



Oncology

Hemophagocytic syndrome in A patient of upper urinary tract urothelial cancer after Bacillus Calmette-Guérin instillation: A case report

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ABSTRACT

Bacillus Calmette-Guérin (BCG) therapy is an adjuvant treatment for urothelial carcinomas of the upper urinary tract (UTUC). BCG therapy can result in various side effects. We present a case of a 67-year-old female with a history of UTUC who developed disseminated tuberculosis following BCG instillation into the upper urinary tract after conservative management. This complex clinical scenario required a multidisciplinary approach, including antibiotic therapy, immunoglobulin infusion, and tailored tuberculosis treatment. The case underscores the importance of vigilance, early detection, and tailored interventions in managing disseminated tuberculosis arising from BCG therapy and rare complications like hemophagocytic syndrome.

1. Introduction

Bacillus Calmette-Guérin (BCG) stands out as a frequently utilized and effective intravesical immunotherapy for superficial bladder cancer.^{1,2} A strategy for the prevention of recurrent urinary bladder urothelial carcinoma (UC) is BCG instillation.³ There is also a therapeutic topical upper urinary tract instillation as adjuvant treatment after conservative management of urothelial carcinomas to treat urothelial carcinomas of the upper tract (UTUC).⁴ According to the European Association of Urology (EAU) guideline, the instillation of BCG via either retrograde or antegrade catheter may reduce the recurrence. However, possible side effects can occur if reflux or the presence of obstruction.⁵

BCG therapy's reported side effects encompass a range of manifestations including fever, urinary tract infections, allergic reactions, tuberculosis systemic infections, contracted bladder, mycotic pseudoaneurysm, sepsis, and immune-allergic reactions.^{6,7} While managing BCG side effects has garnered attention, including more common symptoms like urinary urgency, frequency, and discomfort, more severe consequences such as bladder irritation, inflammation, and BCG infection can also arise.⁸ Systemic tuberculosis infection after BCG instillation in

terms of BCGitis has been a systematic review.⁹ Moreover, the occurrence of hemophagocytic syndrome post-BCG instillation is exceedingly rare, characterized by hyperactive immune response, consequential inflammation, and tissue damage. This syndrome's limited cases of occurrence after BCG therapy have been documented.¹⁰⁻¹³ We report and literature review a serious complication of hemophagocytosis following BCG instillation in a patient with upper urinary tract urothelial carcinoma.

2. Case report

This is a 67-year-old female patient without smoking history had a medical history of left sphenoidal ridge meningioma, and left ureteropelvic junction urothelial cell carcinoma (UCC) for which she had previously undergone laparoscopic left nephroureterectomy 3 years ago. Pathology report revealed infiltrating urothelial carcinoma, high grade, in the left renal pelvis, with no involvement of hilar lymph nodes. The pathological stage was determined as pT3 N0, cM0, corresponding to stage III according to the AJCC 8th edition classification. She has been regularly followed including cystoscopy, urinary cytology and abdomen

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computed tomography (CT). She was found to have right upper ureteral tumor with hydronephrosis at this year from CT image (Fig. 1). The solitary papillary tumor was located at upper ureter and was excised during ureteroscopy with laser after biopsy. The pathology was urothelial carcinoma, low grade. She refused suggestion of further surgery of nephroureterectomy because of not willing to accept permanent hemodialysis after operation. The patient's initial admission was prompted for which underwent right ureter catheter for intrapelvic BCG instillation. We administered BCG using 3 vials in 100 mL of normal saline via gravity drip through a 4 French ureteral catheter, with the drip lasting approximately 2 hours.

Following the procedure, the patient developed fevers, nocturnal joint discomfort, and anorexia. Initial blood tests revealed neutropenia [white blood count (WBC) $0.9 \times 10^3/\mu\text{L}$, neutrophil segment 38.9%, lymphocyte segment 60.4%], accompanied by septic shock. Subsequent lab analyses demonstrated elevated liver transaminase levels [alanine aminotransferase (ALT) 70 IU/L]. Antibiotics, specifically Tazocin, were administered immediately upon the onset of fever suspected to be indicative of a typical urinary tract infection (UTI). However, despite antibiotic treatment, the fever persisted. Consequently, we sought consultation with an infectious disease specialist for suspected extrapulmonary tuberculosis (TB) infection. Urine acid-fast stain (AFS) indicated a positive result, raising suspicion of BCG-induced tuberculosis and necessitating exclusion of extrapulmonary TB. Anti-TB medication was initiated on day 5. The initiation of anti-TB medication occurred on day 5 following consultation with an infectious disease specialist. The anti-TB regimen comprised isoniazid 250 mg once daily, rifampicin 525 mg once daily, ethambutol 800 mg once daily, and moxifloxacin 400 mg once daily, resulting in gradual fever resolution.

Despite initial improvement, the patient experienced a relapse characterized in a critical condition by jaundice, fever and diminished appetite, prompting her readmission. Despite ongoing tuberculosis treatment, her condition deteriorated further. We began to consider whether there were other causes that could induce such severe symptoms, including jaundice, and arranged for further examination. Hematological assessments revealed neutropenia (neutrophil count $2.7 \times 10^3/\mu\text{L}$) and anemia (hemoglobin level 10.3 g/dL). A high-sensitivity inflammatory marker of C-reactive protein (hsCRP) level of 17.49 mg/L was significantly elevated. Elevated bilirubin levels were also observed, with total bilirubin at 3.23 mg/dL and direct bilirubin at 2.26 mg/dL. Liver function abnormalities were apparent through increased levels of aspartate aminotransferase (AST) at 76 U/L, alkaline phosphatase (ALP) at 232 U/L, and gamma-glutamyl transferase (r-GT) at 293 U/L. Additionally, the patient exhibited a high ferritin level of 5978 ng/mL, an elevated lactate dehydrogenase (LDH) level of 636 U/L.

Her clinical status did not significantly improve with antibiotics, although partial relief was noted with hydrocortisone. Recurrent fevers,



Fig. 1. Computed tomography revealed mild ureter wall thickness at right ureter (arrowhead).

elevated ferritin levels, and bicytopenia led us to investigate other potential causes besides systemic tuberculosis. Consequently, a bone marrow aspiration was performed due to a high suspicion of hemophagocytosis, and the pathological result confirmed it. For further treatment, intravenous immunoglobulin (IVIG) at a total dose of 2 g/kg over five days, in conjunction with dexamethasone (5 mg intravenously every 12 hours), was administered to address hemophagocytosis. Positron emission tomography (PET) demonstrated increased FDG uptake in the spleen and liver, suggesting a hemophagocytic process and disseminated TB (BCG-induced) infection (Fig. 2). Antibiotic therapy comprising Amikacin, Levofloxacin, and Ethambutol was initiated due to impaired liver function. Dexamethasone was subsequently tapered, and a regimen of Rifampicin, Ethambutol, and Levofloxacin was introduced for definitive BCG treatment. This comprehensive clinical approach underscores the challenges posed by disseminated TB in the context of BCG-induced infection and highlights the importance of tailored therapeutic strategies. Her general conditions improved gradually and regularly treated in an OPD section.

3. Discussion

The utilization of intravesical BCG to manage high-risk superficial bladder cancer, it has proven to be an effective treatment method with a generally favorable safety profile. Commonly observed adverse effects encompassed BCG-induced cystitis, bacterial infections,¹⁴ increased urinary frequency, noticeable blood in the urine (frank hematuria), general discomfort (malaise), and fever.^{15,16} Notably, a large cohort of 6753 patients, 1% developed BCG infections in the study period.¹⁵ Another cohort of 418 patients, the incidence of severe complications was about 1.7%.¹⁷

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by the overactivation of macrophages, leading to extensive tissue inflammation and damage.¹¹ Additionally, HLH can also arise secondarily due to various factors like hematologic malignancies, autoimmune disorders, or infections. Initial suspicion of hemophagocytic syndrome arose from clinical indicators such as fever and hepatosplenomegaly, along with biochemical findings including pancytopenia, elevated ferritin levels, and hypertriglyceridemia. Subsequent confirmation was achieved through a bone marrow aspiration. Manganas et al. reported a case involving a 64-year-old man who exhibited hemophagocytic lymphohistiocytosis (HLH) subsequent to BCG instillation.¹¹ Despite the administration of anti-TB therapy (isoniazid, rifampin, ethambutol) alongside Levofloxacin, high-dose prednisone (1 mg/kg/day), and intravenous immunoglobulin (IVIG) (400 mg/kg/day for five days), these interventions proved ineffective. Consequently, the authors recommended the utilization of Dexamethasone at a dose of 10 mg/m² for confirmed HLH. However, corticosteroid treatment in our patient did not reveal greater improvement clinically until immunoglobulin therapy add on.

The case report emphasizes the intricate interplay between BCG-induced tuberculosis, disseminated infection, and associated hematological and hepatic manifestations. Previous adjuvant chemotherapy with Gemcitabine 3000 mg and Carboplatin 360 mg was administered subsequent to nephroureterectomy. This history of chemotherapy may be a contributing factor to immunosuppression. Additionally, there was no history of exposure to tuberculosis (TB) prior to this occurrence. The utilization of a comprehensive approach involving antibiotic therapy, immunosuppression, and tailored tuberculosis treatment showcases the multidisciplinary efforts required to manage such complex clinical scenarios.¹⁸ This case underscores the importance of constant vigilance, early detection, and appropriate management strategies in the context of disseminated tuberculosis arising from BCG therapy.

In conclusion, hemophagocytosis is rare complication following intra-pelvis instillation of BCG for the treatment of urothelial carcinoma. The clinical presentation including an unusual persist fever, leucopenia, elevation of inflammatory marker, liver function impairment,

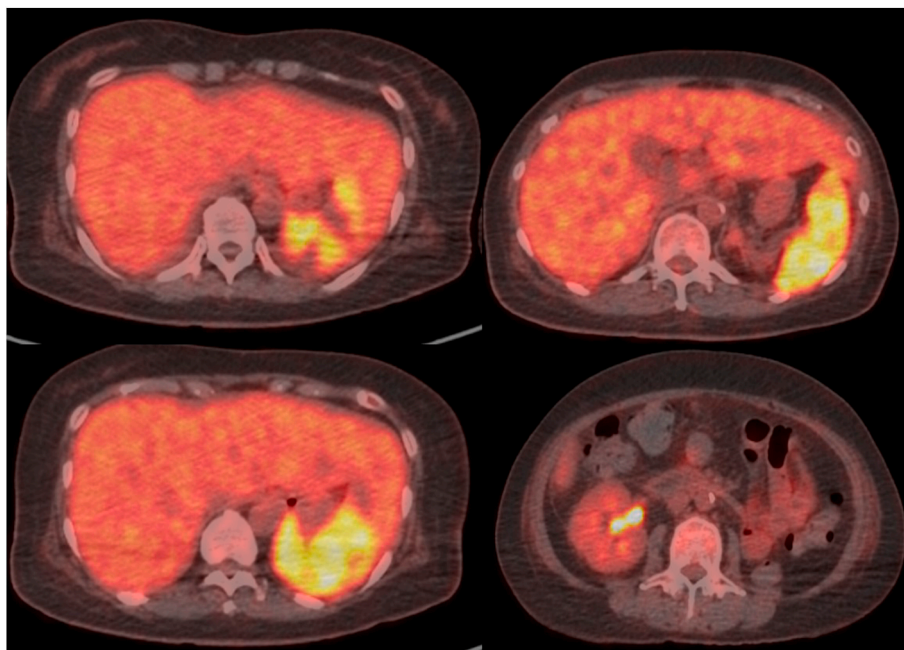


Fig. 2. Positron emission tomography (PET) scan reveals enhanced FDG uptake in spleen and liver, indicating hemophagocytic activity and disseminated BCG-induced TB infection.

splenomegaly, high ferritin serum level and elevation of LDH. One should pay attention to the unusual symptoms in patient of UC after intra-pelvic instillation of BCG. Intravenous infusion of immunoglobulin with steroid has clinical effect in this patient.

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Institutional review board statement

The present study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. However, as this was a retrospective case report and did not involve any interventions or modifications to the patient's treatment plan, ethical review and approval were waived by the institutional review board. Although ethical approval was not required in this case, patient privacy and confidentiality were maintained throughout the study. It is important to note that ethical considerations are of paramount importance in medical research, particularly when conducting studies involving human subjects. Informed consent, confidentiality, and protection of vulnerable populations are just a few examples of the ethical principles that must be upheld in such studies. While retrospective case reports may not require ethical approval in all cases, it is still crucial for researchers to be aware of and adhere to ethical guidelines in order to protect patient rights and ensure the integrity of the research.

Informed consent statement

Informed consent was obtained from the subject involved in the case report.

Data availability statement

All of the data are available upon request to the corresponding

author.

CRediT authorship contribution statement

Ting-Lien Li: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Chi-Ping Huang:** Methodology, Investigation. **Chia-Yu Lin:** Methodology, Investigation. **Mao-Wang Ho:** Methodology, Investigation. **Chia-Hui Cho:** Methodology, Investigation. **Yung-Hsiang Chen:** Writing – review & editing, Validation, Supervision, Funding acquisition, Formal analysis. **Wen-Chi Chen:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest.

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