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Case Report

From Bladder to Joints: Reactive Arthritis Secondary to Intravesical-Bacillus Calmette-Guérin Immunotherapy

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ABSTRACT

Reactive arthritis is a rare complication following Bacillus Calmette-Guérin (BCG) therapy for bladder cancer, often presenting with joint pain and systemic symptoms. A patient with high-risk non-muscle-invasive bladder cancer underwent Transurethral Resection of the Bladder Tumor (TURBT) followed by 4 doses of intravesical BCG therapy. Four weeks after treatment, the patient developed bilateral knee pain, swelling, difficulty walking, and fever, consistent with BCG-induced reactive arthritis. The patient's symptoms improved with oral prednisolone, and BCG therapy was discontinued. A flare during steroid tapering was managed with methylprednisolone and sulfasalazine. At follow-up, C-Reactive Protein (CRP) levels normalized, indicating clinical improvement. BCG-induced reactive arthritis, though rare, should be considered in patients presenting with new-onset arthritis after BCG therapy. Early recognition and appropriate treatment are crucial for optimal management.

Keywords: Intravesical BCG Therapy, Reactive Arthritis, TURBT, Bladder Tumor.

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INTRODUCTION

The most prevalent kind of bladder cancer, urothelial cancer (previously called transitional cell carcinoma), develops from the urothelial cells lining the inside of the bladder, ureters, and renal pelvis. The most commonly impacted area is the bladder. The main diagnostic and treatment method for non-muscle-invasive urothelial cancer is Transurethral Resection of Bladder Tumour (TURBT). Using a resectoscope, visible bladder tumours are endoscopically removed through the urethra. It provides local control by excising superficial lesions, helps confirm the diagnosis through histopathological analysis, establishes the stage and grade of the tumour, and guides decisions about further treatment, such as starting BCG therapy in high-risk cases. One type of immunotherapy called intravenous BCG therapy is mainly used to treat Non-Muscle-Invasive Bladder Cancer (NMIBC).

It entails using a catheter to introduce a live, attenuated strain of *Mycobacterium bovis* (Bacillus Calmette-Guérin) straight into the bladder. By inducing a local immune response in the bladder wall, the treatment helps eliminate cancer cells and lowers the chance of tumour progression and recurrence. A noteworthy clinical finding in this instance was the identification and documentation of the uncommon occurrence of reactive arthritis that developed during intravesical BCG therapy. Understanding this rare but serious immune-mediated side effect emphasises how crucial it is to exercise caution when taking BCG.

CASE PRESENTATION

A 72-year-old man with a known history of systemic hypertension, coronary artery disease, Chronic Obstructive Pulmonary Disease (COPD), and Past Pulmonary Tuberculosis (PTB) was diagnosed with carcinoma of the bladder in 2022, for which he underwent Transurethral Resection of Bladder Tumor (TURBT).

In September 2024, he was readmitted with a recurrence of bladder carcinoma and underwent a repeat TURBT. He was subsequently started on intravesical Bacillus Calmette-Guérin (BCG) therapy and received four doses on 22/10/2024, 05/11/2024, 12/11/2024, and 19/11/2024.

In December 2024, the patient was admitted again with complaints of bilateral knee pain and swelling, difficulty in movement and walking, and a recent episode of fever. There was no history of trauma. Clinically, he was initially diagnosed with acute inflammatory arthritis, and synovial fluid aspiration was performed. Laboratory investigations (Table 1) revealed elevated C-Reactive Protein (CRP) and rheumatoid factor. Approximately 20 mL of straw-colored synovial fluid was aspirated from the knee joint. Analysis of the fluid revealed no crystals, and culture grew *Staphylococcus cohnii* (a coagulase-negative *Staphylococcus*),

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which was considered a likely skin contaminant. Based on clinical presentation, laboratory findings, and recent history of BCG therapy, a diagnosis of BCG-induced reactive arthritis was made.

He was started on oral prednisolone, to which he showed a good clinical response. Further BCG therapy was discontinued. However, during steroid tapering, the patient experienced a flare, for which a single dose of methylprednisolone 80 mg was administered, along with sulfasalazine 500 mg once daily and continued prednisolone. At a follow-up outpatient visit after three weeks, CRP was negative and the patient reported symptomatic improvement. However, he developed rashes, which were attributed to sulfasalazine. Consequently, sulfasalazine was discontinued, and Methotrexate 7.5 mg once weekly was initiated, along with folic acid and a tapering dose of prednisolone. Due to persistent mild arthralgia, Hydroxychloroquine 200 mg twice daily was added.

Subsequent follow-ups showed significant symptomatic improvement, with only mild mechanical knee pain persisting. This case adds to the limited body of evidence and reinforces the need for clinician alertness to atypical adverse effects.

DISCUSSION

BCG immunotherapy for bladder cancer does not act directly on tumor cells. Instead, clinical and laboratory evidence indicates that its antitumor effect is localized to the site of installation, supporting the role of local immune responses in its therapeutic action. Following BCG administration, there is an initial infiltration of granulocytes into the bladder wall, which is subsequently followed by mononuclear cells, primarily CD4+ T lymphocytes (Prescott *et al*., 1992).

Complete Transurethral Resection (TURBT) of superficial bladder tumors, followed by intravesical immunotherapy in patients at risk of recurrence or progression, has been shown to enhance clinical outcomes (Cheng *et al*., 2004).

Adverse effects of various types have been reported following intravesical BCG immunotherapy. Various complications have been observed following intravesical BCG therapy. These include local reactions, such as aseptic cystitis due to localized inflammation; locoregional complications, such as granulomatous prostatitis and epididymitis; and systemic immune-related reactions, including fever, dizziness, and nausea. More severe systemic complications may involve pulmonary and hepatic involvement. Osteoarticular side effects are rare. According to a pharmacovigilance study, rheumatologic adverse events were reported in 18 out of 22,600 patients treated with intravesical BCG (Debois *et al*., 2001).

Arthritis following BCG immunotherapy is often associated with HLA-B27 positivity. Belmatoug *et al*. documented four such cases, with two testing positive for the HLA-B27 antigen. Among nine reported cases overall, four were found to be HLA-B27 positive (Belmatoug *et al*., 1991).

Data on the precise mechanism of aseptic arthritis following intravesical BCG therapy are limited, and the condition is likely multifactorial. It is thought to result from an antigenic response triggered by repeated exposure, combined with genetic susceptibility, particularly involving the Human Leukocyte Antigen (HLA) B27 (Van Eden *et al*., 1989). Unfortunately, testing for this antigen was not performed in our patient.

Tinazzi *et al*. conducted a systematic review of 48 studies encompassing 61 cases of autoimmune manifestations associated with intravesical BCG therapy. Their analysis revealed that 64% of patients experienced joint pain and/or arthritis, 24% developed Reiter's syndrome, 4% presented with both arthritis and fever, another 4% had peripheral arthritis in the context of Ankylosing Disorders (AD), while psoriatic arthritis and Sjögren's syndrome were each reported in 2% of cases. The most commonly affected joints reported were the knees (84.3% of cases), followed by the ankles (55.1%), hands (39.3%), wrists (32.6%), feet (28.1%), sacroiliac joints (9%), and the spine (7.9%) (Tinazzi *et al*., 2006).

Symptoms of reactive arthritis typically emerged after an average of 5.8 BCG installations (SD±5.0). The average interval between the last installation and the onset of Reactive arthritis symptoms was 13.5 days, with a median of 5 days. Detailed clinical evaluations to confirm the diagnosis of Reactive arthritis were conducted in 56 cases (63.0%). Hospitalization was required in 31 out of the 38 patients for whom this information was available (Bernini *et al*., 2013).

Polyarthritis is the most frequent clinical presentation of reactive arthritis following intravesical BCG therapy, occurring in 55.1% of cases. It manifests almost equally in both symmetric and asymmetric patterns, with a prevalence notably lower than the 70% previously reported in a study of 43 cases (Clavel *et al*., 1992).

In our case we observed the arthritis symptoms after the fourth dose of intravesical BCG therapy, for precisely after 6 days of the fourth dose of BCG therapy with the above-mentioned pain. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were administered as monotherapy in 49.4% of cases, while 10.3% of patients received NSAIDs in combination with corticosteroids. Corticosteroids alone were used in 21.8% of cases.

Antitubercular therapy was prescribed in 12.6% of patients (11 individuals), typically alongside NSAIDs and/or corticosteroids. Disease-Modifying Antirheumatic Drugs (DMARDs) were used in only four cases. The addition of isoniazid has been suggested in cases where there is no response to initial treatment, or immediately in severe presentations. However, this approach remains controversial, as isoniazid may reduce the therapeutic efficacy of BCG against bladder tumors (De Boer *et al*., 1992). BCG-induced reactive arthritis, treated successfully with

Table 1: Laboratory findings.

Laboratory Parameters	Date			
	24/9/24	2/12/24	5/12/24	11/12/24
ESR	-	93 mm/hr	104 mm/hr	58 mm/hr
CRP	321.1 mg/L	-	181.7 mg/L	8.8 mg/L
RA Factor	27.2 IU/mL	-	-	10.4 IU/mL
Hb	13.6 gm/dL	14 gm/dL	12.4 gm/dL	13.2 gm/dL
WBC	12990 cells/cumm	10690 cells/cumm	10900 cells/cumm	10360 cells/cumm
Neutrophil	84.1%	84.4%	87.4%	86.2%
Lymphocyte	11.2%	7.1%	9.5%	8.6%
Platelets	221×10^3/µL	255×10^3/µL	307×10^3/µL	285x 0^3/µL

tocilizumab, has been reported (Kwan *et al.*, 2012). Discontinuing intravesical BCG therapy is essential, as continued treatment has been associated with worsening arthritis symptoms in 83.3% of reported cases (Tinazzi *et al.*, 2006).

The first step in treating BCG-induced reactive arthritis is discontinuing intravesical BCG therapy until symptoms resolve, with a benefit-risk assessment before resuming treatment. First-line therapy includes Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), while corticosteroid eye drops are recommended for conjunctivitis/uveitis. Refractory cases may require oral steroids, intra-articular corticosteroid injections, or second-line treatments like systemic corticosteroids (prednisolone 10-20 mg daily) and Disease-Modifying Antirheumatic Drugs (DMARDs), such as sulfasalazine or methotrexate, for severe or chronic cases (Raheem OA *et al.*,2012; Bernini L *et al.*, 2013; Carter JD). In our case, the patient was initially started on a combination of corticosteroids and NSAIDs, which led to symptomatic improvement. However, a flare of arthritis occurred during steroid tapering, necessitating a switch to Disease-Modifying Antirheumatic Drugs (DMARDs).

CONCLUSION

We present a case of Intravesical BCG therapy induced reactive arthritis. The patient exhibited characteristic symptoms, and our diagnosis was based on clinical assessment and laboratory findings. Employing conventional therapies, the patient showed symptomatic improvement and was discharged in a stable condition. We believe that this case report could contribute valuable insights for further research. The patient improved with proper management. However, significant complications can be prevented through proper education and early detection of symptoms.

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ABBREVIATIONS

BCG: Bacillus Calmette-Guérin; **CRP:** C-reactive protein; **COPD:** Chronic obstructive pulmonary disease; **DMARD:** Disease-Modifying Anti-Rheumatic Drug; **NMIBC:** Non-muscle-invasive bladder cancer; **NSAID:** Nonsteroidal anti-inflammatory drugs; **PTB:** Pulmonary tuberculosis; **TURBT:** Transurethral resection of the bladder tumor; **WBC:** White blood cells.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from the patient's legal guardian.

SUMMARY

A 72-year-old male with systemic hypertension, coronary artery disease, chronic obstructive pulmonary disease, and past pulmonary tuberculosis was diagnosed with bladder carcinoma, treated with Transurethral Resection of Bladder Tumor (TURBT). He underwent repeat TURBT for recurrence and started intravesical Bacillus Calmette-Guérin (BCG) therapy. Subsequently, he developed bilateral knee pain, swelling, fever, and mobility issues. Elevated C-reactive protein and rheumatoid factor confirmed BCG-induced reactive arthritis. Oral corticosteroids improved symptoms, and BCG therapy was discontinued. A flare during steroid tapering was managed with additional immunosuppressive therapy. At follow-up, symptoms improved, but a drug-related rash led to a change in medication, with further treatment adjustments for persistent arthralgia. This case highlights BCG-induced reactive arthritis as a rare complication, underscoring the need for vigilant monitoring and

tailored immunosuppressive management in patients receiving BCG therapy for bladder cancer.

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