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CASE REPORT

Multi-organ failure with atypical liver granulomas following intravesical Bacillus Calmette-Guerin instillation

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Abstract

Bacillus Calmette-Guerin (BCG) intravesical instillation has been adopted in the treatment of patients with superficial bladder cancer. BCG-induced disseminated infection, though rare, has been associated with the histological finding of epithelioid granulomas in different organs, including the liver. We report the case of an adult patient with multi-organ failure, who developed sepsis, acute respiratory failure and acute hepatic failure with encephalopathy whose liver biopsy confirmed the presence of atypical, granulomatous-like lesions. Recovery was observed only after empirical therapy for *Mycobacterium bovis* with isoniazid, rifampicin, ethambutol and steroids was introduced. This case highlights the importance of a thorough patient assessment in order to exclude other more common causes of hepatic granulomas and to confirm diagnosis. Histological findings may be non-specific when the liver is involved in BCG-induced disseminated infection.

Key words: Bacillus Calmette-Guerin; Multi-organ failure; Hepatic granulomas; "Bacillus Calmette-Guerin-itis"

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INTRODUCTION

Bacillus Calmette-Guerin (BCG) is an attenuated live-strain of *Mycobacterium bovis (M.bovis)*, initially developed as a vaccine against *Mycobacterium tuberculosis*, which is currently used in the treatment of superficial bladder carcinoma[1,2].

Minor side-effects, such as irritative bladder symptoms, hematuria, fever, arthralgia and myalgia, are the rule in up to 90% of patients treated[3,4]. Significant adverse reactions are uncommon (< 5%), but systemic complications such as severe sepsis, pancytopenia, acute respiratory failure, abscess formation, mycotic aneurysms and haemolytic-uremic syndrome have also been reported[3,4]. BCG-induced disseminated *M.bovis* infection has been associated with

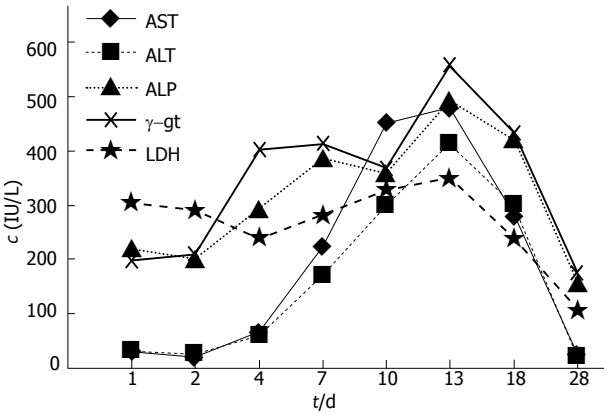

Figure 1 Timescale of liver biochemistry deterioration. AST: aspartate aminotransferase (nr:10-37 IU/L); ALT: alanine aminotransferase (nr: 10-37 IU/L); ALP: alkaline phosphatase (nr: 34-104 IU/L); LDH: lactate dehydrogenase (nr: 135-225 IU/L); γ-gt: γ-glutamyl transferase (nr: 9-40 IU/L); nr: normal range.

the histological appearance of epithelioid granulomas in various organs, such as the liver, prostate, lungs and bone marrow[5-8].

We report the case of an adult, immunocompetent patient with multi-organ failure comprising sepsis, acute respiratory failure and acute hepatic failure with encephalopathy that had atypical histological findings on liver biopsy and responded well on standard treatment for *M.bovis*.

CASE REPORT

A 52-year-old Caucasian male was admitted to our hospital complaining of high fever (39.0℃) with chills, productive cough, dysuria and gross hematuria that started eight days earlier after a traumatic session of intravesical BCG-instillation.

He was diagnosed with a stage Ⅱ (T3aN0) papillary bladder carcinoma a year previously, had undergone two endoscopic operations and introduced on a BCG-instillation protocol.

Upon admission, he was febrile (39.0℃) with BP: 125/80 mmHg, HR: 90 beats/min sinus rhythm, RR: 25 breaths/min and SatO2 = 93% (on ambient air). Clinical examination was unremarkable apart from a few scattered bibasal inspiratory crackles. ECG was consistent with sinus tachycardia and ABGs revealed mild hypoxemia/hypocapnia. His liver biochemistry was only mildly affected. The chest X-ray showed a right-sided pleural effusion. Figure 1 shows the time-related deterioration of liver biochemistry parameters.

Although, intravenous Piperacillin/Tazobactam (4/0.5 g qds) was initiated on admission for a probable lower respiratory tract infection, he became septic with acute respiratory failure on day 4. A chest CT scan showed alveolar-type consolidating lesions at both lung bases. Therefore, we initiated empirical therapy with isoniazid (5 mg/kg od), rifampicin (10 mg/kg od), ethambutol (20 mg/kg) and prednisolone (15 mg od), after discontinuation of Pip/Tazo (Table 1). Although there was improvement in the patients' haemodynamic and respiratory parameters by day 7, his laboratory tests continued to deteriorate and, on day 10, he became acutely jaundiced with early signs of hepatic encephalopathy (i.e. flapping and resting tremor). At that point, his liver biochemistry was more consistent with acute hepatitis. Oral lactulose and neomycin were added to the treatment in order to halt the progression of hepatic encephalopathy. A liver fine needle biopsy (FNB) was performed in order to investigate the cause of the persistently deteriorating hepatic function and to exclude drug-related hepatitis as a cause. The biopsy specimen revealed several small, non-specific, granulomatous-like lesions, including histiocytes, findings which were inconclusive for a type-specific hepatitis (Figure 2 A,B). Ziehl-Nielsen staining and a polymerase-chain-reaction (PCR) performed on the biopsied liver tissue were negative while his liver biochemistry kept deteriorating.

Blood, urine, sputum and bone marrow cultures were all negative for *mycobacteria* and common bacteria. PCR failed to detect mycobacterial DNA in any of these samples. Serological testing for several gram-positive and gram-negative bacteria, as well as, fungi spp was negative. Viral testing was also negative. Ziehl-Nielsen staining performed on both sputum and urine samples and IFN-γ Release Assay (QuantiFERON-TB Gold) were also negative. Mantoux skin-test at 48 h was less than 5 mm. The results of tumour marker and autoantibody screening were negative. Serum angiotensin-converting enzyme, serum calcium, ferritin, B12 and folate levels were measured within the normal range. An abdominal CT scan was normal and no vegetations were detected on a transthoracic ultrasound heart examination. Bone marrow biopsy findings were inconclusive for a specific diagnosis. Bronchoscopy was not performed due to patient's hemodynamic decompensation. Apart from liver biopsy, all diagnostic tests were performed prior to the introduction of anti-mycobacterial drugs and steroids (Table 1).

While the patient continued on triple anti-mycobacterial treatment and prednisolone, his liver function began to improve only after day 18 and he was discharged, on day 28, afebrile and with near-normal liver biochemistry. A triple anti-mycobacterial regimen (isoniazid, rifampicin, ethambutol) was continued for for six months and of oral prednisolone for three months post-discharge. A follow-up liver FNB was scheduled after completion of his therapy.

DISCUSSION

Disseminated infection ("BCG-itis") following intravesical BCG instillation is a rare, though well-recognized, side-effect of this treatment modality that may present with an early or late onset[3-9]. In particular, biopsy-proven, BCG-induced granulomatous hepatitis and pneumonitis may occur in up to 0.7% and 0.2% of cases, respectively[3,4].

Two possible mechanisms have been implicated in the pathogenesis of systemic BCG infection; hematogenous spread of *M.bovis* and a delayed-hypersensitivity reac-

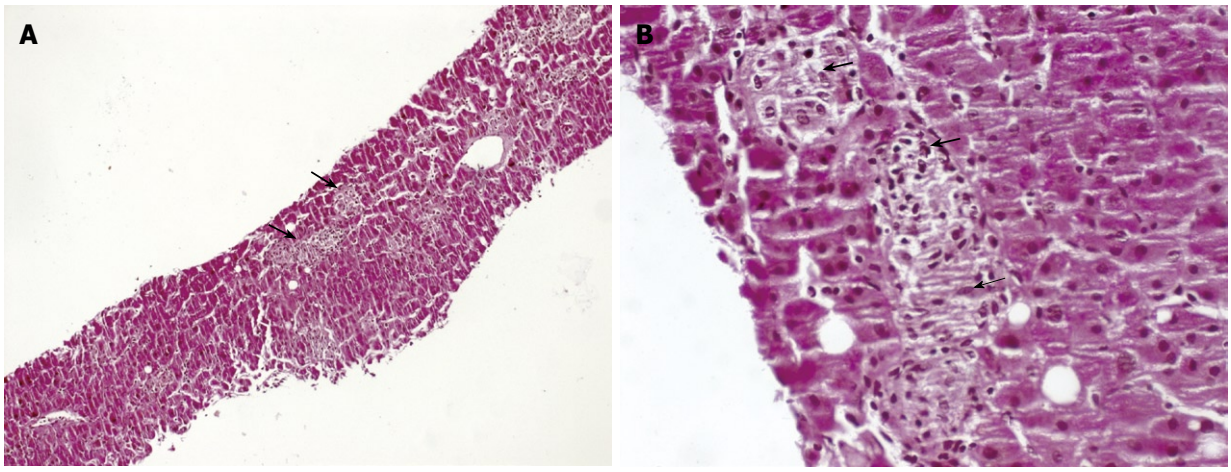

Figure 2 Small granulomatous-like lesions (coarse arrows), including histiocytes (fine arrow), in liver FNB material stained with Hematoxylin and Eosin. A: × 100; B: × 400. FNB: fine needle biopsy

Table 1 Response of the laboratory parameters and fever to the applied therapy

Procedure	Cultures, acid-fast, PCR blood, urine, sputum		Chest CT scan		FNB and liver PCR			
Day	1	2	4	7	10	13	18	28
Bilirubin	0.4	0.6	1.4	2.0	3.6	3.3	2.7	1.4
CRP	3.7	5.7	18.6	16.2	14.5	6.0	5.6	3.8
Hb	14.8	13.6	11.9	9.4	9.5	8.7	9.6	10.6
WBC	4.2	3.7	3.3	3.2	2.9	2.0	2.4	5.3
PLT	440.0	300.0	92.0	66.0	74.0	87.0	134.0	342.0
Fever	Y	Y	Y	Y	Y	N	N	N
Pip/Tazo	STx	Tx	DTx	-	-	-	-	-
Isonia	-	-	STx	Tx	Tx	Tx	Tx	Tx
Rifamp	-	-	STx	Tx	Tx	Tx	Tx	Tx
Ethamb	-	-	STx	Tx	Tx	Tx	Tx	Tx
Prednis	-	-	STx	Tx	Tx	Tx	Tx	Tx

CRP: C-reactive protein (nr: < 0.3 mg/dL); Hb: haemoglobin (nr: 12.2-18.1 g/dL); WBC: white blood cells (nr: 4.5-10.2 × 103/μL); PLT: platelets (nr: 140-450 × 103/μL); Pip/Tazo: piperacillin/tazobactam; Isonia: isoniazid; Rifamp: rifampicin; Ethamb: ethambutol; Prednis: prednisolone; Y: yes; N: no; STx: start treatment; Tx: treatment; DTx: discontinue treatment; FNB: fine needle biopsy; PCR: polymerase chain reaction; CT: computed tomography; nr: normal range.

tion[5,10]. Although, hematogenous spread seems to be the dominant pathogenetic mechanism, this may not always be supported by solid evidence. The demonstration of *mycobacteria* may become very cumbersome, as cultures of urine, blood, sputum or biopsied tissues (bone marrow, liver, lungs), as well as acid-fast smears and PCR, are often negative[5,6,10]. Liver biopsies have been reported with positive acid-fast staining in less than 10% of liver tuberculosis cases[6]. This should not inhibit physicians from instigating the recommended anti-mycobacterial regimen (a combination of isoniazid, rifampicin and ethambutol; *M.bovis* strains are usually resistant to pyrazinamide) for three to six months combined with steroids for three months, as this therapeutic scheme has been reported to be effective in most of the cases of suspected *M.bovis* disseminated infection[3,5,7,8]. Thus, although in this case we could not isolate *M.bovis* from any of the different biological specimens (blood, urine, sputum, bone marrow and liver), we strongly considered the possibility of a BCG-induced disseminated infection, in agreement with observations by other colleagues [5,10].

A dramatic improvement in respiratory and haemodynamic parameters was noticed following introduction of a triple anti-mycobacterial/steroids regimen and withdrawal of broad-spectrum iv antibiotics. This response is consistent with that reported by several authors when a possible BCG-related pneumonitis was suspected[7,10]. Usually, the liver is only mildly affected during BCG-related disseminated infection[4,5,8] and this is usually associated with the presence of granulomas containing Langhan's giant cells[5,7,8]. Our patient, however, developed a severe form of acute hepatic failure, early signs of which were evident even before the introduction of anti-mycobacterial therapy (Figure 1 and Table 1). The applied therapeutic scheme definitely improved his liver biochemistry, and possibly led to the altered findings from FNB(performed on the 6th day of combined anti-mycobacterial/steroids treatment), where we observed small, granulomatous-like lesions rather than the typical giant-cell granulomas. Epithelioid granulomas have been reported in 2-15% of unselected liver biopsies[11]. The etiological classification of diseases causing epithelioid-hepatic granulomas is broad ranging

(infectious, hepatobiliary, neoplastic, idiopathic and drug-related), but only a few diseases (primary biliary cirrhosis, sarcoidosis and Q-fever) can be linked directly to specific histological findings[12-14]. Therefore, it is possible that other rarer and less studied causes of granulomatous hepatitis, such as "BCG-itis", could present with more atypical histological characteristics, as depicted in our case. Steroids could have contributed to the overall clinical and histological response although the extent of their effect cannot be predicted. The timing of liver FNB and the therapy being applied when the biopsy is performed are factors that may influence histological findings.

Finally, the recovery of all blood cell counts only after several days of combined therapy indicates the possible involvement of bone marrow in the BCG-disseminated infection (Table 1).

In conclusion, BCG-induced disseminated disease can cause multi-system failure. Standard, triple anti-*M. bovis* therapy with steroids led to recovery of our patient' s multi-organ failure. Atypical histological liver findings cannot exclude the diagnosis of BCG-induced liver failure when this is strongly supported by clinical data and therapeutic response.

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