The Brazilian Journal of
INFECTIOUS DISEASES

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Letter to the Editor

Disseminated Bacille Calmette-Guérin disease in immunocompetent adult patients

Dear Editor,

Intravesical administration of Bacille Calmette-Guérin (BCG), with live attenuated strain of *Mycobacterium bovis*, is the mainstay therapy of superficial bladder cancer. BCG disease is uncommon in immunocompetent adults, accounting for less than 5% of patients[1] who underwent intravesical administration of BCG for superficial bladder cancer. It may present with a wide spectrum of clinical presentation, severity and variability of onset after the first intravesical administration of BCG immunotherapy. Therefore, it poses a diagnosis challenge for clinicians. We report two cases of disseminated BCG, a rare complication of intravesical BCG administration, which presented with distinct features regarding time between the first intravesical administration and onset of presentation and clinical manifestations.

Case 1

A 66-year old man, with a past history of Pott disease in his childhood, underwent intravesical administration of BCG for eight weeks. One week after the last treatment he presented with fever and urinary symptoms. Although antibiotic was initiated, the patient progressed with clinical worsening and onset of respiratory symptoms. A thoracic CT revealed ground-glass opacification throughout both lungs. Due to his past history of tuberculosis and imagiologic features he was admitted to the hospital for further investigation. The latter was unremarkable including both bronchial aspirate and urine mycobacterial culture which returned negative. Since there was a close temporal relationship between the BCG instillation and the development of symptoms and no other cause was identified, a systemic BCG disease with pneumonitis was assumed and 6-month triple therapy was initiated. However, and due to persistent fever despite treatment, corticosteroids were introduced with posterior apyrexia and clinical and radiological improvement.

Case 2

A 63-year-old man, presented with fever with no apparent focus and elevated hepatic enzymes only one day after the first intravesical treatment with BCG. The patient was started on empiric antibiotics with no clinical or laboratory improvement. Tumor markers, serum antibodies and serology were unremarkable and microbiologic exams returned negative. Since the patient evolved with pancytopenia a myelogram was performed that revealed phagocytosis phenomena. In the absence of response to antibiotics and since no other cause was identified for the presented features, disseminated BCG infection with hemaphagocytic syndrome was assumed and triple therapy was administered. Soon after, hepatic enzymes elevated and a non-hepatotoxic regimen was temporarily made. After full laboratory recovery, triple therapy was introduced without new toxicity and with clinical improvement.

Complications associated with BCG intravesical instillation are very uncommon and highly variable, ranging from prostatitis to pneumonitis and sepsis. They are classified as local disease, if manifestations are limited to genitourinary tract, or systemic if disseminated BCG disease, persistent fever with bone marrow, hepatic or pulmonary involvement are demonstrated.[1]

Gonzalez et al. stratified BCG disease spectrum into early and late-presentation disease if manifestations appear within three months after the first instillation or one year after the first BCG treatment, respectively.[2] There is a significant overlap between the two classifications since early-presentation disease is generally characterized by systemic manifestations and late-presentation disease is almost exclusive of genitourinary tract.

Pathogenesis is not fully known[1] but some authors consider that BCG disease is not unequivocally caused by an active infection, but also by some degree of hypersensitivity reaction to *Mycobacterium bovis*. This is particularly important

in early-presentation disease where hypersensitivity features predominate and significant improvement occur when corticosteroids are introduced.[3] First-line treatment consist in a combination of rifampicin, isoniazid, and ethambutol[4] although there is no consensus regarding its duration.[1]

Diagnostic criteria are not established but response to antituberculosis treatment, with or without corticosteroids, and the exclusion of other causes is considered the cornerstone for BCG disease diagnosis, since cultures often return negative.[1]

Although the patients generally display a good prognosis with a mortality rate around 5%, in patients with 65 years or older disseminated BCG disease or with vascular involvement have higher mortality.[1]

In conclusion, the reported cases are representative of the highly variable spectrum of BCG disease manifestations and, although they occurred during BCG treatment which allowed a prompt diagnosis and treatment, sometimes a high index of suspicion based on history of previous exposure to BCG and clinical awareness is needed since complications have been diagnosed in up to 17 years after BCG intravesical administration.[1]

Conflicts of interest

The authors declare no conflicts of interest.

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Received 10 March 2016
Accepted 24 March 2016

http://dx.doi.org/10.1016/j.bjid.2016.03.009
Available online 4 June 2016