CASE REPORTS

UDC: 616.62-006-089-085.37-036.88
DOI: https://doi.org/10.2298/VSP210412065S

Severe hemophagocytic syndrome after intravesical BCG instillation with a fatal outcome

Težak hemofagocitni sindrom nakon intravezikalne instilacije BCG sa fatalnim ishodom

Stevan Stojanović*†, Saša Vojinov*†, Žarko Dimitrić*, Ivan Levakov*†, Dimitrije Jeremić*†, Tanja Lakić†‡

University Clinical Center of Vojvodina, *Clinic for Urology, ‡Center for Pathology and Histology, Novi Sad, Serbia; †University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Abstract

Introduction. Hemophagocytic syndrome (HS) after *Bacillus Calmette-Guérin* (BCG) immunotherapy is extremely rare in everyday practice. Only three cases of HS have been reported in the world until now. BCG is used for preventing the recurrence of superficial tumors of the urinary bladder. Severe complications after BCG immunotherapy are rarely seen. **Case report.** A 55-year-old patient was transferred to the Clinic for Urology after the second round of BCG immunotherapy, in bad condition, after transurethral resection of a bladder tumor. Computed tomography of the abdomen and lesser pelvis was performed, which did not indicate any clear signs of organ failure or disease. Antitubercular, antibiotic, corticosteroid, and symptomatic therapies were applied. The achieved effect of therapy was not satisfactory. HS after BCG immunotherapy was suspected. During further hospitalization, the patient's already severe condition further deteriorated and became more complicated in the form of multiorgan dysfunction syndrome. Death occurred on the sixth day of hospitalization. A urine culture test was performed *post-mortem* and three months later, it was positive for *Mycobacterium xenopi*. **Conclusion.** Secondary HS after BCG immunotherapy is an extremely rare disease accompanied by a severe general condition of the patient, with many life-threatening complications that can lead to death. We have presented a case of severe HS after BCG immunotherapy that caused the death of the patient. This case was unique because, for the first time, the possible causative agent was isolated – *Mycobacteria*.

Key words:
bcg vaccine; lymphohistiocytosis, hemophagocytic; multiple organ failure; mycobacterium xenopi; urologic surgical procedures.

Apstrakt

Uvod. Hemofagocitni sindrom (HS) nakon *Bacillus Calmette-Guérin* (BCG) imunoterapije se u svakodnevnoj praksi sreće izuzetno retko. Do sada su opisana samo tri slučaja HS u svetu. BCG imunoterapija se koristi u prevenciji recidiva površinskih tumora mokraćne bešike. Teške komplikacije nakon BCG imunoterapije su izuzetno retke. **Prikaz bolesnika.** Bolesnik star 55 godina premešten je na Kliniku za urologiju u lošem stanju nakon druge doze BCG imunoterapije, nakon transuretralne resekcije tumora mokraćne bešike. Načinjena je kompjuterizovana tomografija abdomena i male karlice, koja nije ukazivala na jasne znake oboljenja ili zatajenja organa. Primenjena je antituberkulozna, antibiotska, kortikosteroidna i simptomatska terapija kojom nije postignut zadovoljavajući efekat. Postavljena je sumnja na postojanje HS uzrokovanog primenom BCG imunoterapije. U daljoj hospitalizaciji došlo je do produbljivanja bolesti i razvoja komplikacija u vidu multiorganskog disfunkcionalnog sindroma. Smrt je nastupila šestog dana hospitalizacije. Posle smrti bolesnika, urađena je urinokultura koja je tri meseca nakon zasejavanja bila pozitivna na *Mycobacterium xenopi*. **Zaključak.** Sekundarni HS nakon BCG imunoterapije je izuzetno retko oboljenje, praćeno teškim opštim stanjem bolesnika, uz mnoštvo pretećih komplikacija koje mogu dovesti do smrtnog ishoda. Prikazali smo bolesnika kod koga se HS nakon BCG imunoterapije završio smrtnim ishodom. Ovo je jedinstven slučaj, jer je prvi put izolovan mogući uzročnik – mikobakterija.

Ključne reči:
bacillus calmette-guerin; limfohistiocitoza, hemofagocitna; insuficijencija više organa; mycobacterium xenopi; hirurgija, urološka, procedure.

Correspondence to: Stevan Stojanović, University Clinical Center of Vojvodina, Clinic for Urology, Hajduk Veljkova 1–9, 21 000 Novi Sad, Serbia. E-mail: stevan.stojanovic@mf.uns.ac.rs

Introduction

Hemophagocytic syndrome (HS) is an extremely severe, life-threatening condition. HS is the result of an excessive immune response of the organism, and it can be primary and secondary. In 1976, Morales et al. [1] devised a treatment protocol that is still used successfully today. Until now, no severe or fatal outcomes have been reported after BCG immunotherapy instillation. The clinical symptoms of HS are not easily recognizable because they are usually accompanied by general symptoms in the form of fever. Unfortunately, this disease is recognized at an advanced stage after a series of extensive clinical and laboratory examinations. There is no specific therapy. Only three cases of HS have been reported after *Bacillus Calmette-Guérin* (BCG) immunotherapy so far. The aim of this paper was to present a case of secondary HS after BCG immunotherapy, which ended in death due to complications. For the first time, a possible causative agent was isolated. The question is whether there is any possibility that *Mycobacteria* can cause this type of immune response. There is a hope that further research will determine the exact cause of HS, as well as specific therapy.

We present a patient with HS caused after immunotherapy with BCG performed after surgical treatment, transurethral resection of bladder tumor (TURBT), for superficial bladder tumor.

Case report

A 55-year-old patient was transferred to our Clinic in bad condition characterized by fever symptoms, initial signs of liver and kidney failure, and abdominal pain under the right rib cage. From the anamnestic data, the patient did not take any drugs and did not suffer from other chronic diseases. The patient was hospitalized in the General Hospital a week after the second round of instillation of BCG immunotherapy into the urinary bladder. A cystoscopy and surgical treatment were performed before the transfer to our Institution. Cystoscopy revealed two tumors about 2 × 1 cm large on the right bladder wall. That was the first presentation of the tumor. TURBT surgery was performed. The pathohistological examination indicated papillary transitional cell carcinoma (TCC), pT1-high grade. The Morales treatment was applied 30 days after the TURBT surgery. After the first dose of BCG immunotherapy, the patient did not feel any signs of local or general side effects. However, after the second dose, the patient started shivering with fever and displaying general weakness and fatigue. The patient was prescribed the antituberculosis drug rifampicin and dual antibiotic therapy with amikacin and ceftriaxone. The treatment worsened the patient's condition, causing abdominal pain and pain under the right rib cage, after which the patient was transferred to our Clinic.

The latest laboratory results before being transferred to our Clinic were as follows: total bilirubin 103.9 μmol/L [reference range (RR) 3.0–21.0 μmol/L], direct bilirubin 81.4 umol/L (RR 0.1–4.2 μmol/L), amylases 36 U/L (RR 20–102 U/L), alkaline phosphatase (ALP) 557 U/L (RR 43–115 U/L), alanine aminotransferase (ALT) 515 U/L (RR 5–63 U/L), aspartate aminotransferase (AST) 747 U/L (RR 5–37 U/L), gamma-glutamyl transferase (GGT) 1.181 U/L (RR 3–55 U/L), C-reactive protein (CRP) 111.1 mg/L [normal values (NV) < 5.0 mg/L].

New laboratory analysis indicated leukopenia 3.2 × 10^9/L (RR of white blood cells is 4.0–10.0 ×10^9/L) and hemostasis disorder. Activated partial thromboplastin time (aPTT) was 2.45 ratio (R) (NV < 1.30 R), prothrombin time (PT) was 1.37 R (NV < 1.30 R), fibrinogen was 0.89 g/L (RR 2.20–4.96 g/L), a slight rise in nitrogens – urea 10.7 mmol/L (RR 2.2–7.1 mmol/L), creatinine 126 mmol/L (RR 49–115 mmol/L), potassium 4.4 mmol/L (RR 3.5–5.1 mmol/L), and a slight decrease in ALT, AST, ALP, GGT, and CRP values were found. Values of the other tested laboratory parameters were as follows: procalcitonin (PCT) 1.15 ng/mL (NV < 0.05 ng/mL), beta 2 microglobulin > 15.99 mg/L (RR 0.97–2.64 mg/L), total cholesterol 2.74 mmol/L (NV < 5.21 mmol/L), triglycerides 2.38 mmol/L (NV < 1.71 mmol/L), D-dimer > 10,000 ng/mL (NV < 500 ng/mL), ferritin 3,224 ug/L (RR 15–30 ug/L), albumins 27 g/L (RR 35–55 g/L), lactate dehydrogenase 591 U/L (RR 120–246 U/L), cholinesterase 3,640 U/L (RR 4,389–10,928 U/L). Reverse transcription polymerase chain reaction (RT-PCR) for cytomegalovirus, hepatitis C virus (HCV), hepatitis B virus, human immunodeficiency virus as well as latex-RF test, Waller-Rose test, hemoculture and urine culture were negative. Antistreptolysin O test was < 200 u/mL (NV up to 200 u/mL). A computed tomography (CT) scan of the abdomen and lesser pelvis showed liver enlargement with signs of periportal edema and an edematous gallbladder wall without intraluminal contents. CT scan also showed an enlarged spleen with slight perisplenic effusion and slight effusion in the lesser pelvis. Antibiotic ceftriaxone and amikacin and antituberculotic drug rifampicin treatments were stopped. Triple antibiotic treatment was prescribed: linezolid 600 mg/12 hrs, meropenem 1g/8 hrs, and metronidazole 500 mg/8 hrs.

Due to the deterioration of the patient's condition on the second day of hospitalization, he was transferred to the intensive care unit. HS caused by BCG immunotherapy was suspected. The treatment was changed, by adding the following: immunoglobulin, in doses of 10 g per 8 hrs; methylprednisolone sodium succinate, in doses of 40 mg per 8 hrs, according to the following schedule: 80 mg + 40 mg + 40 mg; one dose of cryoprecipitate, a second-generation fluoroquinolone 100 mg/8 hrs, was included as an additional antibiotic; metronidazole treatment was stopped, and hemodialysis was conducted. On the third day of hospitalization, the patient's breathing deteriorated, and hemoptysis occurred; thus, the patient received mechanical ventilation. Laboratory values were in decline: aPTT 9.36 R, PT 2.37 R, urea 23.2 mmol/L, creatinine 282 mmol/L, direct bilirubin 107 μmol/L, total bilirubin 148.6 μmol/L, ALP 542 U/L, AST 641 U/L, GGT 1.247 U/L, ALT 222 U/L, potassium 5.5 mmol/L, PCT 21.32 ng/mL. The peripheral blood film indicated anisopoikilocytosis. Results of chemiluminescent immunoassay (CLIA) and fluorescence immunoassay (ELFA) VIDAS anti-HCV assays were as follows: CLIA, anti-HCV

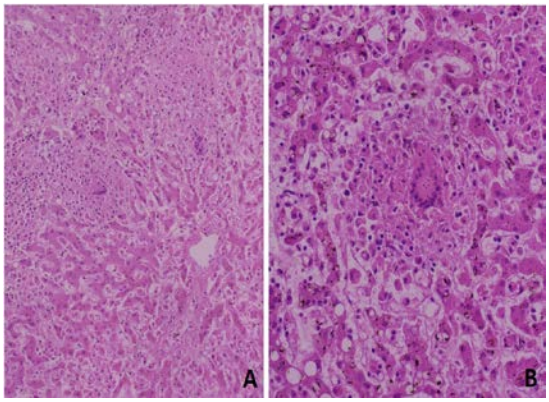

Fig. 1 − Granulomatous hepatitis:
A) hematoxylin-eosin (HE), ×100; B) HE, ×200.

– reactive 8.4 (normal < 1, reactive/positive ≥ 1) and ELFA VIDAS, anti-HCV – reactive 17.51 (normal < 1, reactive/positive ≥ 1). Antinuclear antibodies (ANA), antimitochondrial antibodies, antiparietal cell antibodies, anti-smooth muscle antibodies, and ANA HeP-2 cells screening were negative. A repeated CT scan of the thorax and abdomen showed consolidation of both sides of the lung parenchyma (of inflammatory etiology) and bronchiectasis in the inferior lobes on both sides with minor pleural effusion, hepatosplenomegaly, ascites, and portal hypertension. A bronchoscopy was done on the fourth day.

Due to a severely bad general condition, sepsis, suspicions of secondary HS caused by BCG immunotherapy, and the consequential multiple organ dysfunction syndrome (MODS), death occurred on the sixth day of hospitalization.

The patient's body was sent for autopsy. The autopsy confirmed a severe case of HS with signs of hepatorenal syndrome, pulmonary edema, ascites, endogenous intoxication, and consequential MODS, while histopathological analysis proved the existence of granulomatous hepatitis with granulomas composed of lymphocytes and individual Langhans multinucleated giant cells, with smaller focused areas of necrosis (Figure 1). Liver weight was 3,400 g. The Ziehl-Neelsen stain was used for liver tissue, and granulomatous structures were negative for the presence of acid-alcohol-resistant bacillus. The urinary bladder was without signs of residual tumor tissue and no granulomas, but granulation tissue had been found as the result of previous transurethral resection. Spleen weight was 1,300 g with a very soft cut surface, and pathohistological findings showed slight atrophy of white pulp and histiocytic infiltration of the spleen parenchyma with some erythrophagocytosis and no granulomas.

Tests of blood and urine culture for *Mycobacterium* that were done *post-mortem* were negative. After three months of cultivation, urine culture microscopically proved positive for *Mycobacterium xenopi (M. xenopi).*

Discussion

BCG immunotherapy for preventing the recurrence of superficial tumors of the urinary bladder is considered a safe treatment [2]. It was first described by Morales et al. [1] and has since been in use in urologic oncology. The most common adverse effects are mild and light, while more severe ones are rarely encountered (< 5%). Severe adverse effects are often localized inflammatory processes combined with an immunological response and happen within the first three months of intravesical BCG instillation [3].

HS is a collection of disorders that includes sepsis and conditions similar to sepsis, cytopenia, hepatosplenomegaly, coagulation disorders, disorders of the immune system, etc. There are two types of HS: hereditary (autosomal recessive, most common in children) and acquired (as a secondary outcome of other diseases in adults). HS was recorded with infectious viral diseases [2], associated with several cases of tuberculosis [4], and after BCG immunotherapy in three recorded cases worldwide. The commonality between all previously recorded HS cases after BCG immunotherapy is a good outcome [5–7]. The patient was transferred to our Institute with a progression of the primary disease and abdominal pain under the right rib cage, mild leukocytopenia, insignificant hemoglobinemia with a preserved hemostatic mechanism, uremia, azotemia, and high CRP. Additional differential diagnostics indicated a possible complicated form of cholecystitis, but laboratory and radiological parameters indicated an immunological disorder. Based on the CT scan (a consolidation of both lungs of inflammatory etiology and bronchiectasis with effusion, portal hypertension, ascites, hepatosplenomegaly), negative RT-PCR tests, anisopoikilocytosis, sepsis, hyperferritinemia, hyperlipidemia, a hemostatic disorder, and hemoptysis, the diagnosis was secondary HS caused by BCG immunotherapy [8, 9]. According to Morales et al. [1], hyperferritinemia with values almost 11 times higher than normal is not a specific HS marker, while a result of over 10,000 mg/L can be considered a pathognomonic sign. Significantly higher values of D-dimer, hypertriglyceridemia, pancytopenia, and hypofibrinogenemia are considered clear signs of HS [10, 14]. Pathophysiological HS is completely unstudied. It is believed that uncontrolled activation of T-lymphocytes starts an immune response by activating macrophages *via* Th_1 cytokines [8]. According to De Kerguenec et al. [15], this process occurs in 34% of patients who receive BCG treatment, leading to liver damage and elevated rates of liver enzymes. In Thevenot et al. [7], the cause of HS and proven granulomatous

hepatitis is a hypersensitive reaction and not BCG-caused HS (*Mycobacterium* was not isolated), as well as a positive response to corticosteroid and antibiotic treatment. In our case, the initially prescribed anti-tuberculosis (and later stopped), antibiotic, symptomatic, and anti-inflammatory treatment did not have a positive effect. Replacement therapy with plasma and immunoglobulin had a short-term positive effect. *M. xenopi* was isolated for the first time in our case after three months of cultivation. A case of isolating any strain of *Mycobacterium* has not been recorded until now [5–7, 14, 16, 17]. We have confirmed by autopsy that the issue was a systemic inflammatory response, HS, and MODS as a consequence.

Conclusion

HS is an immunologic-hematologic disorder that can occur as a secondary effect after BCG immunotherapy and is hard to diagnose. The fact that it has only been recorded a few times as a consequence of BCG immunotherapy makes it more difficult to recognize. Contributing factors are bacterial infections which can lead to death.

M. xenopi can be considered one of the potential factors which contribute to the BCG immunotherapy-caused HS mortality rate. The therapy has not been researched enough, but we can conclude that antibiotic therapy has no beneficial effect. Replacement therapy (immunoglobulin, cryoprecipitates, symptomatic) had a short-term but positive effect. Antituberculosis therapy should be the first choice, considering we are dealing with a *Mycobacterium* strain, as well as systemic therapy with maximal doses of corticosteroids to reduce the systematic inflammatory response.

We stress that it is necessary to recognize the symptoms in time and follow the precise instructions for treating recurring tumors of the urinary bladder, which decreases the possibility of a fatal outcome.

Conflict of interest

The authors declare that they have received no financial support and have no conflict of interest.

Acknowledgment

The authors are grateful to Prof. Dr. Karmen Stankov for her valuable scientific suggestions and comments.

REFERENCES

1. *Morales A, Eidinger D, Bruce AW.* Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976; 116(2): 180–3.
2. *Emmenegger U, Schaer DJ, Larroche C, Neftel KA.* Haemophagocytic syndromes in adults: current concepts and challenges ahead. Swiss Med Wkly 2005; 135(21–22): 299–314.
3. *Lamm DL.* Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer. Clin Infect Dis 2000; 31(Suppl 3): S86–90.
4. *Brastianos PK, Swanson JW, Torbenson M, Sperati J, Karakousis PC.* Tuberculosis-associated haemophagocytic syndrome. Lancet Infect Dis 2006; 6(7): 447–54.
5. *Misra S, Gupta A, Symes A, Duncan J.* Haemophagocytic syndrome after intravesical bacille Calmette-Guérin instillation. Scand J Urol 2014; 48(3): 328–30.
6. *Schleinitz N, Bernit E, Harle JR.* Severe hemophagocytic syndrome after intravesical BCG instillation. Am J Med 2002; 112(7): 593–4.
7. *Thevenot T, Di Martino V, Lagrange A, Petrella T, Faucher JF, Fontan J,* et al. Granulomatous hepatitis and hemophagocytic syndrome after bacillus Calmette-Guerin bladder instillation. Gastroenterol Clin Biol 2006; 30(3): 480–2.
8. *Koumadoraki E, Madouros N, Sharif S, Saleem A, Jarvis S, Khan S.* Hemophagocytic Lymphohistiocytosis and Infection: A Literature Review. Cureus 2022; 14(2): e22411.
9. *Liu Y, Lu J, Huang Y, Ma L.* Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guérin for Bladder Cancer. J Oncol 2019; 2019: 6230409.
10. *Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL.* Hemophagocytic lymphohistiocytosis in texas: Observations on ethnicity and race. Pediatr Blood Cancer 2010; 54(3): 424–8.
11. *Okamoto M, Yamaguchi H, Isobe Y, Yokose N, Mizuki T, Tajika K,* et al. Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. Intern Med 2009; 48(10): 775–81.
12. *Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T,* et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: Analysis of 30 cases. Rheumatology (Oxford) 2008; 47(11): 1686–91.
13. *Elhence A, Aggarwal A, Goel A, Aggarwal M, Das P, Shalimar.* Granulomatous Tubercular Hepatitis Presenting as Secondary Hemophagocytic Lymphohistiocytosis: A Case Report and Systematic Review of the Literature. J Clin Exp Hepatol 2021; 11(1): 149–53.
14. *Yang W, Pan Y, Ding S, Geng Y, Xu X.* Case Report-A case of hemophagocytic syndrome caused by mycobacterium abscess and literature review. Int J Clin Exp Med 2020; 13(7): 5218–22.
15. *de Kerguenec C, Hillaire S, Molinié V, Gardin C, Degott C, Erlinger S, Valla D.* Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. Am J Gastroenterol 2001; 96(3): 852–7.
16. *Elhence A, Aggarwal A, Goel A, Aggarwal M, Das P, Shalimar.* Granulomatous Tubercular Hepatitis Presenting as Secondary Hemophagocytic Lymphohistiocytosis: A Case Report and Systematic Review of the Literature. J Clin Exp Hepatol 2021; 11(1): 149–53.
17. *Shi W, Jiao Y.* Nontuberculous Mycobacterium infection complicated with Haemophagocytic syndrome: a case report and literature review. BMC Infect Dis 2019; 19(1): 399.

Received on April 12, 2021
Revised on June 9, 2022
Accepted on June 10, 2022
Online First June 2022