

Reactive arthritis following intravesical *Bacillus Calmette–Guérin* therapy in a patient with kidney failure—a case report

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Intravesical *Bacillus Calmette–Guérin* (BCG) is the standard adjuvant therapy for high-risk non-muscle-invasive bladder cancer (NMIBC), leveraging local immune activation for anti-tumor efficacy.^{1–3} Although BCG-related side effects are often mild and self-limited, rare systemic complications such as reactive arthritis (ReA) can occur. ReA is a sterile inflammatory arthritis associated with preceding mucosal or genitourinary infections and has been reported following BCG therapy, particularly in genetically predisposed individuals such as human leukocyte antigen B27 (HLA-B27) positive cases—but it also occurs in HLA-B27-negative patients.^{1,4,5} We report a case of severe BCG-induced ReA in a haemodialysis-dependent individual requiring hospitalisation and surgical intervention.

Case

A 60-year-old woman with hypertension, secondary hyperparathyroidism, and kidney failure on maintenance dialysis was diagnosed with high-grade pT1 NMIBC following transurethral resection of bladder tumour (TURBT). Induction intravesical BCG therapy was initiated 3 weeks later, planned as weekly instillations for 6 weeks.

Following the fourth BCG dose, she experienced transient dysuria and lower abdominal discomfort—that resolved spontaneously. One week later, she developed bilateral conjunctivitis (more pronounced in the left eye), followed by polyarthritis involving the knees and wrists, leading to immobility and a fall, prompting a visit to the emergency department.

On presentation, she was febrile and hypotensive, with bilateral knee effusions (Table 1, Figure 1). Arthrocentesis yielded haemarthrosis without crystals or identifiable organisms. Initial inflammatory markers were significantly elevated (C-

reactive protein [CRP] 180mg/L; white blood cell $15 \times 10^9/L$), peaking at CRP 550mg/L during admission. Despite empiric intravenous antibiotics and surgical washout of the knees and right wrist (which revealed purulent material), all microbiological cultures remained negative—except for a single isolate of *Staphylococcus hominis*, considered a contaminant.

A transthoracic echocardiogram excluded infective endocarditis. Serological investigations were unremarkable, with negative antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and HLA-B27. Viral screening for hepatitis B, hepatitis C, HIV and parvovirus B19 was also negative. Radiographs of affected joints demonstrated soft tissue swelling without erosions or joint space narrowing, consistent with non-destructive inflammatory arthritis. In the context of recent BCG exposure, sterile purulent arthritis, systemic inflammation and negative infectious and autoimmune workup, a diagnosis of BCG-induced ReA was made in consultation with immunology and rheumatology teams. Non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen 250mg twice daily) were commenced, resulting in rapid clinical improvement and reduction of CRP to 217mg/L within 2 weeks. Antibiotics were discontinued, and disease-modifying anti-rheumatic drugs (DMARDs) were not required. With multidisciplinary team support, she regained mobility and remained symptom-free at 6-month rheumatology follow-up. BCG therapy was discontinued. A follow-up cystoscopy 3 months later showed an unhealed TURBT site, and she is currently awaiting bladder biopsies.

Discussion

BCG immunotherapy is the mainstay treatment for high-risk NMIBC, particularly for pT1 tumours.

Although generally well tolerated, BCG therapy can, rarely, cause systemic complications such as ReA, occurring in less than 1% of cases.^{1,2} Typically, it presents as seronegative oligoarthritis, primarily affecting the lower limbs, with associated conjunctivitis and urethritis, resembling Reiter's syndrome.⁶

Our individual exhibited bilateral conjunctivitis followed by the rapid onset of asymmetric arthritis in the knees and wrists shortly after her fourth BCG dose, which is characteristic of BCG-induced ReA.^{6,7} Systemic inflammatory response features including fever, purulent joint effusions and hypotension initially raised suspicion for septic arthritis. However, repeated cultures were sterile, and joint aspirates lacked crystals or organisms. A single *Staphylococcus hominis* isolate was deemed a contaminant. Negative autoimmune serology and failure to respond to antibiotics further supported a diagnosis of BCG-induced ReA.⁴ Rapid improvement with NSAIDs confirmed the clinical suspicion. Echocardiographic evaluation ruled out endocarditis, excluding another potential source of infection.

The pathogenesis is thought to involve local immune activation in the bladder post-BCG, triggering T-helper 17 (Th17) responses and cytokine release (e.g., IL-6, IL-17, TNF- α), which may result in systemic immune cell migration and synovial inflammation.^{4,7} Molecular mimicry—especially involving heat shock proteins (HSP65 and HSP60)—may also lead to autoimmunity.⁸ While HLA-B27 increases susceptibility and disease severity,⁷ our patient was HLA-B27-negative. Importantly, patients with kidney failure have impaired immune regulation and reduced antigen clearance, likely increasing the risk and severity of systemic immune responses to BCG.⁵

Diagnosing ReA requires exclusion of other causes of inflammatory arthritis, especially infection. Joint aspiration, cultures and autoimmune testing are essential. The presence of conjunctivitis, sterile effusions and the close temporal link to BCG instillation supported the diagnosis in our case.

Management involves halting BCG therapy and initiating anti-inflammatory treatment. NSAIDs are first-line and were effective in our patient, though they must be used cautiously in dialysis-dependent individuals due to risks like gastrointestinal bleeding and fluid retention. We chose NSAIDs in view of negligible residual kidney function in our case. Corticosteroids or DMARDs may be needed in refractory cases.⁹ A multidisciplinary approach, including rheumatology, oncology, nephrology and rehabilitation, is key to optimal recovery. Most patients with BCG-induced ReA recover within 1–3 months. Chronic or relapsing arthritis is uncommon, though more likely in HLA-B27-positive individuals.¹⁰ In our patient, symptoms resolved fully with NSAIDs, though BCG therapy was discontinued, and cystoscopy later revealed an unhealed TURBT site—underscoring the importance of ongoing oncologic monitoring.

This case highlights the diagnostic challenge of distinguishing ReA from septic arthritis, particularly in immunocompromised patients. Awareness of this rare complication is crucial to prevent misdiagnosis, guide appropriate treatment and ensure coordinated multidisciplinary care.

Conclusion

BCG-induced ReA is a rare but significant complication of intravesical BCG therapy for high-risk NMIBC. While typically presenting as seronegative oligoarthritis with features resembling Reiter's syndrome, its clinical course can be challenging, often mimicking septic arthritis and posing diagnostic dilemmas. A thorough diagnostic workup—including exclusion of infection and autoimmune disease—is essential for accurate diagnosis. Prompt discontinuation of BCG and initiation of anti-inflammatory therapy can lead to full recovery. Regular follow-up and rehabilitation are crucial to support functional recovery, particularly when BCG therapy is interrupted. Clinicians must remain vigilant for this rare yet reversible complication to ensure timely management and optimal outcomes.

Table 1: Time of the blood investigations.

	Before initiation of BCG therapy	During ReA	After initiation of NSAIDs	Current
White cell count	8.0x10 ⁹ /L	14.9x10 ⁹ /L	12x10 ⁹ /L	9.1x10 ⁹ /L
Neutrophil	4.1x10 ⁹ /L	12.1x10 ⁹ /L	7.9x10 ⁹ /L	7.0x10 ⁹ /L
C-reactive protein	<0.6mg/L	539mg/L	217mg/L	6.1mg/L
Calcium	2.5mmol/L	2.03mmol/L	2.48mmol/L	2.47mmol/L
Phosphate	1.32mmol/L	1.94mmol/L	1.37mmol/L	2.04mmol/L
Parathyroid hormone	74.7pmol/L	-	-	50.7pmol/L

BCG = Bacillus Calmette–Guérin; ReA = reactive arthritis; NSAIDs = non-steroidal anti-inflammatory drugs.

Figure 1: a) X-ray of the knee and b) wrist at presentation.

COMPETING INTERESTS

Nil.

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