Systemic Bacillus Calmette–Guerin infection secondary to inadvertent intravenous injection

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INTRODUCTION

Bacillus Calmette–Guerin (BCG) is a live attenuated strain of *Mycobacterium bovis*. It has an established role in preventing recurrence and progression of high-risk non-muscle-invasive bladder cancer. It acts by binding to fibronectin within the bladder wall, leading to cytokine induction and up-regulation of interferon-gamma, interleukin-2, and interleukin-12. This response leads to the activation of cell-mediated cytotoxic mechanisms, which is believed to be responsible for BCG’s efficacy in the prevention of progression and recurrence.[1] Inadvertent intravenous (IV) injection of BCG has been reported only once in the English literature.[2] We report two cases that we treated.

CASE REPORTS

Case 1

A 40-year old male presented to the urology outpatient department (OPD) with high-grade fever and jaundice following the first dose of IV administration of BCG 15 days previously. He underwent transurethral resection of bladder tumor (TURBT) elsewhere and was advised intravesical BCG for pTa high-grade urothelial carcinoma bladder 6 weeks after TURBT. However, it was inadvertently given intravenously. The BCG strain and dose used were not known. He had fever, tachycardia, and icterus on examination. He was admitted and evaluated in consultation with the infectious diseases department. His liver function tests (LFT) were deranged. The contrast CT abdomen and pelvis showed mild hepatosplenomegaly [Figure 1a]. Blood cultures and Gene-Xpert® TB of the blood were negative. Mycobacterial culture (Lowenstein-Jensen medium) of bone-marrow showed mycobacterium after 10 weeks of incubation, which was sensitive to isoniazid, rifampicin, ethambutol, and streptomycin.

ABSTRACT

Disseminated BCG infection (BCG–osis) secondary to intravesical BCG given for high-risk non-muscle invasive bladder cancer has been reported. We report the successful management of two cases of BCG–osis secondary to inadvertent intravenous BCG injection. Both cases are recurrence-free at the follow-up of 12 and 18 months, respectively. There is only one such case reported in English literature so far to the best of our knowledge.
A trans-jugular liver biopsy showed granulomatous inflammation suggestive of mycobacterium infection [Figure 1b]. He was treated with isoniazid, rifampicin, ethambutol, levofloxacin, and pyridoxine (HREL for 2 months and HRE for 7 months). On therapy, his fever subsided in 1 week, and he clinically improved. Further, intravesical BCG was stopped, and he is on cystoscopic surveillance for the bladder tumor. He was asymptomatic, had no late sequelae and was recurrence-free at follow-up of 12 months.

Case 2

A 57-year old male underwent TURBT at our institute and was advised intravesical BCG for pTa high-grade urothelial carcinoma. He wished to take the intravesical BCG at his hometown. The BCG was inadvertently given intravenously elsewhere. The BCG strain and dose used were not known. He reported to the Urology OPD with high-grade fever for ten days. He also had jaundice for 5 days, left upper abdominal pain, and cough for 3 days. On examination, he had tachycardia, icterus with tender hepatosplenomegaly. His LFT was deranged. Mycobacterial workup of blood and bone marrow was negative. The histopathological examination of the bone marrow and liver showed a granuloma, which was negative for acid-fast bacilli. He was afebrile within a week of initiating anti-tubercular treatment (ATT). He was treated with HRE and pyridoxine for 9 months. The intravesical BCG was stopped and he is on surveillance cystoscopy and remains recurrence-free at 18 months’ follow-up. He did not have any late sequelae at last follow-up.

DISCUSSION

Intravesical BCG administration is associated with many side effects, and BCG-osis is a rare but serious complication.3–6 Gonzalez et al. analyzed 41 patients BCG infection after intravesical BCG immunotherapy and stratified BCG infection based on the timing of presentation from BCG instillation as early (within 3 months) and late (more than 12 months). Patients with early presentation tend to have more generalized symptoms such as fever and systemic symptoms with liver and lung involvement, while those who present late have mostly localized disease.4 There is only one case of BCG-osis secondary to inadvertent IV BCG injection in the published literature to the best of our knowledge, which reported a patient with fever, cough, nausea, and fatigue hours after inadvertent IV BCG injection. The treatment used in that case report was isoniazid and ethambutol for 6 months, cycloserine-C and ofloxacin for 2 months, and streptomycin for 1 month. Rifampicin was discontinued after the initial 2 weeks in view of elevated liver enzymes and methylprednisolone was given in tapering dose for 4 days.2 Both our cases developed symptoms within 5 h and had systemic manifestations in the form of fever and jaundice. Granulomas were seen in both our patients; the growth of Mycobacteria was seen in the bone marrow biopsy of only one patient. Granulomas are present in almost all cases of BCG-osis.8 The mycobacterial culture was positive in 14 out 41 (36%) patients with only two blood cultures positive (4.8%) for mycobacterium in the retrospective review of systemic BCG infection following intravesical instillation of BCG by Gonzalez et al.4 There is no consensus regarding the ATT regimen for systemic BCG-osis. Multidrug regimen with or without steroids for 6–9 months should be considered. Pyrazinamide is avoided as M. bovis is resistant to it.5–7 Corticosteroids have a role in severe BCG-osis (as hypersensitivity plays a role in granuloma formation and multi-organ dysfunction), and in cases of respiratory involvement.8 The recommended dose of steroid is prednisolone 40 mg daily with a tapering regimen.6,9 In our patients, there was no evidence of lung involvement, and both had improvement with ATT without any paradoxical worsening. Therefore, steroids were not started. Prior BCG–osis is an absolute contraindication to Intravesical BCG reinstillation.5 Thus, intravesical BCG therapy was not given to either of our patients.

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The role of the urologist in educating and enforcing the correct route of intravesical BCG administration to the patient cannot be overemphasized. Patient education and enforcement of the intravesical route of BCG instillation by a qualified and experienced person are essential. A proper prescription with the route of administration should be written in capital and full form as “INTRAVESICAL” and not as “IV.” Proper prescription, clear instructions, and education of the patient may go a long way in preventing liability of negligence also. In the rare event that this complication occurs, prompt evaluation and treatment are needed.

CONCLUSION

Inadvertent IV BCG administration leading to systemic BCG-osis is a very rare but serious complication. This can be prevented by educating the patient regarding the correct route of administration and giving a clear, unambiguous recommendation at the time of discharge. In the rare event it occurs, prompt evaluation and treatment with anti-tubercular treatment are needed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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