Medicinal chemistry
ISSN: 2161-0444

Piñero et al., Med chem 2014, 4:7
DOI: 10.4172/2161-0444.1000190

Short Review Open Access

A Case of Granulomatous Hepatitis and Pancytopenia Secondary to Bacillus Chalmette Guerin Immunotherapy (BCG)

Federico Piñero*, Sebastián Marciano and Adrián Carlos Gadano

Liver Unit, Hospital Italiano, Buenos Aires, Argentina

Abstract

We describe the case of a 69-year-old female who developed pancytopenia and acute hepatitis as a complication of intravesical BCG instillations for the treatment of bladder urothelial carcinoma. Liver and bone marrow biopsies revealed multinucleated giant epithelioid cells and non-caseating granulomas. Treatment with antituberculosis drugs achieved complete resolution. This case illustrates an infrequent but severe complication of intravesical BCG instillations, whichcan be successfully treated without steroids.

Keywords: Jaundice; Bone Marrow; Tuberculosis; Bladder cancer

Abbreviations: ALT: Alanina Aminotransferase; ALF: Alkaline Phosphatase; BCG: Bacillus Calmette Guerin; GGT: gamma glutamyl transpeptidase; HIV: Human Immunodeficiency virus; Ht: Hematocrit; Hb: Hemoglobin; PCR: Polymerase Chain Reaction; WBC: White Blood cell Count; ESR: Erithro-sedimentation rate

Intravesical Bacillus Calmette Guerin (BCG), a live attenuated strain of Mycobacterium bovis, is currently the treatment of choice for superficial bladder urothelial carcinoma [1]. This therapy eradicates urothelial tumors in 60-70% of the patients [2]. It is known that BCG precludes a local anti-cancer effect by immune mediated mechanisms. This induced cytotoxicity is predominantly mediated by activation of T cells and natural killer cells [3]. Several adverse events such as generalized symptoms, fever, malaise and fatigue are observed in a significant proportion of patients. However, distantnon-caseating granulomatous reaction and organ involvement is an infrequent but serious complication. Severe lung, liver, bone marrow and soft tissue compromise have been reported [4-7]. We describe the case of an adult patient who developed acute hepatitis and pancytopenia secondary to intravesical BCG instillations.

A 69-year-old female was admitted for malaise, fatigue, weight loss, persistent fever and jaundice that gradually developed 12 weeks after the first intravesical BCG instillation for the treatment of a multifocal high-grade urothelial carcinoma. On physical examination, jaundice and hepatosplenomegaly were observed. Noother findings were present. The admission laboratory revealed the following abnormalities: total bilirubin 10.5 mg/dL; alanine aminotransferase637 UI/L; alkaline phosphatase 799 UI/L; hemoglobin 9.8 g/dL; white blood cell count 3,150 /mm^3; platelets 82,000 /mm^3 (Table 1). Viral hepatitis A, B and C, cytomegalovirus, Ebstein Barr virus,herpes viruses and HIV were negative. Additionally, drug toxicity and autoimmune hepatitis were ruled out. Blood and Urinary cultures were negative. A contrast enhanced lung and abdominal computed tomography confirmed the hepatosplenomegaly, without other pathological findings. Liver and bone marrow biopsies were performed revealing multinucleated giant epithelioid cells and non-caseating granulomas. Ziehl Neelsen stains and Polymerase Chain Reaction (PCR) for mycobacteria were negative in both tissues.

Isoniazid, Rifampicine and Ethambutol were started for the treatment of disseminated BCG. After 5 days of treatment, fever resolved. However, liver function tests worsened thereafter. We decided to switch to Levofloxacin plus Ethambutol suspecting hepatotoxicity. The patient was treated for six months.After treatment complete clinical and laboratory resolution was achieved (Table 1).

Disseminated BCG with severe involvement of the liver and bone marrow is very infrequent. Even though the exact mechanism underlying organ dysfunction is unknown, two mechanisms are postulated: hypersensitivity reaction or direct hematogenous spread of BCG [3].Both mechanisms most likely occur simultaneously and are supported by the finding of granulomas in the affected tissues. The fact that Mycobacterium bovis is not consistently identified in biopsy specimens could be related to the low number of organisms present in the samples and culture related issues.

There are no clear risk factors for disseminated BCG. However, the presence of urogenital epithelium disruptions might confer some risk. In these cases, BCG instillation should be deferred. Our patient was not suspected to be at risk since no difficult bladder catheterizations were performed, or urinary tract infections were observed during the prior months. As it was previously reported, our patient developed the

Laboratory	Pre BCG	Post BCG	After Treatment
Ht %/Hb g/dl	41 / 14	28 / 9.8	39 / 13
WBC (mm^3)	6580	3150	5360
Platelets	288000	82000	133900
ESR mm/h	9	14	6
Bilirubin (mg/dl)	0.6/0.10	10.5/6.4	0.7 / 0.3
Albumin (g/dl)	3.9	2.2	3.6
Protrombine time %		82	
AST/ALT (UI/l)	32/35	563/637	33/39
ALF/GGT (UI/l)	69	799 / 175	77
Creatinine (mg/dl)	0.8	0.7	0.7

Note: Normal values: Ht 35-45%, Hb 13-15 gr/dl. WBC 4000-10000 /mm^3. ESR 0-15 mm/hour. AST and ALT 10-40 UI/L. ALF 30-100 UI/L, GGT 10-50 UI/L.
Abbreviations: Ht, Hematocrit. Hb, Hemoglobin. WBC, white blood count. ESR, erithro-sedimentation rate. AST, Aspartate aminotransferase. ALT, Alanine aminotransferase. ALF, alkaline phosphatase. GGT, gammaglutamil transpeptidase.

Table 1: Laboratory values before and after Immunotherapy with Bacillus Chalmette Guerin Immunotherapy (BCG).

***Corresponding author:** Federico Piñero, MD, Liver Unit, Hospital Italiano, Buenos Aires, Argentina Av Juan Domingo Perón 4190 / C1199ABD/ Bs As / Argentina, Tel/Fax: (540230) 448-2236; E-mail: fedepinero@gmail.com

Received February 21, 2014; **Accepted** March 22, 2014; **Published** March 24, 2014

Citation: Piñero F, Marciano S, Gadano AC (2014) A Case of Granulomatous Hepatitis and Pancytopenia Secondary to Bacillus Chalmette Guerin Immunotherapy (BCG). Med chem 4: 531-532. doi:10.4172/2161-0444.1000190

clinical picture 12 weeks after the first BCG instillation. However, this can occur earlier or even after one year since the first instillation [4,5,7-11].

Antituberculous are the recommended treatment for disseminated BCG. Controversy exists regarding the concomitant treatment with or without steroids.Mycobacterium bovis is susceptible to most of the antituberculous drugs with the exception of pyrazinamide and cycloserine. In cases of extra-vesical involvementa multidrug antibiotic therapy is recommended for at least three to six months [9,10]. We decided to start empirical treatment with Isoniazid, Rifampicine and Ethambutol. However, we rapidly switched it to Levofloxacin and Ethambutol when hepatotoxicity was suspected. Even though some experts suggest treatment with steroids [10,11], we decided to evaluate the initial response to antibiotics alone, in order to avoid steroids adverse events. Since a rapid improvement was observed, steroids were not further indicated.

In conclusion, Levofloxacin and Ethambutol without steroids might be an adequate treatment for disseminated BCG. We believe this approach is especially adequate for patients with severe liver involvement. Moreover, it might be advisable to save steroids for cases without adequate initial response to antituberculous treatment.

References

1. Morales A, Eidinger D, Bruce AW (1976) Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 116: 180-183.
2. Lamm DL (2000) Efficacy and safety of bacilleCalmette-Guerin immunotherapy in superficial bladder cancer. Clin Infect Dis 31 Suppl 3: S86-90.
3. Prescott S, Jackson AM, Hawkyard SJ, Alexandroff AB, James K (2000) Mechanisms of action of intravesicalbacilleCalmette-Guerin: local immune mechanisms. Clin Infect Dis 31 Suppl 3: S91-93.
4. Thompson D, Cumming J (1990) Granulomatous hepatitis following intravesical BCG therapy. Br J Urol 66: 432-433.
5. Steg A, Leleu C, Debre B, Boccon-Gibod L, Sicard D (1989) Systemic bacillus Calmette-Guerin infection in patients treated by intravesical BCG therapy for superficial bladder cancer. Prog Clin Biol Res 310: 325-334.
6. Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, et al. (1992) Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 147: 596-600.
7. Proctor DD, Chopra S, Rubenstein SC, Jokela JA, Uhl L (1993) Mycobacteremia and granulomatous hepatitis following initial intravesical bacillus Calmette-Guerin instillation for bladder carcinoma. Am J Gastroenterol 88: 1112-1115.
8. Lamm DL (2000) Efficacy and safety of bacilleCalmette-Guerin immunotherapy in superficial bladder cancer. Clin Infect Dis 31 Suppl 3: S86-90.
9. Viallard JF, Denis D, Texier-Maugein J, Parrens M, Faure I, et al. (1999) Disseminated infection after bacilleCalmette-Guerin instillation for treatment of bladder carcinoma. Clin Infect Dis 29: 451-452.
10. Fradet V, Gaudreau C, Perrotte P, Cote J, Paquin JM (2007) Management of hepatic granulomatous tuberculosis complicating intravesical BCG for superficial bladder cancer. Can UrolAssoc J 1: 269-272.
11. Gonzalez OY, Musher DM, Brar I, Furgeson S, Boktour MR, et al. (2003) Spectrum of bacilleCalmette-Guerin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis 36: 140-148.