

Intra-vesical BCG induced granulomatous hepatitis and disseminated Koch's: Our experience

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ABSTRACT

Bacille Calmette-Guerin (BCG) vaccine, developed by Calmette and Guerin at Institute Pasteur (Lille, France), is a live-attenuated *Mycobacterium bovis* strain. There are many therapeutic uses of the species have been described, Intravesical BCG has been established as an effective treatment of superficial bladder cancer. A 66-year old gentleman with newly diagnosed superficial high-grade papillary transitional cell carcinoma involving lamina propria (T1) of the bladder underwent 3 cycles of intravesical BCG. First 2 cycles were uneventful and tolerated well. After 3rd BCG cycle, patient developed granulomatous hepatitis with disseminated Koch's. BCG-induced sepsis after intra-vesical instillation for bladder cancer is a rare complication. Pathophysiology remains largely unknown, but BCG's low virulence suggests that immunological hypersensitivity reaction probably plays a role. There have been no prospective studies to evaluate the optimal treatment for BCG infection.

Keywords: Bacille Calmette-Guerin (BCG), *Mycobacterium bovis* strain, granulomatous hepatitis.

Intravesical instillation of bacilli Calmette-Guerin (BCG) has been established as an effective modality for superficial bladder cancer. Complication of intravesical BCG ranges from dysuria to disseminated Koch's. Complications can appear early (within 3 months after instillation) or years after first BCG treatment [1]. Early presenting disease is characterized by generalized symptoms, hepatitis and pneumonitis. Late presenting disease is usually localized, with no systemic manifestations and the infection involves often the genitourinary tract and other sites that are typical for reactivation of mycobacterial disease, such as the vertebral spine or retroperitoneal tissue [1]. Certain aspects concerning its diagnostic and treatment are still debatable [2]. We herein report 65 year male developing granulomatous hepatitis with disseminated Koch's secondary to Intravesical BCG.

CASE REPORT

A 66-year-old gentleman with newly diagnosed superficial high-grade papillary transitional cell carcinoma involving lamina propria (T1) of the bladder underwent 3 cycles of intravesical BCG. First 2 cycles were uneventful and tolerated well. After 3rd BCG cycle, patient presented with fever, and dysuria. Initially, he was treated as grade 1 BCG adverse reaction with supportive treatment. After few days down the line, patient presented with jaundice, on and off fever, joint pain, and malaise. On investigations, liver function test was deranged (Total serum bilirubin-6.5mg/dl, indirect component-3.8, SGPT-650U, SGOT-540U, Alkaline phosphatase-170IU/L) and had leukopenia (WBC-2100) routine aerobic urine culture and blood culture did not yield any pathogen. Chest X-ray was unremarkable. Ultrasonography of abdomen suggestive of

hepatomegaly with altered ecotexture of liver parenchyma. Patient underwent Contrast Enhanced CT scan of Abdomen and pelvis; suggest hepatomegaly, heterogeneous liver parenchyma with gall bladder edema.

In view of deranged LFT and CT scan findings, CT guided liver biopsy was performed which showed granulomatous hepatitis with non-caseating granuloma (fig. 1) suggestive of tubercular etiology. Worsening pancytopenia prompted a bone marrow biopsy that revealed multiple large noncaesating granulomas.

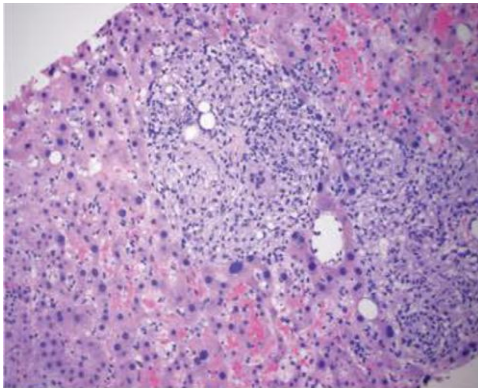


Fig 1: liver biopsy showing granulomatous hepatitis With multinucleate giant cell epithelioid granuloma

Liver biopsy tissue and bone marrow biopsy tissue also sent for AFB culture and TB PCR. TBPCR was negative. AFB cultures were also negative after 8 weeks of incubation (BD MGIT 320 TB SYSTEM). In view of biopsy report, patient was put on anti-koch's therapy for 6 month (Isoniazid 5mg/kg/day; pyrazinamide 50mg/kg/day; ethambutol 15mg/kg/day) and short course of corticosteroid (prednisolone 20mg twice a day and tapered gradually). Patient gradually improved and his fever subsided within several day of anti-tuberculosis therapy.

DISCUSSION

The intravesical administration of BCG has become modality of treatment for superficial bladder cancer [3, 4]. Bacille Calmett-Guerin (BCG) is a low virulence mycobacteria originated from successive culture of mycobacterium bovis [5]. Initially BCG was used to vaccinate the cattle to prevent tuberculosis and later used in humans [1].

Mechanism of action of BCG in bladder cancer is largely unknown and probably is specific anti-BCG cell mediated immunity, inducing the production of large

amounts of cytokines that draw cytotoxic activity by natural killer cells against transitional cancer cells [6]. The pathogenic mechanism underlying the development of complications is unclear, but BCG's low virulence suggests that immunological hypersensitivity reaction probably plays a role. Complication ranges from lower urinary tract symptoms (LUTS) to organ involvement and disseminated infection. Localized and late infection can involve bone, muscle, vessels (aneurysms and pseudoaneurysm), eyes (granulomatous anterior uveitis, endophthalmitis, and autoimmune retinopathy) and genitourinary tract (cystitis, sterile pyuria, nephritis and epididymo-orchitis) [7-9]. Diagnosis of BCG related sepsis frequently challenging since symptoms are indistinct from the other causes of sepsis like bacteremia, urinary tract infections, respiratory infections (pneumonia), viral hepatitis, etc.

Pre-existing cystitis or persistent hematuria following transurethral resection of bladder tumor is main predisposing factor [8]. Lamm *et al.* [10] have suggested that fever or shivering during or shortly after BCG intravesical instillation may be predictive for the risk of developing severe infection. Previous tuberculosis or latent tuberculosis infections do not seem to be higher risk of BCG complications [1]. It is known that diabetic patient have greater risk of developing tuberculosis and that poor glycemic control is associated with complication from intravesical BCG [1]. Quanti FERON-TB Gold test positivity only indicates previous contact with Mycobacterium tuberculosis and it is not useful for diagnosis of BCG complications. Staining of specimens for acid-fast bacilli, cultures and PCR testing for mycobacterial DNA should be performed in any patient with suspected disseminated BCG infection, even though all of these procedures can be negative in some cases.

Concurrent prophylactic use of isoniazid with intravesical instillation has largely been unsuccessful. On the contrary, prophylactic use of fluoroquinolones may be more effective [11, 12]. Some authors recommend screening with Mantoux test. Active tuberculosis has to be ruled out. Use of corticosteroid is convincing in early course of therapy.

CONCLUSION

Post intravesical BCG complication and adverse reactions has wide range of presentation from dysuria to

disseminated sepsis. Even initial cycles were well tolerated; subsequent dosage can leads to complications. Usually the symptomatology is nonspecific, hence need high index of suspicion for the diagnosis and to prevent further complications. Systemic 3 drug anti-tuberculous therapy has well proven role in literature for post BCG sepsis.

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