Letters to the Editors

Sustained remission of ankylosing spondylitis following intravesical Bacillus Calmette et Guérin immunotherapy for bladder cancer

Sirs,

Intravesical instillation of Bacillus *Calmette et Guérin* (BCG) is an effective immunotherapy used in the treatment of non-muscle invasive bladder cancer (1). Osteoarticular manifestations following this treatment are uncommon and include joint complaints that resemble reactive arthritis (2).

The patient was a 52-year-old white male with HLA-B27 positive ankylosing spondylitis (AS) that was diagnosed 25 years ago. He was initially treated with non-steroidal anti-inflammatory drugs (NSAIDs). Due to a secondary loss of response to NSAIDs and a high disease activity (BASDAI: 6.4; ASDAS: 4.4; CRP: 41 mg/L), etanercept (25 mg twice weekly) was introduced in 2012. This treatment gave partial response (BASDAI: 3.4; ADAS: 2.1; CRP: 7.5 mg/L). In 2016, the patient presented with macroscopic haematuria, leading to the diagnosis of high-risk bladder cancer (urothelial *in situ* carcinoma, pT1). He was subjected to transurethral resection of the tumour and three months later, he underwent a course of 6 intravesical BCG instillations. When the bladder tumour was diagnosed, and according to the French recommendations (3), etanercept was stopped. The patient subsequently had no flare of his AS. He denied spinal pain and did not require NSAIDs. His disease activity was low (BASDAI: 1; ASDAS: 0.7) and CRP levels were normal (2.5 mg/L). Three years after the BCG immunotherapy, he is still in remission and has no recurrence of axial symptoms or the bladder tumour.

Intravesical BCG instillations are considered to be an effective immunotherapy for non-invasive bladder cancer (1). After BCG instillations, both local and systemic immune responses are generated. Urothelial cells and mucosal-resident macrophages are activated, leading to the production of various cytokines and chemokines, the recruitment of neutrophils and mononuclear cells and ultimately, to a granulomatous reaction. $CD4^+$ T regulatory (Treg) cells may also be induced (4). Frequent mild side effects of BCG immunotherapy are local bladder symptoms, including dysuria, haematuria, cystitis or fever (1). Diverse joint symptoms have been described following BCG immunotherapy for bladder cancer, including arthralgia, polyarthritis or oligoarthritis (2, 5, 6). The joint adverse reactions have been attributed to a mechanism of reactive arthritis (2, 7). These joint clinical features have been exceptionally reported in patients with a pre-existing inflammatory rheumatic disease, rheumatoid arthritis (RA) or AS (2, 6). Our patient had a long-standing AS that was still active when he received immunotherapy. Following this treatment, he was in long-term remission and normalised his acute phase reactants. It is conceivable that the BCG treatment may be linked to this favourable outcome on the axial disease. Indeed, one may hypothesise that a Treg population has been generated by BCG antigenic stimulations. A T-cell suppressive microenvironment has been described after BCG immunotherapy, altering in part the anti-tumour response (4). Etanercept is a fusion protein including the TNFR2 receptor. TNFR2 is expressed on the cell surface of Treg cells, and this expression identifies a subset with high suppressive capacity (8). In RA, it has been demonstrated that adalimumab has the ability to enhance the expression of TNFR2 expressed by Treg cells, driving Treg cell expansion (9).

Finally, BCG is also responsible for trained innate immunity (10). Whether this trained immunity may limit pathogenic effector cell functions involved in AS (*i.e.* IL-17-secreting cells, MAIT cells) remains to be determined. Conversely, we cannot exclude a spontaneous favourable evolution of the rheumatic disease, independently of the bladder treatment. To the best of our knowledge, similar cases have not been described so far. Thus, it would be important to collect the clinical course of patients with pre-existing inflammatory rheumatic disease and treated by BCG immunotherapy, especially those under a TNF inhibitor.

Ethics approval

According to the French Regulatory Authority for clinical studies, prospective and retrospective studies consisting solely in observational analysis do not require approval from Committees for the protection of persons participating in research. The cases reported in this paper and the study design received no opposition from the local ethics committee.The patient gave his written informed consent to publish his case.

E. Toussirot[1-5], *MD*
G. Guichard[6], *MD*
P. Saas[1,2,5], *MD*

[1]INSERM CIC-1431, CHU de Besançon, Centre d'Investigation Clinique Biothérapie, Pôle Recherche, Besançon;
[2]Fédération Hospitalo-Universitaire INCREASE, CHU de Besançon;
[3]Rhumatologie, Pôle PACTE (Pathologies Aiguës Chroniques Transplantation Éducation), CHU de Besançon;
[4]Département Universitaire de Thérapeutique, Université de Bourgogne Franche-Comté Besançon;
[5]Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, RIGHT Interactions Greffon-Hôte-Tumeur/Ingénierie Cellulaire et Génique, Besançon;
[6]Urologie, CHU de Besançon, France.

Please address correspondence to:
Eric Toussirot,
Department of Rheumatology,
University Hospital J. Minjoz,
25000 Besançon, France.
E-mail: etoussirot@chu-besancon.fr

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