


CASE REPORT

Open Access



Granulomatous myocarditis arising from intravesical Bacillus Calmette–Guérin therapy leading to death diagnosed by postmortem examination: a case report

Saroja D. Geetha^{1*} , Hector D. Chavarria¹, Mohammed Abdelwahed¹, Nidhi Kataria¹, Vanesa Bijol¹ and Kasturi Das¹

Abstract

Background Intravesical Bacillus Calmette–Guérin (BCG) is used as a standard adjuvant therapy for non-muscle invasive urothelial cancer. Most patients tolerate the treatment well, with mild side effects. Systemic complications are extremely rare, occur due to BCG dissemination and are associated with immunocompromised state and urothelial breach.

Case presentation We present a case of a 78-year-old male, a former smoker, with history of non-muscle invasive urothelial carcinoma status post partial resection followed by intravesical BCG therapy. An autopsy was performed due to the sudden nature of his death. Autopsy showed multiple necrotizing granulomas in the brain, atrium, ventricles, lungs, kidneys, and urinary bladder. Stains for acid-fast bacilli and fungi were negative. In addition, bilateral lungs showed evidence of bronchopneumonia secondary to cytomegalovirus.

Conclusion Granulomatous myocarditis arising from BCG therapy is extremely rare. Our patient with urothelial cancer treated with BCG developed multiorgan granulomas, most likely due to a hypersensitivity reaction to intravesical BCG. Arrhythmia induced by granulomatous myocarditis was the cause of his death. Although there have been few cases of systemic BCG-osis causing fatal sepsis leading to death, a cardiac cause of death is unique.

Keywords Cardiac granuloma, Granulomatous myocarditis, Arrhythmia, Urothelial cancer, Bladder cancer, BCG therapy, Intravesical BCG, Systemic BCG-osis, Multiorgan granulomas, Death

Background

Bacillus Calmette–Guérin (BCG) is the live attenuated form of *Mycobacterium bovis* used as a vaccine for protection against tuberculosis and non-tuberculous

mycobacterial infection. Later, intravesical BCG installation became one of the treatment options for non-muscle invasive bladder cancer. This therapy is associated with a variety of adverse events, most of which are tolerable or controllable with supportive care. Few patients suffer severe side effects resulting from disseminated BCG infection, such as hepatitis, prostatitis, pneumonitis, arthritis, and mycotic pseudoaneurysms. Sepsis with fatal outcomes have been reported but are rare. Here we report a unique case of systemic BCG-osis with development of cardiac granulomas causing death.

*Correspondence:

Saroja D. Geetha
sgeetha1@northwell.edu

¹ Northwell Health, Department of Pathology, Zucker School of Medicine, North Shore University Hospital/Long Island Jewish Medical Center, 2200 Northern Blvd, Suite 104, Greenvale, NY 11548, USA



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Case presentation

We present a case of a 78-year-old man, a former smoker, with multiple chronic medical conditions on whom an autopsy was performed due to the sudden nature of his death. His cardiovascular history was significant for coronary artery disease, atrial fibrillation, and aortic stenosis status post-aortic valve replacement. A year prior, he had been diagnosed with non-invasive urothelial carcinoma and had undergone partial bladder resection followed by BCG therapy. His cancer was in remission. On follow up visits, he was found to have on and off fevers, following thorough multi-disciplinary investigations it was deemed to be a fever of unknown origin. One fine day, he collapsed at home and died. The sudden nature of his death, prompted a post-mortem examination. No specific gross findings were identified. However, microscopic examination revealed scattered necrotizing granulomas in the heart (Fig. 1A), both atria and ventricles, kidneys, bladder, and brain (Fig. 1C). Lungs showed non-necrotizing granulomas with bilateral bronchopneumonia (Fig. 1D) secondary to cytomegalovirus (CMV) infection as confirmed by CMV staining. The granulomas were

negative for acid-fast bacilli (AFB) (Fig. 1B) and Grocott's methenamine silver (GMS) stain.

Discussion and conclusions

Bladder cancer is the sixth most common cancer in the United States of America [1]. Incidence of bladder cancer increases with age, with the median age of diagnosis being 73 years [2]. The most common presenting symptom is painless hematuria. Histologically, bladder tumors can be classified as urothelial and non-urothelial. Urothelial cancer, also known as transitional cancers, are the most common type, accounting for 90% of all bladder cancers [3]. Management options are dependent on the depth of tumor invasion [3]. For muscle invasive tumors, radical cystectomy and chemotherapy is the mainstay. For superficial tumors, which includes carcinoma *in situ*, and non-muscle invasive tumors, transurethral resection of the bladder tumor followed by intravesical chemotherapy or BCG are the treatment options.

BCG primarily used as a vaccine for protection against severe and disseminated tuberculosis infection was discovered by bacteriologist–veterinarian duo, Albert Calmette and Camille Guérin. It was found that development

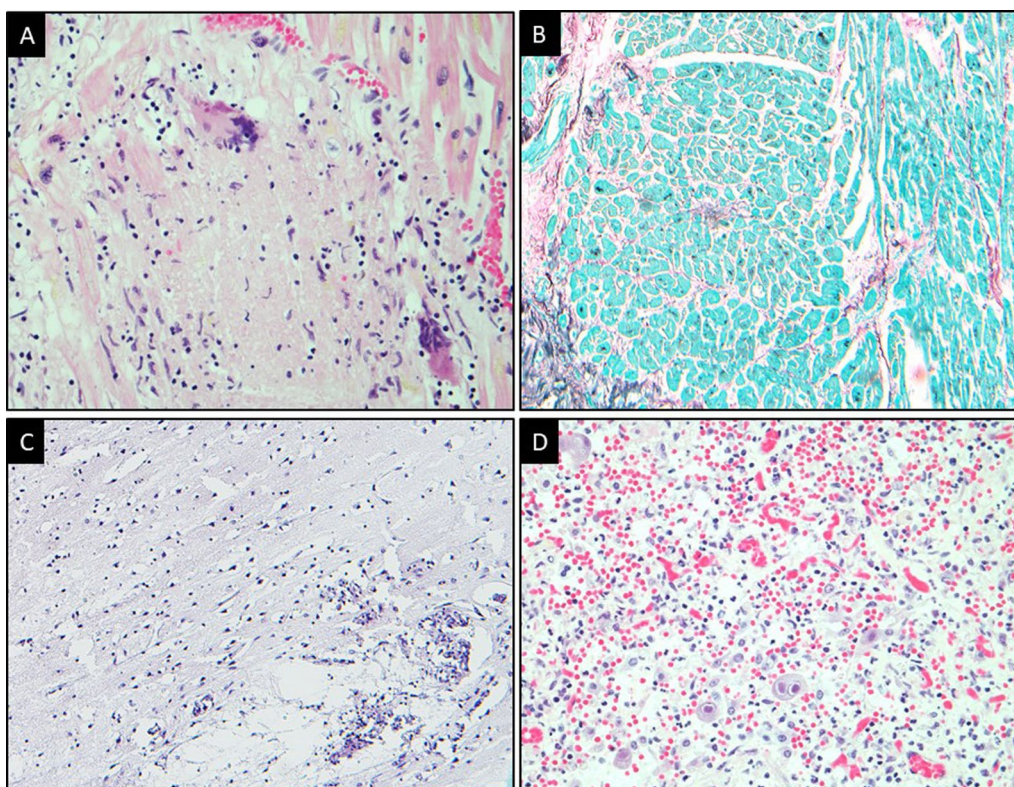


Fig. 1 **A** Granulomatous inflammation of the myocardium with multinucleate giant cells (H&E, 40x). **B** Absence of acid bacilli in the myocardial tissue (AFB stain, 10x), **C** Cerebral tissue with microglial nodules (H&E, 10x), **D** Lung tissue exhibiting pneumonia with cells showing prominent basophilic nuclear inclusions and clear halo consistent with CMV effect (H&E, 40x) are shown

of bacterial infections in patients with lymphosarcoma was known to cause disease remission, which resulted in the use of bacterial extracts as adjuvant therapy for head and neck tumors [4]. Further studies showed that patients with active tuberculosis infections were less likely to develop cancer and that cancer survivors had a higher incidence of tuberculosis infection compared with those who succumbed to cancer [5]. Soon studies were published demonstrating the usage of BCG in treatment of systemic lymphoblastic leukemias, primary cutaneous melanomas, and metastatic melanomas [6, 7]. Treatment efficacy was observed to be better with small, localized tumors, and with tumors that had direct contact with BCG. Based on these findings, Morales et al. [8] used intravesical BCG as adjuvant therapy for superficial urothelial carcinomas, which was a major success. Theories behind its anticancer effects are still evolving and the most studied include antiproliferative and cytotoxic effects on tumor cells [9, 10].

As with every immunotherapy, use of BCG is associated with side effects. Fever following BCG installation is the most common. Although it is indicative of good immune activation, it may also be the initial sign of sepsis. Allergic reactions include arthralgias, cramps, and rash. Local side effects are noted in majority of patients and result due to direct irritation of the urogenital lining. These include chemical cystitis, bladder contracture, epididymitis, prostate abscess, and urethral strictures [11–13]. Systemic complications occur due to BCG dissemination and are rare. It can be seen in immunocompromised individuals such as pregnant women, patients with diabetes, hematologic malignancies, or acquired immunodeficiency syndrome (AIDS). Another risk factor associated with dissemination is a breach in the urothelium, which promotes hematogenous spread and is commonly seen in the setting of catheterization [14]. Systemic complications include spondylodiscitis, mycotic pseudoaneurysm, pneumonitis, peritonitis, and granulomatous inflammation involving kidneys, prostate, liver, and lymph nodes [13, 15–17]. However, viable bacteria are not always identified. In such cases, a type four hypersensitivity reaction to BCG has been postulated [18, 19]. Granulomatous cardiomyopathy is a rare entity and can be seen in tuberculosis infection. They are known to cause ventricular tachycardia and arrhythmias [20]. To our best knowledge, BCG therapy causing cardiac granulomas is extremely rare and has not been reported before.

We present a BCG-treated patient with urothelial cancer with postmortem findings of multiple granulomas in the brain, heart, lungs, bladder, and kidneys, most likely due to systemic BCG-osis. AFB stain was negative for viable microorganisms favoring the hypersensitivity reaction rather than direct infection. An immunodeficiency

state demonstrated by CMV pulmonary infection could have been a predisposing factor. Arrhythmias induced by granulomatous myocarditis was the cause of his death. Although there have been few cases of systemic BCG-osis causing fatal sepsis leading to death, a cardiac cause of death from this complication is unique.

Abbreviations

BCG Bacillus Calmette-Guérin
CMV Cytomegalovirus

Acknowledgements

None.

Author contributions

SDG was a major contributor in writing the manuscript. HDC performed the autopsy. MA captured images. NK helped with manuscript edits. VB performed histologic examination of kidneys and helped polish the manuscript. KD is the primary pathologist who performed histologic examination of all other slides and signed out the autopsy report. All authors read and approved the final manuscript.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate.

Not required for case reports as per our institutional IRB policy.

Consent for publication

Written informed consent was obtained from the next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Received: 2 May 2023 Accepted: 6 December 2023

Published online: 10 January 2024

References

1. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA. Epidemiology of bladder cancer. *Med Sci (Basel)*. 2020;8(1):15.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7–34.
3. Bellmunt J, Orsola A, Maldonado X, Kataja V, Group EGW. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(Suppl 5):v134–6.
4. Nauts HC, McLaren JR. Coley toxins—the first century. *Adv Exp Med Biol*. 1990;267:483–500.
5. Pearl R. Cancer and tuberculosis. *Am J Hyg*. 1929;9:97–159.
6. Davignon L, Robillard P, Lemonde P, Frappier A. B.C.G. vaccination and leukemia mortality. *Lancet*. 1970;2(7674):638.
7. Morton DL, Eilber FR, Holmes EC, Hunt JS, Ketcham AS, Silverstein MJ, et al. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Ann Surg*. 1974;180(4):635–43.
8. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol*. 2017;197(2S):S142–5.

9. Riemensberger J, Böhle A, Brandau S. IFN-gamma and IL-12 but not IL-10 are required for local tumour surveillance in a syngeneic model of orthotopic bladder cancer. *Clin Exp Immunol*. 2002;127(1):20–6.
10. Brandau S, Riemensberger J, Jacobsen M, Kemp D, Zhao W, Zhao X, *et al*. NK cells are essential for effective BCG immunotherapy. *Int J Cancer*. 2001;92(5):697–702.
11. Steg A, Adjiman S, Debré B. BCG therapy in superficial bladder tumours—complications and precautions. *Eur Urol*. 1992;21(Suppl 2):35–40.
12. Oates RD, Stilmant MM, Freedlund MC, Siroky MB. Granulomatous prostatitis following bacillus Calmette-Guerin immunotherapy of bladder cancer. *J Urol*. 1988;140(4):751–4.
13. Brausi M, Oddens J, Sylvester R, Bono A, van de Beek C, van Andel G, *et al*. Side effects of Bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol*. 2014;65(1):69–76.
14. Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, *et al*. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol*. 1992;147(3):596–600.
15. Mody GN, Tran V, Landman J. BCGosis: case report of intravesicular bacille Calmette-Guérin causing upper tract granulomas simulating a renal mass without evidence of ipsilateral vesicoureteral reflux. *Urology*. 2009;73(2):444.e9–10.
16. Abu-Nader R, Terrell CL. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical BCG use. *Mayo Clin Proc*. 2002;77(4):393–7.
17. Pérez-Jacoiste Asín MA, Fernández-Ruiz M, López-Medrano F, Lumberras C, Tejido Á, San Juan R, *et al*. Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. *Medicine (Baltimore)*. 2014;93(17):236–54.
18. Leebeek FW, Ouwendijk RJ, Kolk AH, Dees A, Meek JC, Nienhuis JE, *et al*. Granulomatous hepatitis caused by Bacillus Calmette-Guerin (BCG) infection after BCG bladder instillation. *Gut*. 1996;38(4):616–8.
19. Lyons D, Miller I, Jeffers A. Systemic hypersensitivity reaction to intravesical BCG. *Scott Med J*. 1994;39(2):49–50.
20. Bohora S, Mumtaz Z, Phadke M, Bhute V, Bhatia V, Vora A, *et al*. Long-term, real world experience of ventricular tachycardia and granulomatous cardiomyopathy. *Indian Pacing Electrophysiol J*. 2022;22(4):169–78.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

