August 18

Guideline on the Management of Complications of Intravesical BCG

Chris Dawson

June 2018

Introduction

- Although usually well tolerated, intravesical BCG treatment may be followed by both local and systemic complications.

- These events are uncommon but there may be a wide range of presentations and grades of severity

- The pathogenesis of complications is still not fully understood. It is not clear if they are due to a form of hypersensitivity reaction, or due to active mycobacterial infection

- BCG works by triggering an immune response and activating the production of cytokines and other factors which cause death of tumour cells. As a result of this inflammatory response most patients experience symptoms such as

    - Urgency
    - Dysuria
    - Frequency
    - Occasionally haematuria
    - Flu-like symptoms (including low grade fever and malaise for less than 24-48 hours after instillation

- These phenomena, far from being considered as adverse events, have been regarded as a marker for an adequate anti-tumour effect exerted by the BCG
- Systemic BCG infection occurs in 3-7% of cases. The variability of clinical features and the fact that the onset of the complications can be delayed months to years after the last instillation may hinder prompt diagnosis and treatment
- The predisposing factors for BCG infection are not well characterised but are regarded as poor technique during BCG administration with traumatic instillation, or concurrent urinary tract infection as the major risk factors

Recommendations

When to suspect this complication?

The occurrence of mild voiding or flu-like symptoms within the first 24–48 hours following intravesical instillation is usually explained by the inflammatory reaction triggered by the BCG. Conversely, BCG infection should be suspected in any patient having previously received intravesical BCG who develops moderate-to-severe genitourinary or systemic symptoms (including high-grade fever for $\geq$72 hours) with no apparent cause.

How to approach the diagnosis?

- Obtain samples for microbiologic diagnosis according to the clinical manifestations (i.e., blood, sputum, bronchoalveolar lavage, abscess drainage, synovial fluid).
- Note the low positive predictive value of isolating *M. bovis* in urine culture.
- If feasible, obtain a tissue biopsy specimen for conventional culture and histologic examination (in order to identify granulomatous inflammation).
- In presence of systemic symptoms, perform a chest imaging examination (preferably CT scan over conventional radiography) to rule out miliary involvement.
- Thoroughly exclude alternative diagnoses that could account for the clinical picture.

How to treat BCG infection?

- NSAIDs or corticosteroids may be sufficient in cases of arthritis or uveitis with no microbiologic documentation of *M. bovis*.
- A 3-drug antituberculosis regimen should be used in the remaining cases with either local or systemic involvement (preferably INH, RIF, and EMB for 2 months followed by INH and RIF for $\geq$4 further months).
- Consider corticosteroid adjuvant therapy in presence of extensive miliary involvement and/or respiratory failure.
- Consider surgical treatment in presence of abscess, prosthetic or vascular infection, or genitourinary tract obstruction.

Algorithm for Diagnosis and Treatment of suspected BCG infection

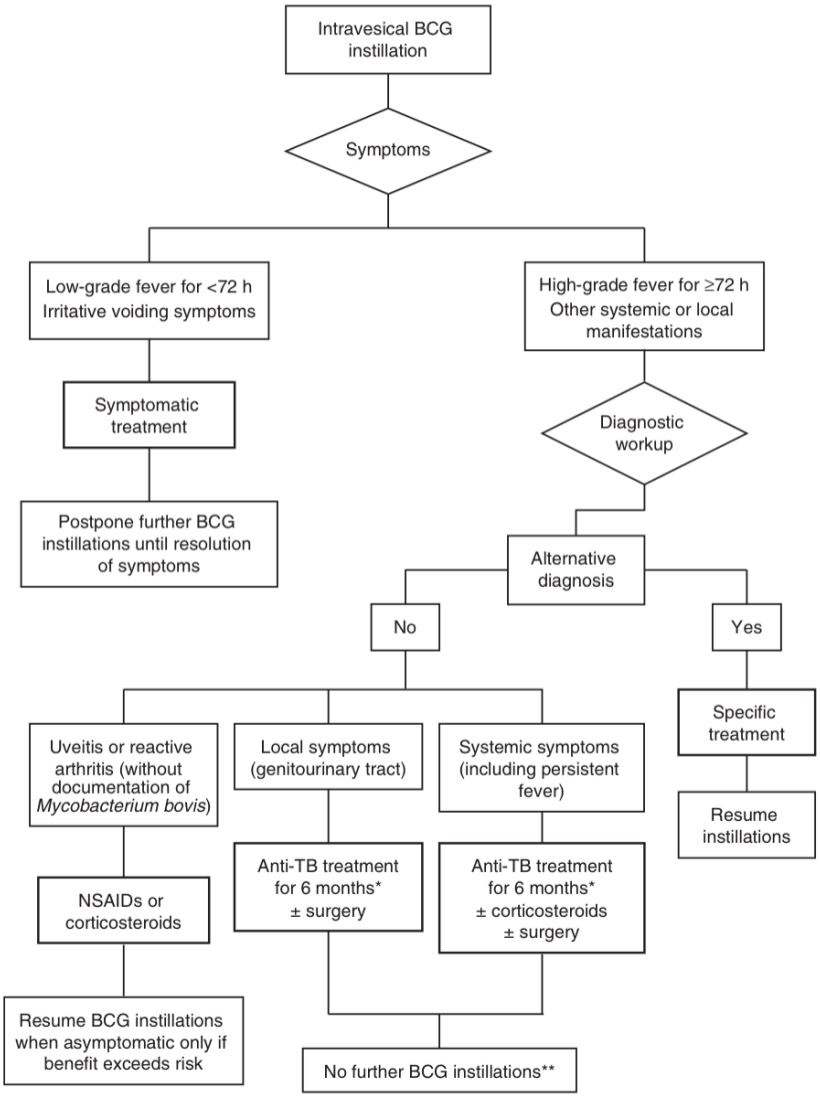

FIGURE 1. Proposal of a diagnostic and therapeutic algorithm for patients with suspected BCG infection following BCG instillation. The terms "low-grade" and "high-grade fever" refer to body temperature <37.9°C and ≥38°C, respectively. *Antituberculosis treatment should include INH, RIF, and EMB for 2 months, and INH and RIF for 4 more months. **Continuation of BCG instillations could be considered in patients with persistent fever and no miliary pattern on chest imaging, once antituberculosis treatment has been completed, and only if the expected benefits of BCG therapy clearly exceed the risks (that is, high-grade carcinoma).

Source:

Pérez-Jacoiste Asín, M.A., Fernández-Ruiz, M., López-Medrano, F., Lumbreras, C., Tejido, A., San Juan, R., Arrebola-Pajares, A., Lizasoain, M., Prieto, S. & Aguado, J.M.,

Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature,

Medicine, 93(17), pp. 236-54. 2014