

## CASE REPORT

## Reactive arthritis induced by intravesical BCG therapy for bladder cancer

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**SUMMARY**

Cancers of the bladder could be treated with intravesical instillation of BCG therapy. This treatment could lead to some complications. Osteoarticular ones are relatively uncommon. We describe an original observation, illustrating the development of reactive arthritis after intravesical BCG therapy. A 60-year-old man was followed for a T1G3 transitional papillary carcinoma of the bladder and was treated with intravesical BCG immunotherapy. Within the sixth intravesical instillation, he presented with polyarthritis confirmed by musculoskeletal ultrasound. The erythrocyte sedimentation rate was 100 mm without leukocytosis. The viral and bacterial serologies and immunological tests were negative. The ophthalmological examination revealed left conjunctivitis. Treatment with non-steroidal anti-inflammatory drugs was started, combined with the discontinuation of the intravesical instillation. No recurrence has been reported with a current decline of 2 years.

**BACKGROUND**

Cancers of the bladder are mainly represented by transitional cell carcinomas. The superficial forms, which are the most common, are treated with transurethral resection. When they are at a medium or high risk of recurrence and/or progression, adjuvant treatment with intravesical instillation of BCG therapy is indicated.<sup>1</sup> This treatment could lead to locoregional or systemic complication.<sup>2-4</sup> Osteoarticular complications are relatively uncommon. Joint pain is the most frequent manifestation, whereas arthritis is much rarer.

We describe an original observation, illustrating the development of reactive arthritis after intravesical BCG therapy followed by a review of the literature.

**CASE PRESENTATION**

A 60-year-old man was followed for a T1G3 transitional papillary carcinoma of the bladder and was treated with intravesical BCG immunotherapy. Within the sixth intravesical instillation, he presented with inflammatory joint pain without rachialgia. Physical examination revealed pain on palpation of the proximal interphalangeal joint of the left third finger and joint effusion of the knees without fever. Joint aspiration was not performed due to the patient's refusal.

**INVESTIGATIONS**

Laboratory examinations showed an erythrocyte sedimentation rate of 100 mm and a C reactive protein of 12 mg/dL without leukocytosis. The

urine culture was sterile. The viral and bacterial serologies (cytomegalovirus, Epstein-Barr virus, chlamydia, B and C hepatitis) were negative. The immunological tests (rheumatoid factor, anticitrullinated peptide antibodies, antinuclear antibodies) were also negative. The ophthalmological examination revealed a conjunctiva inflammation of the left eye. Plain X-ray (hand, foot and pelvis) showed no erosion. However, the musculoskeletal ultrasound showed a flexor tenosynovitis of the third left finger and synovitis of the first metacarpophalangeal and metatarsophalangeal joint. The diagnosis of reactive arthritis induced by intravesical BCG therapy was established according to the anamnestic, clinical and biological features.

**DIFFERENTIAL DIAGNOSIS**

Several diagnoses were discussed: specific BCG infection, septic arthritis, immunological disorder.

**TREATMENT**

Treatment with non-steroidal anti-inflammatory drugs was started, combined with the discontinuation of the intravesical instillation.

**OUTCOME AND FOLLOW-UP**

No recurrence has been reported with a current decline of 2 years.

**DISCUSSION**

Side effects of a different nature have been reported after intravesical BCG immunotherapy<sup>2-5</sup>: local complications (aseptic cystitis secondary to local inflammation), locoregional ones (granulomatous prostatitis, epididymitis), general ones related to a dysimmunity reaction of the BCG (fever, fainting and/or nausea) and finally systemic ones consisting especially of lung and liver diseases. Osteoarticular manifestations associated with intravesical BCG therapy are uncommon. According to a pharmacovigilance survey, rheumatic adverse effects have affected 18 among 22 600 patients who received such treatment.<sup>6</sup> According to Miranda *et al*,<sup>5</sup> the incidence of these manifestations is estimated at 0.5–1%. Osteoarticular manifestations may reflect a specific BCG infection, the most common or a non-infectious complication. The literature review conducted by Bernini *et al*<sup>7</sup> had identified 89 patients with reactive arthritis induced by intravesical BCG therapy.

The symptoms of reactive arthritis occurred on average after the 5.8th instillation of intravesical BCG therapy (SD ±5) and the delay between the instillation and the joint involvement was 13.5 days



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**To cite:** Ben Abdelghani K, Fazaa A, Souabni L, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202741

(median 5.0).<sup>7</sup> Reactive arthritis may have different features, polyarthritis being the most represented (55.1% of cases) almost equally as symmetric and asymmetric patterns, followed by oligoarthritis (37% of cases), while monoarthritis is rare (7.9% of cases).<sup>7</sup> The mainly reported affected sites are the knees (84.3% of cases), followed by the ankle (55.1% of cases), hand (39.3% of cases), wrist (32.6% of cases), foot (28.1% of cases), the sacroiliac joints (9% of cases) and spine (7.9% of cases).<sup>7</sup> Our observation is in agreement with these data, since the patient had developed polyarthritis immediately after the sixth injection of BCG. However, the present case is unusual because of the involvement of the metacarpophalangeal and metatarsophalangeal joint, rarely described previously. It is well known that osteoarthritis of the first metatarsophalangeal joint is a common condition and ultrasound of this joint could show synovitis.<sup>8</sup> However, in our case, neither foot X-ray nor ultrasound had revealed other typical osteoarthritis lesions, though synovitis was probably related to the reactive arthritis. Similarly, tenosynovitis was rarely described and may explain the tenderness of the proximal interphalangeal joint of the left third finger on physical examination. In fact, tenosynovitis was reported in only two cases, related to a seronegative symmetrical synovitis with pitting oedema or RS3PE syndrome.<sup>9–10</sup> There is a lack of data concerning the exact mechanism of aseptic arthritis after intravesical BCG therapy and it is probably multifactorial. It has been linked to an antigenic response generated by repeated stimuli with genetic predisposition (human leucocyte antigen (HLA) B27). The research of this antigen could not be performed in our patient. The role of cross-reactivity between mycobacterial antigens, particularly the heat shock protein 65 kD, and cartilage proteoglycan and/or HLA B27 tissue antigen had also been discussed.<sup>11</sup> HLAB27 has been regarded as a marker of severity and chronicity of arthritis.<sup>12</sup> However, according to Bernini *et al*,<sup>7</sup> these properties of B27 seemed to lose their interest because it was not correlated with any clinical data.

Therapeutic strategies for reactive arthritis related to intravesical BCG therapy are based on a wide spectrum of options and are not well established. The outcome is generally favourable, with no recurrence under non-steroidal anti-inflammatory drugs and after discontinuation of BCG therapy. This outcome was illustrated by our observation. In case of failure, corticosteroid therapy had been proposed by some authors. In the absence of improvement and in case of transition to chronicity, methotrex-

ate could be indicated.<sup>13</sup> Addition of isoniazid have also been proposed if there is no response or immediately in severe cases. However, this attitude remains controversial since isoniazid could lead to a decrease of the efficacy of BCG on bladder tumour.<sup>14</sup> Tanaka *et al*<sup>15</sup> postulated the rationale for the use of tocilizumab due to the upregulation of interleukin 6 in reactive arthritis. To our knowledge, only one case of refractory BCG-induced reactive arthritis, treated successfully with tocilizumab, has been reported.<sup>16</sup> The discontinuation of intravesical BCG instillations is mandatory since a worsening of the arthritis has been reported in 83.3% of the cases that continued the endovesical treatment.<sup>7</sup>

**Contributors** AF, KBA and LS participated in the acquisition of data and drafting and critical revision of the manuscript, LZ participated in a critical revision of the manuscript for important intellectual content and gave his final approval.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

- Cheng CW, Chan SFP, Chan LW, *et al*. 15-Year experience on intravesical therapy of T1G3 urinary bladder cancer: a conservative approach. *Jpn J Clin Oncol* 2004;34:202–5.
- Lamm DL, Stogdill VD, Stogdill BJ, *et al*. Complications of bacillus Calmette–Guerin immunotherapy in 1278 patients with bladder cancer. *J Urol* 1986;135:272–4.
- Lamm DL, Van der Meijden PM, Morales A, *et al*. Incidence and treatment of complications of bacillus Calmette–Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596–600.
- Saint F, Salomon L, Quintela R, *et al*. Classification, facteurs favorisants, prévention et traitement des effets indésirables (EI) associés au bacille de Calmette–Guérin (BCG) dans le traitement des tumeurs superficielles de vessie. *Ann Urol* 2002;36:120–31.
- Miranda S, Vernet M, Héron F, *et al*. Arthrites réactionnelles secondaires à la BCG-thérapie. Deux observations et revue de la littérature. *Rev Med Int* 2010;31:558–61.
- Debois H, Loupi E, Saliou P, *et al*. Évaluation de la tolérance de la BCG thérapie endovésicale en France: analyse des événements indésirables graves notifiés sur une période de trois ans. *ProgUrol* 2001;11:458–65.
- Bernini L, Manzini CU, Giuggioli D, *et al*. Reactive arthritis induced by intravesical BCG therapy for bladder cancer: our clinical experience and systematic review of the literature. *Autoimmun Rev* 2013;12:1150–9.
- Iagnocco A, Rizzo C, Gattamelata A, *et al*. Osteoarthritis of the foot: a review of the current state of knowledge. *Med Ultrason* 2013;15:35–40.
- Mouly S, Berenbaum F, Kaplan G. Remitting seronegative symmetrical synovitis with pitting edema following intravesical bacillus Calmette–Guerin instillation. *J Rheumatol* 2001;28:1699–701.
- El Mahou S, Popa L, Constantin A, *et al*. Remitting seronegative symmetrical synovitis pitting oedema after BCG instillation. *Clin Rheumatol* 2006;25:566–7.
- Van Eden W, Hogerworst E, Van der Zee W, *et al*. The mycobacterial 65 kD heat-shock protein and autoimmune arthritis. *Rheumatol Int* 1989;9:187–91.
- Hannu T. Reactive arthritis. *Best Pract Res Clin Rheumatol* 2011;25:347–57.
- Tinazzi E, Ficarra V, Simeoni S, *et al*. Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int* 2006;26:481–8.
- De Boer LC, Steerenberg PA, van der Meijen APM, *et al*. Impaired immune response by Isoniazid treatment during intravesical BCG administration in the guinea pig. *J Urol* 1992;148:1577–82.
- Tanaka T, Kuwahara Y, Shima Y, *et al*. Successful treatment of reactive arthritis with a humanized anti-interleukin 6 receptor antibody, tocilizumab. *Arthritis Rheum* 2009;61:1762–4.
- Kwan K, Bharadwaj S, Inderjeeth C. Response to treatment with tocilizumab of reactive arthritis induced by intravesical bacillus Calmette–Guérin unresponsive to DMARDs. *Int J Rheum Dis* 2012;15:e73–5.

## Learning points

- ▶ Rheumatic complications should be kept in mind after BCG immunotherapy for bladder tumour.
- ▶ Involvement of the metacarpophalangeal and metatarsophalangeal joint and tenosynovitis is possible in clinical presentation.
- ▶ Non-steroidal anti-inflammatory drugs combined with discontinuation of BCG therapy give good results.

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