Difficulties in Diagnosing and Treating Disseminated Bacillus Calmette-Guérin (BCG) Infection After Intravesical BCG Therapy in a Patient with Liver Cirrhosis: A Case Report

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Data Collection B
Statistical Analysis C
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Patient:	**Male, 62-year-old**
Final Diagnosis:	**BCGitis**
Symptoms:	**Fever • general fatigue**
Medication:	**—**
Clinical Procedure:	**Bone marrow biopsy • liver biopsy**
Specialty:	**Infectious Diseases • General and Internal Medicine**

Objective: Rare coexistence of disease or pathology

Background: Bladder cancer (BC) is the second most common cancer involving the urinary system. In non-muscle-invading BC, transurethral resection of a bladder tumor followed by intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) is the usual treatment. Disseminated (or systemic) BCG infection (BCGitis) represents the most severe adverse effect of intravesical BCG therapy, presenting with high-grade fever, with or without symptoms in the urinary tract, leading to severe sepsis and death if left untreated. The treatment of choice consists of isoniazid, rifampicin, and ethambutol (with or without corticosteroids) for 6 months, and the recovery rate is extremely high. Given the fact that these drugs are hepatotoxic, treating a patient with liver cirrhosis is challenging.

Case Report: We present a patient with a medical history of BC treated with transurethral resection and intravesical BCG therapy, presenting with fever, transaminasemia, and generalized weakness. Liver and bone marrow biopsies revealed liver cirrhosis and granulomas in both organs. A diagnose of BCGitis was made and the patient was treated with isoniazid, rifampicin, and ethambutol; rifampicin was substituted with moxifloxacin after 1 month due to worsening of liver laboratory results, and moxifloxacin was substituted with levofloxacin later on due to tonic-clonic seizures. The patient was treated for 4 more months with levofloxacin and for 7 more months with isoniazid and ethambutol, with no other adverse effects, preserving liver function and achieving cure of BCGitis.

Conclusions: We present the case of a cirrhotic patient presenting with fever and deterioration of liver laboratory results, found to have BCGitis, and discuss possible difficulties in diagnosing and treating such patients.

Keywords: BCG and Salmonella Infection, Disseminated • Isoniazid • Liver Cirrhosis • Rifampin

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Background

Bladder cancer (BC) is the ninth most common malignancy worldwide and the second most common one involving the urinary system; however, in middle-aged and elderly men, BC is the second most common malignancy, after only prostate cancer [1-4]. The majority (75-80%) of BCs are non-muscle-invasive (NMIBC) and the treatment strategy includes transurethral resection of bladder tumor (TURBT), usually followed by intravesical immunotherapy with Bacillus Calmette-Guérin (BCG), which is an attenuated strain of *Mycobacterium bovis*, leading to eradication of residual tumor, delay of disease progression, reduction in need for cystectomy, and prolonging survival [5-8].

Despite the efficacy of intravesical BCG therapy, most patients report local, mild, early complications after instillation, like cystitis (81%), macroscopic hematuria (15%), and urination frequency [9-13]. Although BCG therapy is usually well-tolerated, local and systemic complications can occur [9,10,13]. Local complications involve the genitourinary tract in the form of epididymitis and granulomatous prostatitis, while systemic ones include short-term fever in 5-30% of patients, as well as allergic reactions, reactive arthritis, drug-induced liver injury, granulomatous hepatitis, and nephritis, all with a prevalence of less than 1% [10,12-15].

Disseminated (or systemic) BCG infection (BCGitis) is the most severe adverse effect of intravesical BCG therapy. BCGitis has an incidence of 3% to 7% and presents with high-grade fever and/or various organ involvement with or without symptoms from the urinary tract, leading to severe sepsis and death if left untreated [9,10,16-19]. BCGitis should be suspected in any patient who develops moderate-to-severe genitourinary or systemic symptoms following ≥1 instillation of intravesical BCG when no alternative diagnosis can be established. Microbiological documentation of the infection is required for definitive diagnosis; however, it has low sensitivity, and when histopathology is available, granulomas are commonly found [17]. Due to the aforementioned difficulties, empirical treatment is commonly started upon suspicion; in this setting, improvement of symptoms after treatment initiation is mandatory for establishing the diagnosis [9,14,17]. The treatment of choice for BCGitis consists of isoniazid, rifampicin, and ethambutol (alone or in combination with corticosteroids) for 6 months, and the recovery rate is extremely high [17,20-24]. Unfortunately, all of the above-mentioned drugs are hepatotoxic and can cause liver dysfunction, a problem most often encountered in cirrhotic patients [25]. Here, we report the first case of a cirrhotic patient diagnosed with BCGitis with liver and bone marrow involvement, and we discuss potential therapeutic challenges related to the co-existence of BCGitis and liver cirrhosis.

Case Report

A 62-year-old non-smoker, male patient was admitted to Laiko General Hospital in Athens, Greece, due to a 6-month history of fever and generalized weakness. He had a medical history of non-muscle-invading BC, diagnosed 2 years before presentation and treated with transurethral resection (TURBT) followed by 6 weeks of intravesical therapy with BCG. His medical anamnesis was also notable for coronary artery disease and dyslipidemia. He reported consuming moderate amounts of alcohol daily for the past 20 years, stopping about 4 months ago.

Approximately 2 months before presentation, the patient was hospitalized in another hospital due to fever up to 38.5°C, anemia, and generalized weakness. During his stay there, a cystoscopy was performed that revealed BC recurrence and he received a second course of 6 weekly intravesical BCG infusions. His fever was attributed to BC recurrence, so no further diagnostic evaluation was performed at that time. Due to fever persistence and generalized weakness after treatment completion, he was admitted to our hospital for further evaluation and management.

Upon admission, the patient had an axillary temperature of 37.5°C, a blood pressure of 110/80 mmHg, a heart rate of 93 beats per minute, an oxygen saturation of 89% on ambient air, and a respiratory rate of 22 breaths per minute. On physical examination, he was mildly lethargic with no focal neurological deficits or signs. Lung auscultation revealed bilateral crackles and abdomen examination revealed hepato-splenomegaly with no pain during palpation. The rest of his clinical examination was unremarkable.

Routine laboratory blood results showed mild pancytopenia, elevated serum gamma glutamyl-transferase (GGT) and alkaline phosphatase (ALP) levels, as well as mildly elevated serum C-reactive protein (CRP) aspartate (AST) and normal alanine (ALT) aminotransferases levels (**Table 1**). Urinary testing revealed pyuria and mild hematuria, whereas the urine culture was sterile.

A chest X-ray was performed that demonstrated bilateral pleural fluid accumulation, while abdominal ultrasound revealed a cirrhotic liver, splenomegaly, and mild ascites. No focal hepatic lesions were found. Computed tomography (C/T) scans of the chest and abdomen confirmed the aforementioned findings, without revealing portal or hepatic veins thrombosis.

Ascitic fluid analysis was consistent with portal hypertension-induced ascites (serum-to-ascites albumin gradient of 2.1 g/dl), with no signs of infection or malignancy. Testing for hepatitis B and hepatitis C infections, Leishmaniasis, Q fever, and Brucellosis were negative, as were anti-nuclear, anti-smooth muscle, and anti-mitochondrial antibodies in serum. Serum iron studies, ferritin, ceruloplasmin level, and 24-h urine copper

Table 1. Laboratory results on admission and throughout the follow-up period. Time-points of follow-up as follows: "First follow-up" at one month after hospital discharge, "second follow-up" at one month after levofloxacin initiation and "end of follow-up" at 3 months after treatment completion.

	Admission	Hospital exit	First follow-up	Second follow-up	End of follow-up	Normal range
Hb (g/dl)	13	13	14.2	13	14.3	14-18
WBC (neut/lymph/mono)	3540 (62/27/0.3)	2960 (55/30/0.4)	3510 (72/19/8)	3200 (56/31/12)	5300 (51/40/6)	4500-11000
PLT (K/μL)	119	72	94	107	165	140-440
INR	1.13	1.1	1.4	1.3	1.02	0.85-1.15
AST (IU/ml)	59	35	50	46	22	11-38
ALT (IU/ml)	31	22	30	24	17	11-43
GGT (IU/ml)	258	473	810	262	75	10-60
ALP (IU/ml)	285	401	409	124	52	25-129
Sodium (mEq/L)	134	131	133	140	142	137-150
Potassium (mEq/L)	3.9	3.6	4.2	4	4.4	3.5-5.1
Urea (mg/dl)	48	30	36	26	37	10-50
Creatinine (mg/dl)	0.82	0.49	0.79	0.80	0.98	0.6-1.4
CRP (IU/ml)	25	14	18	6	2	<5
Total bilirubin (mg/dl)	0.96	1.2	0.9	1.02	0.4	0.1-1.2
Direct bilirubin (mg/dl)	0.45	0.63	0.4	0.6	0.18	0.1-0.3

Hgb – hemoglobin; Hct – hematocrit; PLT – platelets; INR – International Normalized Ratio; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma glutamyl-transferase; ALP – alkaline phosphatase; CRP – C-reactive protein.

excretion were within normal limits. Quantiferon testing was negative and an echocardiogram was also normal.

Due to pancytopenia, a bone marrow biopsy was performed. Additionally, a liver biopsy was performed due to progressive deterioration of liver biochemistry results. The bone marrow biopsy revealed non-caseating granulomas and Langhans giant cells (**Figure 1A, 1B**), whereas the liver biopsy showed bridging fibrosis along with multiple, small, non-caseating granulomas and mild portal and lobular inflammation (**Figure 2A, 2B**).

Given the recent history of intravesical BCG therapy and the histological findings of liver and bone marrow biopsies, a diagnosis of BCGitis was made. The patient was started on isoniazid, rifampicin, and ethambutol, had a rapid resolution of symptoms, and was discharged from the hospital 4 days after treatment initiation.

One month after discharge, the patient had further deterioration of GGT and ALP serum levels (**Table 1**), so rifampicin was discontinued and moxifloxacin was initiated instead. Four

weeks after treatment modification, the patient experienced an episode of loss of consciousness with gaze fixation that resolved spontaneously a few minutes later. A brain magnetic resonance imaging (MRI) was ordered, which revealed no pathology, and moxifloxacin was substituted for levofloxacin.

During his next visits, the patient had a slow improvement of liver biochemistry and overall status, so levofloxacin was continued for 4 additional months and isoniazid and ethambutol was continued for 7 additional months (9 months in total). Three months after treatment completion, the patient was afebrile, in good overall status, with normal levels of serum AST, ALT, and ALP, and only mildly elevated GGT levels, with no progression of liver cirrhosis status as defined by MELD and CTP scores.

Discussion

We present the case of a patient with a history of BC treated with intravesical BCG who was concurrently diagnosed with disseminated BCGitis (with bone marrow and liver involvement).
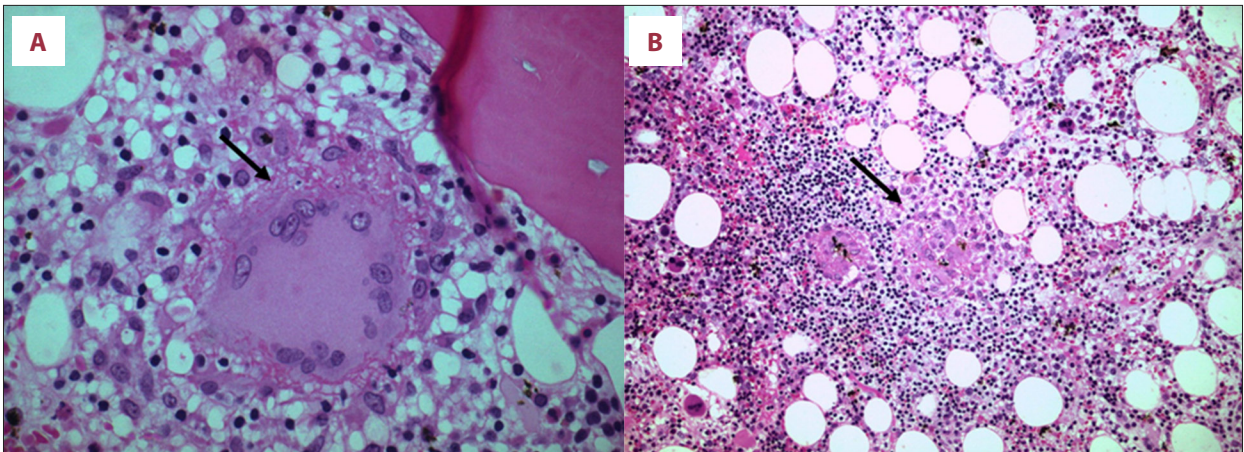
Figure 1. Bone marrow biopsy. (**A**) Langhans-type giant cell in a paratrabecular position (arrow) (HE ×400). (**B**) A collection of histiocytes forming a non-caseating granuloma in the center (arrow) (HE ×100).
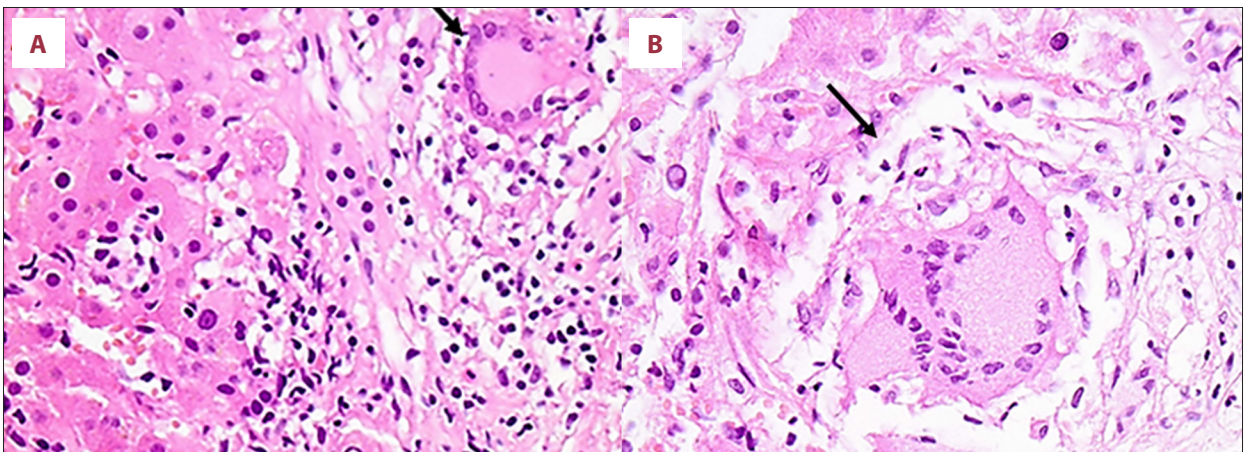

Figure 2. Liver biopsy. (**A**) Small histiocytic granuloma with a Langhans-type giant cell in a portal tract (arrow). Mild portal inflammation is also evident (HE ×200). (**B**) Small histiocytic granuloma with a Langhans-type giant cell located in the parenchyma (arrow) (HE ×400).

BCGitis is a well-known adverse effect of intravesical BCG infusions. Incorrect instillation of BCG with iatrogenic trauma or concurrent urinary infection, previous urinary interventions, and the presence of breaches in the bladder are the most common risk factors [11,16,17,26-29]. Since the attenuated *Mycobacterium bovis* is a live strain preserving a degree of virulence, instillation of BCG in a patient with immunosuppression also carries a risk of BCGitis [30-33]. In our case, the patient was diagnosed with liver cirrhosis, a condition in which reduction in the reticuloendothelial system cell mass (Kupffer cells and sinusoidal endothelial cells) and porto-systemic shunts lead to immune system dysfunction, making BCGitis a possible complication [34-37].

BCGitis should be suspected in every patient having received intravesical BCG infusions, presenting with fever and/or organ involvement, with or without symptoms in the genitourinary tract. However, establishing the diagnosis can be quite challenging, needing, apart from the history of BCG exposure, exclusion of all other causes of fever, as well as clinical improvement after treatment initiation, since microbiological and/or histopathological documentation is rarely feasible. Nevertheless, in our patient, the clinical suspicion was supported by liver and bone marrow histology, which found non-caseating granulomas. Interestingly, unlike tuberculosis, infection with *M. bovis* leads to non-caseating granulomas [38,39]. Moreover, Quantiferon testing is not helpful, since interferon-gamma release assays use stimulating antigens that are present in *M. tuberculosis* and pathogenic *M. bovis* strains but absent in *M. bovis* BCG [40].

Initial treatment for BCGitis consists of isoniazid, rifampicin, and ethambutol, alone or in combination with corticosteroids, for 6 months, and the infection usually resolves with no sequelae. Corticosteroid use is controversial and is usually reserved for severe cases of miliary involvement and respiratory

failure. Treating a cirrhotic patient poses many challenges, since anti-tuberculosis treatment is accompanied with significant hepatotoxicity. Isoniazid is metabolized in the liver, leading to hepatotoxic metabolites in the form of acetyl hydrazine and hydrazine, which cause hepatocellular steatosis and necrosis [25,41,42], with an incidence of 0.6% when used as monotherapy [25,43], although severe isoniazid-induced hepatotoxicity seems to be heavily under-reported [44]. Rifampicin usually causes transient transaminitis that is thought to be benign; however, it has also been associated with centrilobular parenchymal necrosis and elevation of conjugated bilirubin due to cholestasis [45,46], leading to a 4-fold higher incidence of hepatotoxicity when used in combination with isoniazid [47]. Interestingly, according to Park et al, this incidence increases to 17% when a liver disease coexists, irrespective of the presence or absence of cirrhosis [48]. In contrast, ethambutol is not associated with clinically important hepatotoxic effects [25,49].

Due to these adverse effects, treating a patient with liver cirrhosis for BCGitis involves the risk of decompensation or even acute-on-chronic liver failure [25]. According to WHO guidelines, the number of hepatotoxic agents that can be used in a cirrhotic patient depends on the severity of liver disease [50]. Regarding anti-tuberculosis (TB) drugs, some authors propose the use of isoniazid and rifampicin for patients with Child-Pugh ≤7, isoniazid or rifampicin for Child-Pugh 8-10, and none of the hepatotoxic anti-TB drugs for patients with Child-Pugh ≥11 [51,52]. Since hepatotoxicity usually occurs during the first 2 months of treatment, close monitoring of transaminases' levels is mandatory in that period [42,51,52].

Due to the aforementioned problems, our patient was started on isoniazid, rifampicin, and ethambutol, according to guidelines. The patient had a deterioration of liver enzymes serum levels during his first follow-up visit, so rifampicin was changed to moxifloxacin.

With regards to fluoroquinolones (FQs), which are the most commonly used second-line agents, a large case-control safety study showed no significant association between moxifloxacin and levofloxacin exposure and hepatotoxicity risk, while Ho et al found that introduction of FQ in patients with hepatitis induced by first-line agents did not cause additional hepatotoxicity [53,54]. On the contrary, Paterson et al found increased risk of acute liver injury among older patients [55]. Given these results, FQs may be a reasonable option in patients with hepatitis after exposure to first-line anti-TB agents.

Even though this regimen was considered to be safe for a cirrhotic patient, our patient developed seizures attributed to moxifloxacin treatment, which resolved after discontinuation of the medication. Although levofloxacin, ofloxacin, and moxifloxacin have the lowest potential of inducing central nervous system adverse events among the FQ available, case reports exist attributing episodes of seizures to moxifloxacin treatment [56-59]. Our patient's regimen was once more changed and levofloxacin was initiated instead of moxifloxacin, without other significant toxicities.

Although the usual treatment duration for BCGitis is 6 months, no treatment recommendations exist regarding immunocompromised patients, since most data come from children with primary immunodeficiency syndromes for which regimens with various durations were used [60-62]. In a case report presented by Winger et al [63], a 16-year-old patient with systemic lupus erythematosus, diagnosed with intestinal *M. bovis* infection was treated for a total of 9 months, with symptoms resolution. We opted to use a commonly used 3-drug regimen for 6 months and prolonged isoniazid-ethambutol for 3 more months. The levofloxacin treatment was discontinued to diminish the risk of hepatotoxicity.

During his last visit, 3 months after treatment completion (12 months after treatment initiation), the patient was stable, with no fever or deterioration of cirrhosis status.

Conclusions

We report a unique case of concurrent diagnosis of BCGitis and liver cirrhosis in a patient with previous intravesical BCG administration for BC and discuss the difficulties in diagnosing and treating such a patient for BCGitis.

Statement

The patient was hospitalized in the Internal Medicine Clinic of the Pathophysiology Department of Athens Medical School, in Laiko General Hospital, and was then followed up by the Hepatology and Infectious Outpatient Clinics of the same department.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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