

## Granulomatous hepatitis complicating intravesical bacille calmette-guérin (BCG) therapy for high-risk superficial bladder cancer

*Mycobacterium bovis* was identified in 1904 by Nocard and is the cause of bovine tuberculosis. Bacille Calmette-Guérin (BCG) vaccine, developed by Calmette and Guérin at Institut Pasteur (Lille, France), is a live-attenuated *Mycobacterium bovis* strain. Many therapeutic uses of the species have been described. Morales, in 1976, first described a technique of non-specific anti-cancer immunotherapy by bladder instillations of BCG for the treatment of superficial bladder cancer. BCG is the first choice of adjuvant treatment for recurrent or high-grade superficial bladder cancer. Complications related to its use have been described, but serious complications are not widely reported. We report the case of a disseminated *Mycobacterium bovis* BCG infection with biopsy-proven granulomatous hepatitis. We also present a review of literature and the management options.

### Case Report

We present a case of a 67 year old man who was diagnosed with transitional cell carcinoma of the urinary bladder in April 2015 with histology of G2 pTa. The tumour was resected endoscopically and intravesical BCG induction therapy was initiated. The patient received one instillation per week. During each of the two initial instillations he developed cystitis, which was treated conservatively with IV cefoperazone and sulbactam. Two weeks after the third BCG instillation, the patient was admitted with lethargy, loss of appetite, fever, and rigors. There were no urinary or pulmonary symptoms. There was no abdominal pain or pruritus but he complained of yellowish discoloration of urine for 2 weeks.

He was also a known case of type 2 diabetic and hypertension, both well controlled on medication. He was also a reformed smoker with a smoking index of 200, but had been abstinent since April 2015. There was no history

of tuberculosis in the past, nor any recent or remote history of contact with tuberculosis. To our knowledge he was not vaccinated with BCG previously and a BCG scar was not made out in general examination.

The patient was febrile and mildly icteric on examination. Pulmonary examination was unremarkable. The liver was palpable 4 cm below right costal margin and painful to touch. WBC counts were 12,500 cells/mm<sup>3</sup> (polymorphs 23%, lymphocytes 76%, eosinophils 1%) and on peripheral smear there was leucocytosis with a lymphocytic predominance. He had an elevated ESR of 47mm at 1st hour and CRP was 51 g/dl. Chest X ray and urine routine studies were normal. Liver function tests were deranged with a serum bilirubin of 4.2mg/dl (direct fraction 2.4 mg /dl), aspartate aminotransferase 136 U/L, alanine aminotransferase 123 U/L, alkaline phosphatase 1154 IU/L and GGT was 579 IU/L, which was suggestive of cholestasis. Treatment with intravenous cefotaxime was started but his clinical condition deteriorated and fever was persistent.

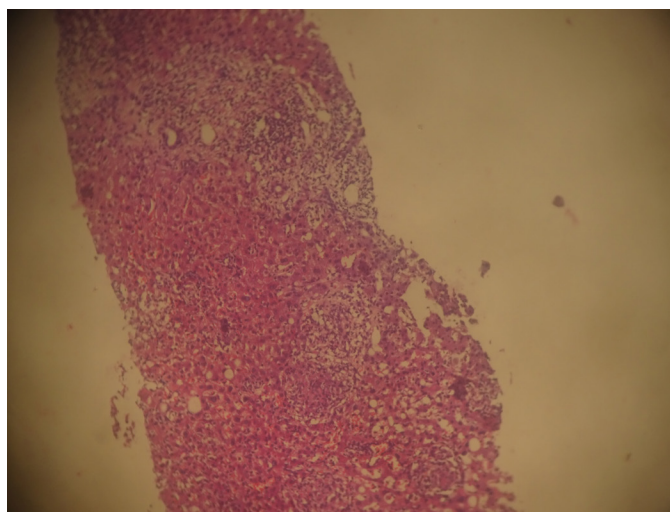
Viral markers including HbsAg and antiHCV, IgG antiHbC were negative. Workup for acute hepatitis including IgM HAV, IgM HEV, IgM Dengue, IgM Leptospira, IgM Scrub typhus, IgM CMV, IgM HSV, IgM EBV, IgM salmonella typhi were negative.

Blood, urine, sputum cultures were negative for common bacteria. Ziehl-Nielsen staining performed on both sputum and urine samples was also negative. Mantoux skin test at 48 hours was negative (less than 5mm). There was no prior history of mantoux positivity. The results of tumour markers and autoantibody screening were negative. Serum angiotensin-converting enzyme, serum calcium, ferritin, B12 and folate levels were found to be within the normal range. Ultrasonography of the abdomen was suggestive of fatty hepatomegaly and there was no evidence of IHBRD. CECT abdomen was suggestive of hepatomegaly with fatty infiltration with mild periportal oedema and diffuse thickening of gall bladder (GB) wall. CECT chest was suggestive of minimal thin smooth pleural thickening in bilateral posterior aspect and apices of the lungs which was more on right side as compared to the left, along with discrete subcentimetric mediastinal nodes. There was no evidence of consolidation, pleural effusion or cavitation.

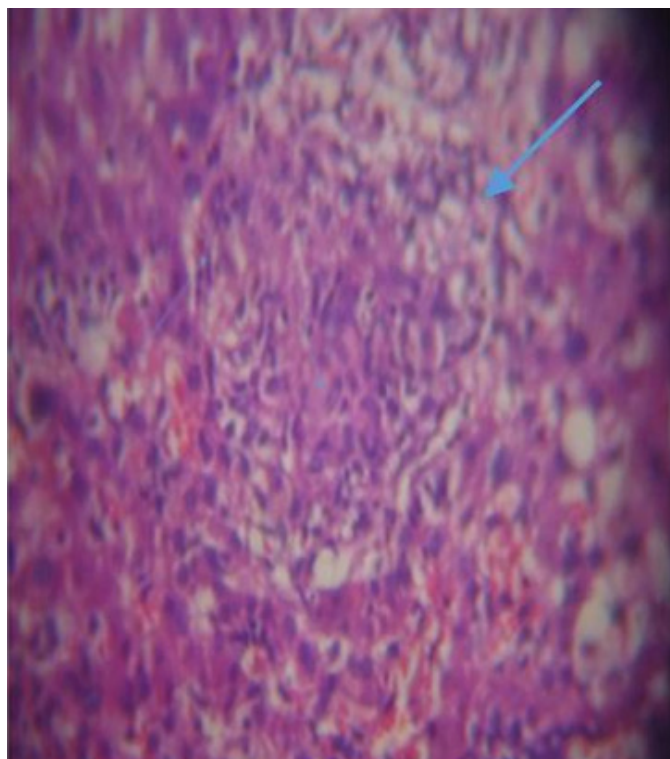
A systemic infection due to BCG was suspected on the basis of the recent BCG instillation and the failure to improve despite several days of antibiotic treatment. A liver biopsy was done which was suggestive of granulomatous hepatitis although AFB stain was negative and there was no caseation. He was started on tab ursodeoxycholic acid 10 mg/kg/day and we continued to give supportive management. Antibiotics were discontinued. Intravesical BCG instillation was stopped and the patient was observed for a month with close LFT monitoring. His LFT's showed improvement over time and the symptoms decreased after stopping BCG therapy. After 1 month, his LFT's were normal and he was started on intravesical Mitomycin C instillation. Total of 3 instillations of intravesical mitomycin C had been given and the patient is now asymptomatic with normal LFT's.

## Discussion

Deboiset al,<sup>3</sup> and Lammet al<sup>2</sup> reported a 45%–90% rate of irritative symptoms and a 35%–43% rate of haematuria. Low- grade fever was reported in 16%–28% of cases, while high-grade fever was reported in 2%–4.2%. Serious complications related to intravesical BCG has an estimated rate of 0.35%–1.9%, the vast majority (70%–75%) of those being systemic. Based on histological diagnoses from liver biopsies, the liver has been reported as a potential site of disseminated disease, but tissue culture of *Mycobacterium bovis* BCG, which is the ultimate proof of the disease after intravesical BCG has not been described in the literature. Lamm and colleagues<sup>2</sup> reported a combined incidence of pneumonitis and hepatitis of 0.9%, but 7 out of 46 (15%) severe systemic complications had indirect proof of disseminated BCG with granulomatous lesions on biopsy and were considered diagnostic. Granulomatous hepatitis is not a specific diagnosis. Differential diagnoses include sarcoidosis, foreign body granuloma (e.g., in intravenous powder drug users) and mycotic infection such as histoplasmosis or toxoplasmosis. Histologically, mycobacterial granulomas are normally located around the centrilobular vein, have a more significant caseation reaction (but not in immunosuppressed patients) and have a predominantly lymphocytic inflammatory infiltrate in addition to well-formed epithelioid granulomas, and an



**Figure 1: Liver biopsy specimen slide in low power view, stained with Haematoxylin and Eosin**



**Figure 2: Granulomatous foci (highpower view), Granulomatous foci (thin arrow) were seen within liver parenchyma with marked inflammation around them, Portal areas are widened due to fibrosis , extensive inflammation is seen and prominent bile ducts are noticeable (thick arrow), No AFB was demonstrated**

absence of Langhans giant cells.

Clinically, fever and malaise are the predominant manifestations. The liver can be enlarged and painful upon palpation. Hepatocellular enzymes are usually elevated, but sometimes only hyperbilirubinemia and elevated alkaline phosphatase are the only abnormalities noted in the laboratory workup

Prevention is the most important management strategy. Recent surgery (2–4 weeks after TUR), traumatic catheterization or cystoscopy, active haematuria, immunocompromised status (i.e., transplant, leukaemia, Hodgkin's disease or AIDS), fever of unknown origin, pregnancy and active urinary tract infection are all contraindications to the administration of intravesical BCG and mandate postponing the treatment. Strict surveillance of patients before treating them with intravesical BCG is of utmost importance, and the severity of symptoms at the beginning of treatment is predictive of the necessity to stop the maintenance BCG treatment. In most of the reported cases with severe BCG-related infectious complications, a traumatic catheter or another contraindication is described. Prophylactic isoniazid has been evaluated during intravesical BCG therapy in a randomized study and is not considered efficacious owing to similar incidence of short-term complications and adverse effects related to isoniazid.<sup>4</sup>

If systemic complications from BCG are suspected, the following mycobacterial cultures are suggested: urine cultures, blood cultures and a liver biopsy for culture and histology, if hepatic granulomatous disease is suspected. Broth cultures are much more sensitive for *Mycobacterium* than are solid media. *M. bovis* BCG is much more fastidious to isolate in broth or on solid media than *Mycobacterium tuberculosis* or *Mycobacterium* of other than the tuberculosis group. PCR can also be performed on tissue or urine (but not on blood) to diagnose the *Mycobacterium tuberculosis* group.

Having a definitive diagnosis, by liquid chromatography or by 16S rRNA gene sequencing, will help tailor the intensity of the therapy. Sensitivity testing to different antimicrobial agents also helps to rule out resistant strains.

*Mycobacterium bovis* BCG and *M. bovis* are intrinsically resistant to pyrazinamide. The suggested

first-line antimicrobial treatment for *M. bovis* BCG is isoniazid 300 mg daily and rifampin 600 mg daily with or without ethambutol 1200 mg daily oral for 6 months.<sup>5</sup> Ethambutol is recommended as complementary treatment for patients with significant systemic disease or to replace isoniazid in patients who do not tolerate the drug owing to adverse effects (i.e., liver dysfunction, fever, malaise or maculopapular eruption). Aluminium containing antacids reduce oral absorption of isoniazid. Monotherapy is not recommended because of the development of resistance. Other alternatives include the addition of ofloxacin, doxycycline and gentamicin.<sup>5</sup> Prednisolone 40 mg daily may be considered for patients with systemic disease as hypersensitivity reaction is initially difficult to differentiate from infectious reaction. If prescribed, corticosteroids should be maintained as long as systemic symptoms are present. They should be gradually tapered off because exacerbation of the hypersensitivity response has been seen in patients who have stopped corticosteroids abruptly.<sup>2</sup>

In our case we did not start the patient on anti tubercular therapy (ATT), but the patient responded to UDCA and symptomatic management. This has not been previously described in literature and we want to highlight the fact that selected patients with only granulomatous hepatitis (limited disease) due to BCG may respond to conservative management alone, thus avoiding the potential hepatotoxicity of ATT. This also holds weight in the current scenario in our country to combat the rising incidence of drug resistant TB.

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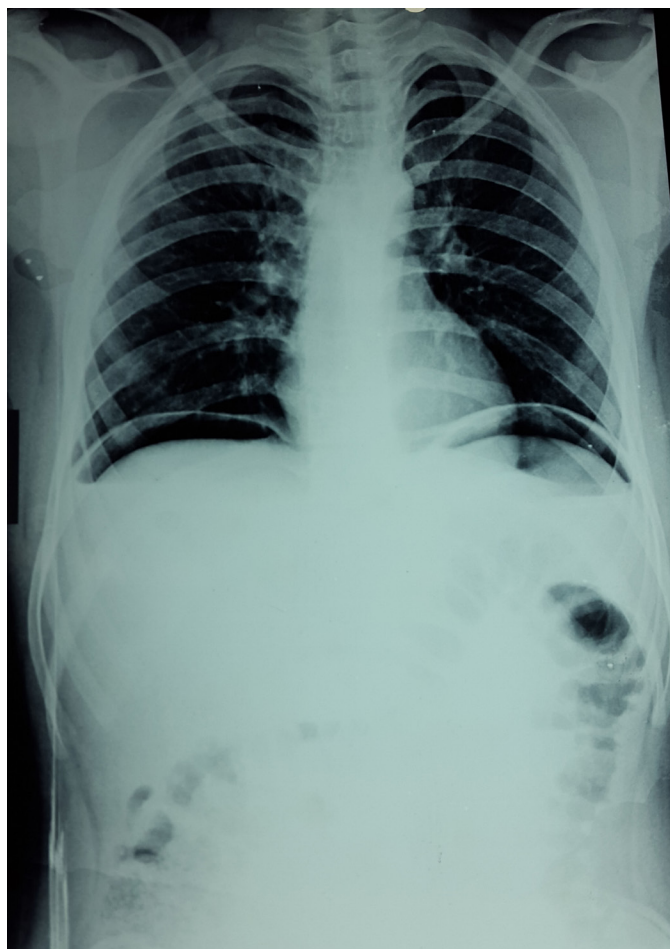
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## Impact of blunt trauma to abdomen in a case of intestinal ascariasis

### Case Report

A 17 years old male was brought to the emergency department with a history of trivial assault to the abdomen. He had severe abdominal pain with multiple episodes of non-bilious vomiting. On examination, the patient had tachycardia and hypotension. Diffuse tenderness and guarding was present throughout the abdomen. An erect X-ray of the abdomen showed free gas under the diaphragm. Ultrasonography showed moderate free fluid with moving internal echoes in the abdomen. Diagnostic tap revealed yellow colored bilious aspirate. On emergency exploratory laparotomy, gross bilious contamination was

present with multiple live worms floating freely in the abdominal cavity. A small mid-jejunal perforation with pouting mucosa and a live worm wriggling out of it was found. Incidentally, a broad base Meckel's diverticulum was also discovered. The jejunum distal to the perforation was loaded with worm bolus, which was dislodged and milked out proximally through the perforation. Primary repair of the jejunal perforation was done in two layers, thorough lavage was performed and the abdomen closed over a drain after confirming hemostasis. Patient vomited a live worm in the postoperative period. and To complete deworming, he was started on anti - helminthic therapy. The patient recovered completely and was discharged on the 10th day. At 6 months follow up, patient is asymptomatic with no history of passage of worms in stools and no evidence of ova on stool examination.



**Figure 1: X-ray-Chest-PA-view-suggestive-of--free-gas-under-diaphragm**