CASE REPORT

Concurrent granulomatous hepatitis, pneumonitis and sepsis as a complication of intravesical BCG immunotherapy

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SUMMARY

Intravesical administration of BCG is a relatively simple procedure used successfully in the treatment of superficial transitional cell carcinoma of the urinary bladder. It is usually well tolerated with few major side effects. The authors report the case of an 80-year-old man who presented with sepsis, jaundice, hepatic and pulmonary failure 10 days after his last BCG instillation therapy, that was attributed to concurrent granulomatous hepatitis and pneumonitis due to *Mycobacterium bovis* dissemination. In rare instances severe life-threatening complications occur in relation with BCG instillation immunotherapy that may involve multiple organs and have different presentations and require a high index of suspicion and clinical awareness in a wide range of medical specialties.

BACKGROUND

Urinary bladder cancer ranks ninth in worldwide cancer incidence and is the most common malignancy of the urinary tract.¹ Its management depends on the depth of tumour invasion into the bladder wall. Transurethral resection is the procedure of choice for superficial cancers localised to the mucosa; however, advanced muscle-invasive cancers require more radical surgery. Immunotherapy in the form of intravesical instillation of attenuated *Bacillus Calmette-Guérin* (BCG) has also been successfully used for quite some time now to treat and prevent the recurrence of superficial tumours.²

The virulence of the attenuated BCG is very low in immunocompetent patients and, therefore, BCG immunotherapy is usually well tolerated.³ Only mild systemic symptoms are usually reported, such as low-grade fever and mild malaise, as well as local lower urinary tract symptoms. Adverse effects of BCG immunotherapy develop in 3–5% of patients and usually consist of local infectious complications, such as bacterial cystitis, granulomatous prostatitis, epididymitis and orchitis.^{3–4} Distant manifestations of BCG dissemination, such as vascular and ocular complications, are even less common,^{3–5–6} while disseminated BCG infections that present as granulomatous pneumonitis or hepatitis are quite rare.⁶ Sepsis has been estimated to occur in approximately 1 in every 15 000 patients treated with intravesical BCG.³

We report the case of an adult, immunocompetent patient with a history of urinary bladder

cancer that presented with sepsis, acute hepatic and respiratory failure following intravesical BCG immunotherapy, due to concurrent granulomatous hepatitis and pneumonitis.

CASE PRESENTATION

An 80-year-old non-smoker male patient was transferred to our hospital due to acute respiratory and liver failure. The patient had a history of superficial urinary bladder carcinoma that was initially treated by transurethral resection 20 months earlier. Two months prior to admission the patient had developed bladder carcinoma relapse and was placed on intravesical BCG immunotherapy. Ten days prior to admission and several hours after his last intravesical BCG instillation therapy the patient developed shortness of breath, dyspnoea and fever (up to 39.6°C). He initially received treatment with ciprofloxacin. Owing to the persistence of symptoms and the appearance of jaundice, the patient was referred to the regional general hospital. He was subsequently subjected to an abdominal and thoracic CT. The former had no remarkable findings, the latter, however, demonstrated diffuse bilateral ground glass opacities as well as areas of bronchial wall thickening and ill-defined small nodular opacities in the middle and lower right lobes (figure 1A).

Owing to the severity of his clinical status, the patient was transferred to our hospital within 24 h. On admission, the patient was with fever (38.6°C), haemodynamically unstable (blood pressure 80/50 mm Hg) and in respiratory distress. Arterial blood analysis showed hypoxaemia with respiratory alkalosis (FiO₂ 0.21, pH 7.52, partial pressure of oxygen 48 mm Hg, partial pressure of carbon dioxide 28 mm Hg, carbonic acid 22 mmol/L). Auscultation revealed bilateral inspiratory and expiratory crackles. He had a heart rate of 112 bpm with sinus tachycardia on ECG, with no indication of pericarditis. The patient was icteric and an abdominal examination revealed mild hepatomegaly.

INVESTIGATIONS

The haematological examination revealed mild leucocytosis (white cell count 11.300/μL, 85% neutrophils) and mild anaemia (Ht 38.1%; haemoglobin 12.9 g/dL) with normal platelet count (227 000/μL). The biochemical analysis revealed increased levels of γ-glutamyl-transpeptidase,

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Figure 1 (A) Thoracic CT of the patient before admission demonstrating diffuse bilateral ground glass opacities as well as areas of bronchial wall thickening and ill-defined small nodular opacities in the middle and lower right lobes. (B) Chest X-ray on admission showing a combination of diffuse alveolar opacities and nodules predominantly in the middle and lower lung zones. (C) Thoracic CT of the patient 20 days after antituberculous treatment in combination with low-dose corticosteroids, showing considerable improvement.

(607 IU/L); bilirubin (total/direct bilirubin, 14.6/7.7 mg/dL); serum glutamate pyruvate transaminase (106 mg/dL); serum glutamic pyruvic transaminase (54 mg/dL) and lactate dehydrogenase (508 mg/dL). The rest of the laboratory findings were unremarkable.

A chest X-ray on admission showed a combination of diffuse alveolar opacities and nodules predominantly in the middle and lower lung zones (figure 1B). The patient underwent an abdominal ultrasound, which showed only a slight increase of size and echogenicity of the liver. Serological tests for viral hepatitis were negative. Furthermore, HIV1/2 antigen/antibody combo screening was performed twice and was negative both times. Antineutrophil cytoplasmic antibodies and anti-DNA antibodies were not detected. IgG, IgM and IgA levels in the serum were slightly elevated (2020, 312 and 442 mg/dL, respectively). Blood, urine and sputum cultures were also negative for mycobacteria, common bacteria and fungi. Tuberculin skin test and interferon- γ release assay (quantiferon TB-Gold) were negative.

Because of the patient's history of recent intravesical BCG treatment, the possibility of multisystemic BCG infection with participation of the liver as well as lungs was raised. The patient was subjected to CT-guided fine needle liver biopsy, as well as flexible bronchoscopy with transbronchial biopsy and bronchoalveolar lavage fluid (BALF) collection. Flow cytometric analysis of the BALF revealed a prevalence of lymphocytes (53%) and a CD4/CD8 ratio of 0.7 (absolute counts CD3 11 200/ μ L, CD4 4668/ μ L, CD8 6884/ μ L). The Ziehl-Neelsen staining performed on the liver and lung tissue specimens, as well as in bronchial washing and BALF was negative. PCR performed on the liver specimen was also negative. However, pathological examination of the hepatic tissue revealed the presence of small epithelioid granulomas in the absence of Langhans giant cells and caseous necrosis (figure 2A). Immunohistochemical staining revealed positivity for CD68 (macrophages) and negativity for cytokeratin 18 (marker for hepatocytes), providing further proof of its granulomatous nature (figures 2B and C, respectively). The histopathological examination of the lung tissue obtained by transbronchial biopsy revealed similar granulomatous structures (figure 2D). Eosinophilic infiltrates were not found in the hepatic and lung biopsy tissues examined; however, scarce eosinophils were identified scattered in the hepatic parenchyma as well as the subepithelial layer of the bronchial tissue. Lymphocytes were present in the vicinity or within the observed granulomas as expected; however, specific immunohistochemical staining to identify different lymphocytic subsets (CD3, CD4, CD8 and CD19) was not performed.

TREATMENT, OUTCOME AND FOLLOW-UP

On admission the patient was started on oxygen therapy and intravenous fluids for haemodynamic stabilisation, as well as empirical broad spectrum antibiotic treatment (piperacillin/tazobactam and ciprofloxacin). Because of the lack of clinical improvement and subsequent suspicion of systemic complications of the intravesical instillation of BCG, antituberculous treatment was added on the third day of hospitalisation (isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 20 mg/kg/day and moxifloxacin 500 mg/day) as well as intravenous prednisolone (0.5 mg/kg/day). On histological confirmation of disseminated granulomatous disease, broad spectrum antibiotic treatment was terminated. A gradual improvement in clinical and laboratory status was achieved within 20 days of antituberculous treatment. The patient was then subjected to a thoracic CT scan that also showed significant radiological improvement (figure 1C). Thereafter, tapering of corticosteroids was initiated with no clinical relapse. The patient was discharged after being treated for a total of 30 days and continued receiving antituberculous therapy with no reported problems for a total of 6 months under the supervision of his hometown physicians.

DISCUSSION

BCG is a vaccine against tuberculosis developed by Albert Calmette and Camille Guérin that was first used in humans almost nine decades ago.⁷ It is prepared from a live but attenuated strain of *Mycobacterium bovis*, which has lost its virulence in humans but has kept its antigenicity. The precise immunological mechanism of BCG therapy is not yet fully understood. It has been suggested that BCG immunotherapy exerts complex reactions that are associated with three distinct processes: the infection of urothelial cells or bladder cancer cells, the initiation of immune reactions and the induction of antitumour effects.⁸

Complications of intravesical BCG instillations can be local or systemic (table 1). More than 95% of patients tolerate BCG without significant morbidity.³ Mild adverse effects of BCG immunotherapy, such as fever, dysuria and urinary frequency, develop in 3–5% of patients.⁴ Less frequent local complications include haematuria, epididymitis, symptomatic prostatitis and ureteral obstruction, each occurring in less than 1% of patients. Distant organ complications are even less common and can manifest, among others, as granulomatous hepatitis, pneumonitis, osteomyelitis, mycotic vascular infections and endophthalmitis.^{3 5 6}

Disseminated BCG infection presenting as pneumonitis or granulomatous hepatitis is rare; in the largest retrospective study

Figure 2 Representative microphotographs of the hepatic and lung tissue obtained through CT-guided fine needle biopsy and transbronchial biopsy, respectively. (A) Staining with H&E of hepatic tissue revealing the presence of small epithelioid granulomas in the absence of Langhans giant cells and caseous necrosis. Immunohistochemical staining revealed positivity for CD68 (B) and negativity for cytokeratin 18 (C). A similar granulomatous structure is shown in the lung tissue obtained by transbronchial biopsy in (D).

reported to date, dissemination occurred in 0.7% of over 2000 patients.⁶ The combination of both conditions, as presented here, could be even less common. Granulomatous hepatitis rarely arises as either an early or late complication of BCG treatment. Patients with granulomatous hepatitis present with symptoms and signs of hepatitis, including fever, anorexia and jaundice. Non-caseating granulomas and eosinophilia can be found on liver biopsies from these patients.^{9–10} Granulomatous pneumonitis can present with a miliary nodular or interstitial

pattern on routine chest radiography and CT scanning. Fever, malaise, fatigue and dyspnoea, possibly followed by severe respiratory failure are the most common symptoms.^{11–13} The most life-threatening condition associated with BCG immunotherapy is sepsis, with hypotension and multisystem organ failure. This occurs in about 0.4% of cases and carries a high risk of mortality.³

The mechanism by which BCG leads to the development of infectious complications is not fully understood. It's not yet elucidated whether infectious complications are a result of a hypersensitivity reaction or of an ongoing active infection. BCG consists not of a single strain but of a number of substrains with distinct phenotypic and biochemical properties, as well as differences in residual levels of virulence.¹⁴ The presence of granulomas in the absence of positive staining for acid-fast bacilli, culture and PCR testing for mycobacterial DNA in some cases, as in ours, are in favour of a hypersensitivity (type IV) reaction.^{9–12} This notion is also supported by the frequent successful use of corticosteroids. In contrast, other case reports have demonstrated viable organisms in a variety of tissues,^{13–15–16} supporting the case of haematogenous systemic infection due to disruptions of the uroepithelial cell lining. Possibly both mechanisms may contribute to the pathogenesis of distant complications.

The management of complications related to intravesical BCG treatment depends on their type and severity. Mild complications, such as low-grade fever and local lower urinary tract symptoms usually require no specific treatment and are resolved

Table 1 Adverse events of intravesical BCG immunotherapy

Local	Systemic
Frequent (mild) adverse events	
Increased urinary frequency	Fever
Haematuria (usually self-limited)	General malaise
Dysuria	Flu-like symptoms
Infrequent serious adverse events	
Granulomatous prostatitis	Allergic reaction
Granulomatous epididymo-orchitis	Ocular complications (endophthalmitis, uveitis and rarely choroiditis)
	Osteomyelitis
	Mycotic vascular infections
	Granulomatous hepatitis
	Hypersensitivity/granulomatous pneumonitis
	Sepsis

quickly. In the presence of relapsing fever with night sweats, or evidence of more serious systemic disease, antituberculous therapy should be initiated. There are no official guidelines regarding treatment, but as *M bovis* is usually resistant to pyrazinamide,¹⁷ a regimen that includes isoniazid, rifampicin, ethambutol and a fluoroquinolone, such as levofloxacin, is usually used for a duration of 6 months.^{5 6 18} This period may extend to 9 months in case of refractory disease or relapse of symptoms.⁹ Empirical treatment with corticosteroids was also shown to be effective in reducing symptomatology in cases where hypersensitivity was suspected;¹⁹ however, great caution needs to be exercised during tapering due to high risk of symptom recurrence and granuloma formation.^{9 20}

Prevention is also very important. As major complications can appear after systemic absorption of the drug, BCG should not be administered during the first 2 weeks after resection, urinary tract infection and traumatic catheterisation or in immunocompromised patients. A significant reduction of local side effects, as well as serious infectious events, was also reported by reducing the optimal BCG dose.²¹ Physicians treating patients receiving BCG immunotherapy can be of a wide range of specialties, but should all exhibit a high index of suspicion and clinical awareness to recognise and manage these rare but life-threatening complications.

Learning points

- ▶ BCG is a vaccine prepared by a live but attenuated strain of *Mycobacterium bovis* that is also widely used in the form of intravesical instillation immunotherapy to treat superficial transitional cell carcinoma of the urinary bladder.
- ▶ BCG immunotherapy is usually well tolerated and is usually followed by minor complications. Life-threatening rare systemic complications, such as granulomatous hepatitis, pneumonitis and sepsis are rare.
- ▶ In the setting of serious systemic disseminated disease, multidrug antituberculous therapy with or without glucocorticoids should be administered for 6 months. If steroids are used, great caution should be exercised on their gradual tapering to avoid relapse.
- ▶ Physicians should always have high index of suspicion and clinical awareness for disseminated BCG disease even in the absence of viable mycobacteria or positive cultures.

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