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Research Article

Chronic Reactive Arthritis Following Bacillus Calmette-Guérin (BCG) Instillations: A Case Report and Review

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Abstract

Background: Reactive arthritis (ReA) is an inflammatory joint condition that typically develops days to weeks after a gastrointestinal or genitourinary infection. While it is often associated with a classic triad of arthritis, urethritis, and conjunctivitis, many patients may not exhibit all three symptoms. Previously known as "Reiter syndrome," named after Hans Reiter, ReA is thought to result from an abnormal autoimmune response to infections caused by pathogens such as Salmonella, Shigella, Campylobacter, or Chlamydia. Recognizing this connection is essential for effective diagnosis and treatment.

Case Description: A 67-year-old male developed reactive arthritis (ReA) following intravesical Bacillus Calmette-Guérin (iBCG) therapy for non-muscle invasive bladder cancer. Elevated inflammatory markers and a negative HLA-B27 result were noted. The symptoms were attributed to iBCG-related ReA, leading to the discontinuation of iBCG treatment.

Outcome: Initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids was ineffective, necessitating disease-modifying antirheumatic drugs (DMARDs) for sustained remission and symptom control. Although chronic arthritis requiring prolonged DMARD therapy is uncommon, the patient required over 1.5 years of DMARD treatment to manage symptoms effectively.

Key words: iBCG intravesical Bacillus Calmette-Guérin, DMARD disease-modifying antirheumatic drugs, NSAIDs nonsteroidal anti-inflammatory drugs

1. **Introduction**

Reactive arthritis (ReA) is a form of sterile arthritis that arises in genetically predisposed individuals following an extra-articular infection, most commonly involving the gastrointestinal tract (e.g., Salmonella, Shigella, Campylobacter, Yersinia) or the genitourinary tract (e.g., Chlamydia trachomatis). It can also develop as a rare complication of intravesical Bacillus Calmette-Guérin (iBCG) therapy, which is derived from attenuated strains of Mycobacterium bovis. iBCG is an effective treatment for non-muscle invasive bladder cancer, particularly in prolonging recurrence-free survival. Despite its general safety, adverse effects can arise, including local genitourinary issues like cystitis and systemic complications such as fever and ReA. ReA occurs in less than 5% of patients undergoing iBCG treatment and is more common in men.

2. **Etiology and pathogenesis of reactive arthritis after IBCG**

Reactive arthritis (ReA) following intravesical Bacillus Calmette-Guérin (iBCG) therapy is caused by a combination of microbial exposure, genetic predisposition, and an aberrant immune response. BCG, introduced into the bladder, can migrate to the synovium, triggering chronic inflammation, particularly in genetically susceptible individuals, such as those positive for HLA-B27 [1]. This immune response involves the production of elevated proinflammatory cytokines and chemokines, leading to joint inflammation. ReA typically develops within 2 to 4 weeks after iBCG initiation, though the exact timing may vary depending on the individual's immune response, genetic predisposition, and the specific characteristics of the BCG strain used [1,2].

3. **Treatment**

The treatment of reactive arthritis (ReA) after iBCG therapy typically begins with the discontinuation of iBCG therapy and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment [1]. In cases involving conjunctivitis or uveitis, corticosteroid eye drops are recommended. If NSAIDs prove insufficient, systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) are employed as second-line options. For refractory cases, biological agents may be considered as third-line treatments. The presence of polyarticular involvement at the onset and delays in discontinuing iBCG therapy are predictors of a chronic course of reactive arthritis [1].

4. **Case presentation**:

A 67-year-old male with a medical history of hypertension, type 2 diabetes, and a history of smoking was referred to a urologist for intermittent macrohematuria lasting 1.5 years. Abdominal ultrasound identified two tumors in the urinary bladder. CT-urography confirmed a 4x4x4 cm tumor on the right side and a smaller tumor on the left, without evidence of bladder wall invasion. The patient underwent a transurethral resection of bladder tumors (TURB) in March 2022, during which possible invasion of the bladder wall was suspected. Histopathological evaluation revealed PT1G2 high-grade urothelial carcinoma without carcinoma in situ. Chest CT showed no evidence of metastasis(Figure 1).

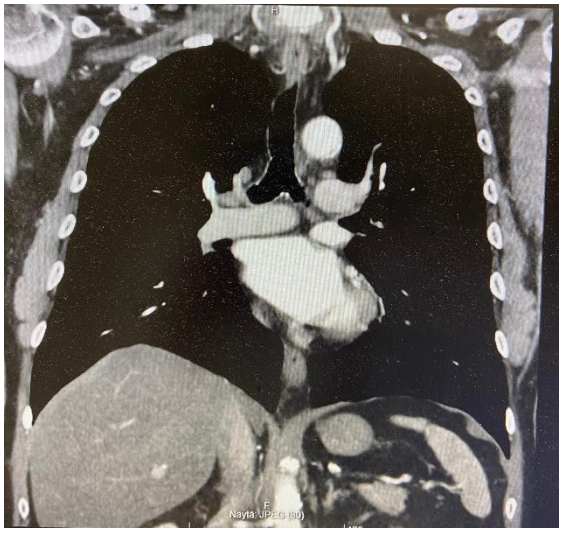

Fig 1: Chest CT performed on 3/22 showing no sign of metastasis.

Treatment Course and Initial Symptoms:
In April 2022, a repeat TURB revealed reactive changes and a 2 mm carcinoma in situ in the urethra. Weekly iBCG treatment was initiated from May to July 2022, with the final treatment occurring on July 13th, 2022. The following day, the patient experienced joint pain in small joints, which gradually spread to the ankles, knees, hips, and elbows. The joints became swollen and inflamed, accompanied by fever.

Emergency Presentation:
On July 19th, 2022, the patient presented to the emergency department with severe joint pain and fever. Examination revealed polyarthritis and bilateral conjunctivitis. Blood tests showed elevated inflammatory markers, including leukocyte levels of 13.1 E9/l, C-reactive protein (CRP) of 303 mg/l, and an erythrocyte sedimentation rate (ESR) of 99 mm/h. Renal and liver function tests were within normal ranges. Tests for common infections and autoimmune markers (e.g., RF, CCPab, HLA-B27) were negative. Imaging studies, including chest X-ray and CT, revealed no evidence of Mycobacterium bovis-related pneumonitis. An infectious disease specialist diagnosed the patient with post-BCG reactive arthritis based on clinical findings and exclusion of other causes(Figure 2,Figure 3, Figure 4, Figure 5 & Figure 6)

Hospitalization and Treatment:
The patient was treated with intravenous cefuroxime for one week and received local corticosteroids for joint symptoms. On July 26th, oral corticosteroids were initiated (prednisolone 15 mg daily), leading to significant improvement in joint pain and resolution of fever. The patient's conjunctivitis resolved, and follow-up blood tests showed decreasing leukocyte levels (11.5 E9/l) and CRP levels (172 mg/l). He was discharged in stable condition on July 29th, 2022, with a follow-up scheduled at the rheumatology clinic.

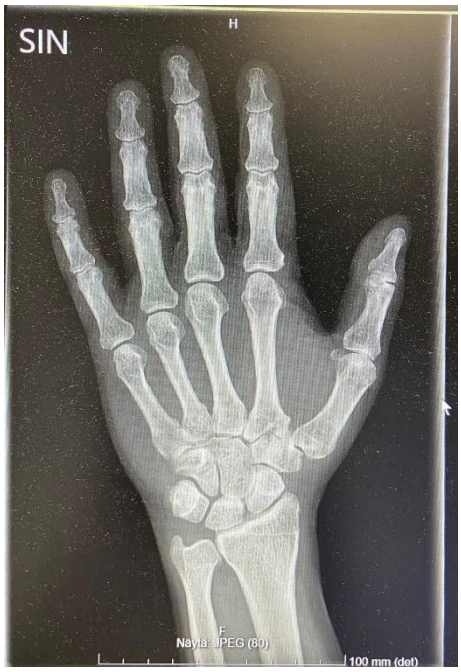

Fig 2. Left hand showing no signs of arthritis or erosion

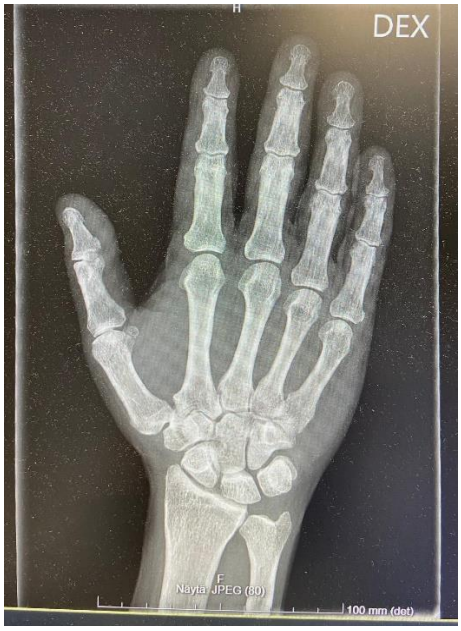

Fig 3. Right hand showing no signs of arthritis or erosion

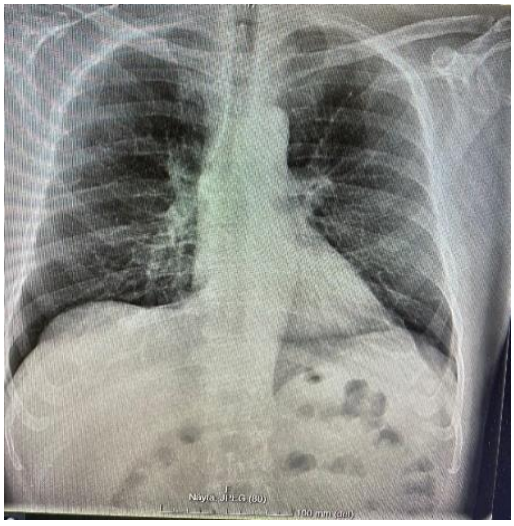

Fig 4. Normal chest x-ray

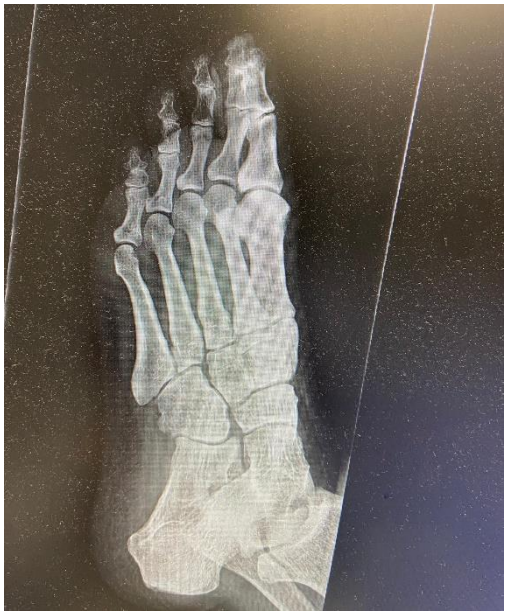

Fig 5. Left foot with no signs of acute arthritis

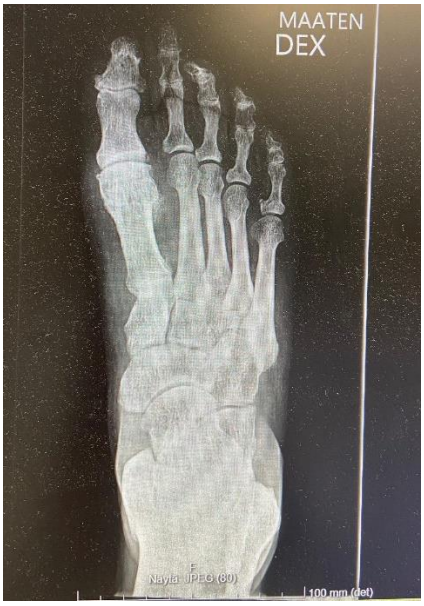

Fig 6. Right foot with no signs of acute arthritis

Subsequent Complications:
On August 28th, 2022, the patient was admitted to the dermatology department with a widespread rash. Skin biopsy confirmed interface dermatitis. Blood tests showed an elevated CRP of 193 mg/l, ESR of 110 mm/h, and leukocyte count of 14.2 E9/l. Prednisolone dosage was increased to 30 mg daily, and topical corticosteroids and antibiotics were prescribed. By the next follow-up in September, the patient's rash had resolved, and joint symptoms improved. The CRP level had decreased to 102 mg/l.

Follow-up and Long-term Management:
Urological follow-ups were scheduled every four months until March 2023, then every six months thereafter. Bladder washes using Mitomycin Emda were performed, and follow-up biopsies and CT urography revealed no recurrence of malignancy based on imaging and biopsy evidence. In November 2022, a rheumatology follow-up revealed eight inflamed joints. Prednisolone dosage was tapered to 10 mg/day, and the patient was started on Salazoprin (500 mg twice daily), with local cortisone injections to affected joints. However, the patient developed side effects from Salazoprin, necessitating discontinuation. In February 2023, methotrexate (20 mg/week) was initiated along with folic acid supplementation. Due to elevated liver enzymes in December 2023, methotrexate was temporarily discontinued and restarted at a lower dose in January 2024, once liver function normalized.

Current Status:
As of August 2024, the patient remains stable on methotrexate (5 mg/week) with no significant reactive arthritis

symptoms. A follow-up in May 2024 revealed no arthritis-related symptoms, although two inflamed finger joints were treated with local corticosteroid injections.

5. Discussion

This case underscores the complex nature of iBCG-induced reactive arthritis (ReA), a rare but significant complication of Bacillus Calmette-Guérin (BCG) therapy, which usually presents within the first six doses of treatment, as seen in our patient [3]. The patient's negative HLA-B27 status, along with negative rheumatoid factor (RF) and cyclic citrullinated peptide antibodies (CCPab), highlights the need to consider ReA even in patients without classic genetic predispositions. Although HLA-B27 positivity is a known risk factor for ReA [1], this case demonstrates that ReA can develop in genetically negative patients, reinforcing the importance of early recognition and appropriate treatment.

The patient's atypical presentation—polyarthritis affecting both small and large joints and bilateral conjunctivitis, without gastrointestinal involvement—adds further complexity. The absence of other common features of chronic ReA, such as spondylarthritis, dactylitis, or psoriasis, necessitated careful diagnostic evaluation. The multidisciplinary team's decision to discontinue iBCG therapy promptly was crucial in preventing further exacerbation of the patient's arthritis. Literature suggests that timely discontinuation of iBCG, guided by clinical judgment, is key to managing ReA, especially in cases with systemic manifestations [3,4].

The subsequent switch to Mitomycin Emda for bladder cancer treatment ensured tumor control without reactivating arthritis, supporting previous studies that advocate for alternative therapies when iBCG is contraindicated [4,5]. This decision, made by a collaborative team of urologists, rheumatologists, and infectious disease specialists, highlights the importance of a multidisciplinary approach in managing such complex cases. Follow-up examinations showed no signs of tumor recurrence, further affirming the efficacy of this treatment strategy.

The patient's persistent symptoms despite initial NSAID and corticosteroid treatment required escalation to disease-modifying antirheumatic drugs (DMARDs), a decision supported by clinical guidelines for managing chronic ReA. The patient remained on DMARD therapy for over 1.5 years, with sustained remission for six months, consistent with findings from studies indicating that long-term DMARD use may be necessary in cases with severe, polyarticular involvement [6].

Age and comorbidities, such as diabetes, likely contributed to the chronicity of the patient's ReA. Advanced age and diabetes are known to alter immune responses, leading to prolonged inflammation and delayed recovery, which may have played a role in the persistence of symptoms in this patient [1,6]. These factors underline the importance of personalized treatment plans that account for the patient's overall health and risk profile.

In conclusion, this case emphasizes the importance of a multidisciplinary approach in managing iBCG-induced ReA, particularly in patients with complex presentations and comorbidities. Early discontinuation of iBCG, careful selection of alternative cancer therapies, and the timely initiation of DMARDs contributed to the patient's favorable outcome. The prognosis for BCG-related complications is generally favorable, but long-term monitoring and individualized treatment strategies remain essential to managing chronic ReA and optimizing patient outcomes [6].

6. Conclusion

Reactive arthritis (ReA) is a rare but significant complication of intravesical Bacillus Calmette-Guérin (iBCG) therapy, which is commonly used to treat carcinoma in situ of the bladder [7]. This case emphasizes the importance of early recognition and timely discontinuation of iBCG therapy to prevent the progression of ReA, even in patients without typical genetic predispositions such as HLA-B27 positivity [1]. Close monitoring of patients during and after iBCG treatment is crucial to promptly identify complications and ensure appropriate management. Further research is needed to better understand the pathophysiology of iBCG-induced ReA and to refine strategies for identifying patients at higher risk of developing chronic disease.

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- **Informed Consent:** The written Informed consent from all the Participants were taken
- **Conflict of Interest Statement**

  The authors declared “No Conflict of Interest” with this publication.

- **Additional Information**

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