Disseminated mycobacteriosis secondary to intravenous Bacille Calmette-Guérin (BCG) vaccine

HARSHDEEP HARSHAD ACHARYA, ANUPA THAMPY, RAJIV KARTHIK, PRISCILLA RUPALI

ABSTRACT

Bacille Calmette-Guérin (BCG) vaccine has been used increasingly in immunotherapy, including treatment of non-muscle-invasive bladder cancer, as an adjuvant therapy in metastatic prostate cancer and metastatic melanoma. However, systemic infection from inadvertent intravenous (instead of intravesical) injection is uncommon and can have systemic ramifications. We encountered 3 patients with disseminated *Mycobacterium bovis* infection that ensued after intravenous BCG injection.

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INTRODUCTION

Intravesical Bacille Calmette-Guérin (BCG) is the standard of care in the treatment of non-muscle-invasive bladder cancer.[1] However, unfamiliarity with this route of administration can often result in an incorrect route resulting in a life-threatening illness. A practitioner in a secondary set-up, tasked with the 2-week follow-up administration of intravesical BCG can often make a mistake regarding the mode of administration, thus causing disseminated mycobacteriosis due to *M. bovis*. Recognition of this rare entity is important as the patients may present within hours to days with a systemic inflammatory syndrome involving an extrapulmonary organ. Invasive techniques may be needed to make an early diagnosis and initiate treatment. Though *M. bovis* is part of the *M. tuberculosis* complex, it is intrinsically resistant to pyrazinamide,[2] and the treating physician needs to be aware of the same. This assumes importance as patients receiving this therapy are often followed up and managed at a non-academic secondary or primary care centre.

THE CASES

Case 1

A 58-year-old man diagnosed with high-grade urothelial carcinoma was advised intravesical BCG injection following trans-urethral resection of bladder tumour (TURBT) at his hometown. He was inadvertently administered BCG intravenously and developed high-grade fever within 4 hours of administration. He presented to us 10 days later with persistent fever and night sweats. Baseline investigations revealed a mild bicytopenia and liver function studies were suggestive of cholestatic hepatitis (Table I). On further evaluation, bone marrow biopsy showed granulomatous inflammation, with negative acid-fast bacilli (AFB) smear and mycobacterial cultures. Histopathology from percutaneous liver biopsy was suggestive of non-caseating granulomatous hepatitis. Considering the temporal relationship of the illness to BCG instillation and evidence of granulomatous inflammation at multiple sites, *Mycobacterium bovis* (*M. bovis*) infection was strongly considered. He was started on non-hepatotoxic weight-based anti-mycobacterial therapy with ethambutol (E), amikacin, levofloxacin (L) and clarithromycin along with tapering doses of steroids. Follow-up of liver biopsy mycobacterial growth indicator tube (MGIT) showed *Mycobacterium tuberculosis* complex (which includes *M. bovis*) confirming the diagnosis (Table II). His fever subsided and liver function tests returned to normal after 2 weeks. The treatment was modified to weight-based regimen comprising isoniazid (H), rifampicin (R), E and L (Table III). The patient was treated for a duration of 12 months and followed up for 3 years, during which there was no relapse of the disease.

Case 2

A 27-year-old man diagnosed with high-grade urothelial carcinoma was advised intravesical BCG following TURBT. He was inadvertently administered intravenous BCG and presented to us 2 weeks later with high-grade intermittent fever starting few hours after the injection, and yellowish discolouration of sclera and pedal oedema for 1 week. Baseline investigations showed deranged liver function with bicytopenia (Table I). Multiple blood cultures obtained at the time of fever showed no growth. A bone marrow examination showed normocellular marrow with focal granulomatous inflammation. A transjugular liver biopsy showed non-necrotizing histiocytic aggregates including granulomas. AFB smears, tuberculosis polymerase chain reaction (TB PCR) and cultures for bacteria and fungi from bone marrow and liver were negative (Table II). In view of onset of illness within few hours of intravenous BCG injection, and evidence of disseminated granulomatous disease, a diagnosis of disseminated mycobacterial infection was considered and the patient was initiated on anti-mycobacterial therapy targeted to *M. bovis* (Table III). Levofloxacin was not given due to features of long QT syndrome in his ECG. His fever subsided within 1 week of initiation of therapy.

TABLE I. Baseline investigations

Investigation	Case 1	Case 2	Case 3
Haemoglobin (g/dl)	10.2	10.4	7.7
Total leukocyte count (cmm)	5200	4900	6300
Platelet count (cmm)	149 000	65 000	113 000
Creatinine (mg/dl)	0.82	0.72	0.72
Total/direct bilirubin (mg/dl)	4.6/4.2	4.4/4.1	13.2/11.6
AST/ALT (U/L)	216/669	394/176	132/81
Alkaline phosphatase (U/L)	644	171	706
Total protein/albumin (g/dl)	6.0/2.6	6.2/2.2	6.6/2.8

AST aspartate aminotransferase ALT alanine aminotransferase

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TABLE II. Results of histopathology and microbiology

Tissue		Case 1	Case 2	Case 3
Histopathology				
Liver		Predominantly lobular non-caseating granulomatous inflammation	Lobular based non-necrotizing histiocytic aggregates including granulomas	–
Bone marrow		Moderately hypercellular marrow with granulomatous inflammation	Normocellular marrow with trilineage haematopoiesis and focal granulomatous inflammation	Consistent with granulomatous inflammation
Microbiology reports				
Liver	AFB smear	Negative	Negative	–
	Xpert TB PCR	Negative	Negative	–
	Culture*	MGIT–*Mycobacterium tuberculosis* complex†	No growth	–
Bone marrow	AFB smear	Negative	Negative	Negative
	Xpert TB PCR	Negative	Negative	Negative
	Culture*	No growth	LJ-*Mycobacterium tuberculosis* complex†	No growth

*Relevant microbiology reports: Cultures were incubated in special media including LJ and MGIT to obtain microbiological confirmation. Identification of causative strain of *Mycobacterium* from culture could not be done, and remains a limitation of the investigation. The strain of BCG vaccine administered could not be obtained for culture and comparison in all cases †Susceptible to isoniazid, rifampicin, streptomycin and ethambutol TB PCR tuberculosis polymerase chain reaction AFB acid-fast bacilli

TABLE III. Treatment regimens

Treatment regimen	Case 1	Case 2	Case 3
Intensive phase regimen (duration in months)	HRLE (3)	HRE*	HRLE (2)
Continuation phase (duration in months)	HRE (9)	HRE (9)	HRE (7)

* Levofloxacin (L) not administered due to ECG findings of long QT syndrome
H isoniazid R rifampicin L levofloxacin E ethambutol

At follow-up, LJ culture reported growth of *Mycobacterium tuberculosis* complex (includes *M. bovis*) from the bone marrow providing microbiological confirmation of the diagnosis.

Case 3

A 57-year-old man diagnosed with non-muscle invasive urothelial cell carcinoma, post-TURBT was recommended intravesical BCG injection. He received inadvertent intravenous injection, and started having high-grade fever after a few hours. He presented to us 3 weeks later with high-grade intermittent fever, abdominal pain and loss of appetite and weight. Liver function was deranged at the baseline. He had bicytopenia and required one red cell transfusion for correction of anaemia (Table I). In view of the history and temporal profile, a strong clinical suspicion of dis-seminated mycobacterial infection was considered and the patient was evaluated. Bone marrow histopathology was consistent with granulomatous inflammation (Table II). He was initiated on anti-mycobacterial therapy targeted to *M. bovis* based on the clinical profile. The patient's symptoms subsided after initiation of therapy, and there was no relapse of disease during a 1-year follow-up period.

All patients were treated with a weight-based regimen composed of HREL, without the addition of pyrazinamide[2] (Table III).

DISCUSSION

The use of intravesical BCG is the standard of care in the treatment of non-muscle-invasive bladder cancer.[1] Multiple doses and unfamiliarity with this route of administration can lead to mistakes regarding the mode of administration, resulting in a life-threatening illness. Factors including patient education and appropriate documentation of route of administration can help prevent the same. In all cases of accidental intravenous injection, patients present with a rapid onset febrile illness within a few hours of the injection. Commonly accompanying features include deranged liver function tests with granulomatous hepatitis on histo-pathology and granulomatous inflammation in the bone marrow.

Haematogenous spread of *M. tuberculosis* seems to show a predilection for the more vascular organs including the liver, spleen, bone marrow and brain. Organ involvement in miliary tuberculosis, caused by haematogenous spread, reports a high incidence of involvement of one or more cell lines (15%–87%), granulomatous hepatitis (79%) with elevated transaminases (42%) and alkaline phosphatase (83%).[3–5] Fiberoptic bronchoscopy, bone marrow biopsy and liver biopsy are the most common investigations, which yield a tissue diagnosis in miliary disease.[3] Seeding of the central nervous system and adrenal has also been noted; however, these rarely seem to cause symptomatic disease.[6,7] *M. bovis* and *M. tuberculosis*, both part of the *M. tuberculosis* complex when grown in special culture media, are closely related and the disease they produce in humans is indistinguishable clinically, radiographically, pathologically or by direct smear microscopy. Though *M. bovis* is part of the *M. tuberculosis* complex, it is intrinsically resistant to pyrazinamide. Early initiation of therapy can help contain the spread and provide symptomatic relief to the patient.

Conclusion

Patients receiving BCG immunotherapy can be at risk of disseminated infection with *M. bovis* in case of incorrect route of administration, and the same needs to be explained to the patient. The presentation of a febrile illness with onset shortly after receiving BCG injection should prompt immediate referral to an infectious disease physician, to proceed with appropriate evaluation and early initiation of treatment.

Conflicts of interest. None declared

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I, Dr PEUSH SAHNI, hereby declare that the particulars given abovc are true to the best of my knowledge and belief

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