50% of the cases and ocular involvement such as uveitis and conjunctivitis. A few cases of authentic Reiter's syndrome were described in the literature [12, 13]. Our patient had thus a typical clinical presentation associating polyarthritis, fever and uveitis. The long term prognosis of this affection is usually benign under NSAIDs, provided the BCG therapy is suspended. However, in severe polyarthritis, cardiac and ocular manifestations, the use of systemic steroids can be necessary [14, 15]. Methotrexate could be indicated in some severe cases [8]. Moreover, anti-tuberculosis drugs (isoniazid /rifampicin) can be suggested but their efficacy remains uncertain. Furthermore these treatments could lead to a decrease of the efficacy of BCG therapy on the bladder tumour [15]. The originality of this case lies in the use of a biological treatment to cure a BCG induced arthritis. Usually, these severe, NSAIDs-resistant forms of reactive arthritis can benefit from an anti-TNFα treatment, which proved its worth in handling all forms of spondyloarthritis. However, in this case, all anti-TNFα drugs were contraindicated considering our patient's cancer. It has been reported that Tocilizumab was successfully prescribed in a single case [16]. Yet, both TNFα blockers and Tocilzumab may lead to systemic mycobacterial infection following use of live intravesical Mycobacterium bovis. After an overall risk-benefit assessment, our decision was to use RTX, a monoclonal chimeric antibody directed against CD20, targeting B lymphocytes. Thus, it causes B cell depletion which may play a role in antigen presentation. Its efficacy is well established in rheumatoid arthritis and spondyloarthritis. Only few case reports and open-label studies have demonstrated its clinical benefits [17, 18]. The main reason of the use of RTX in our case was its good tolerance and its low toxicity profile regarding the history on neoplasm of our patient and the risk of tuberculosis reactivation. To our knowledge, this is the first reported case of reactive arthritis especially intra-vesical BCG induced arthritis successfully treated with this treatment [19,20].

FUNDING STATEMENT

This work did not receive any specific grant from funding agencies.

CONFLICT OF INTEREST

The authors declare no conflict of interest

ETHICAL APPROVAL

Written informed consent was obtained from the patient for the publication of this case report

AUTHORS CONTRIBUTIONS

Nejla ElAmri, Héla Zeglaoui are the physicians directly involved in the study. Khadija Baccouche, Sadok Lataoui, contributed to study conception and design. Dhouha Khalifa and Salma Hmila contributed to redaction. Elyes Bouajina performed study supervision.

All authors reviewed the results and approved the final version of the manuscript.

REFERENCES

[1] Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. Cancer Treat Rev. 2010;36(3):195-205.

[2] Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, et al. Intravesical Therapy for the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. J Urol. 2017;197(5):1189-99.

[3] Lamm DL, Stogdill VD, Stogdill BJ, Crispen RG. Complications of bacillus Calmette-Guerin immunotherapy in 1,278 patients with bladder cancer. J Urol. 1986;135(2):272-4.

[4] Gandhi NM, Morales A, Lamm DL. Bacillus Calmette-Guerin immunotherapy for genitourinary cancer. BJU Int. 2013;112(3):288-97.

[5] Liu Y, Lu J, Huang Y, Ma L. Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guerin for Bladder Cancer. J Oncol. 2019;2019:6230409.

[6] Macleod LC, Ngo TC, Gonzalgo ML. Complications of intravesical bacillus calmette-guerin. Can Urol Assoc J. 2014;8(7-8):E540-4.

[7] Clavel G, Grados F, Lefauveau P, Fardellone P. Osteoarticular side effects of BCG therapy. Joint Bone Spine. 2006;73(1):24-8.

[8] Ikeuchi R, Sunada T, Yoshikawa T, Yoshida T, Tabuchi Y, Kajita Y, et al. [Reactive Arthritis during the Second Course of Intravesical BCG Therapy Requiring Administration of Methotrexate : A Case Report]. Hinyokika Kiyo. 2017;63(8):329-32.

[9] Miranda S, Vernet M, Héron F, Vittecoq O, Levesque H, Marie I. Arthrites réactionnelles secondaires à la BCG-thérapie. Deux observations et revue de la littérature. La Revue de Médecine Interne. 2010;31(8):558-61.

[10] van Eden W, Hogervorst EJ, van der Zee R, van Embden JD, Hensen EJ, Cohen IR. The mycobacterial 65 kD heat-shock protein and autoimmune arthritis. Rheumatol Int. 1989;9(3-5):187-91.

[11] 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):1150-9.

[12] 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):148-51.

[13] Tektonidou MG. Reiter's syndrome during intravesical BCG therapy for bladder carcinoma. Clinical Rheumatology. 2007;26(8):1368-9.

[14] Decaestecker K, Oosterlinck W. Managing the adverse events of intravesical bacillus Calmette-Guerin therapy. Res Rep Urol. 2015;7:157-63.

[15] Witjes JA, Palou J, Soloway M, Lamm D, Brausi M, Spermon JR, et al. Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy–Associated Adverse Events. European Urology Supplements. 2008;7(10):667-74.

[16] Kwan K, Bharadwaj S, Inderjeeth C. Response to treatment with tocilizumab of

reactive arthritis induced by intravesical bacillus Galmette-Guerin unresponsive to DMARDs. Int J Rheum Dis. 2012;15(4):e73-5.

[17] Wendling D, Dougados M, Berenbaum F, Brocq O, Schaeverbeke T, Mazieres B, et al. Rituximab treatment for spondyloarthritis. A nationwide series: data from the AIR registry of the French Society of Rheumatology. J Rheumatol. 2012;39(12):2327-31.

[18] MEASE PJ. Is There a Role for Rituximab in the Treatment of Spondyloarthritis and Psoriatic Arthritis? The Journal of Rheumatology. 2012;39(12):2235-7.

[19] Moore N, Berdai D, Blin P, Droz C. Pharmacovigilance : the next chapter. Therapies 2019;74:557- 67.

[20] Miremont Salamé G, Théophie G, Haramburu F, Bégaud B. Causality assessment in pharmacovigilance : the French method and its successive updates. Therapies 2016;71:179-86.

Hosted file

`color figure.docx` available at https://authorea.com/users/427318/articles/531516-the-recovery-of-an-intravesical-bcg-induced-arthritis-after-rituximab-treatment