Original Article

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Exploring the Role of Granuloma Formation in the Prognosis of BCG-treated Bladder Carcinoma

Yasemen Adalı Ruşen[1], Uğur Mungan[2], Kutsal Yörükoğlu[3]

[1]*İzmir Democracy University Faculty of Medicine, Department of Pathology, İzmir, Türkiye*
[2]*Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Türkiye*
[3]*Dokuz Eylül University Faculty of Medicine, Department of Pathology, İzmir, Türkiye*

Abstract

Objective: Bacillus Calmette-Guérin (BCG) therapy continues to be a fundamental component in the treatment of non-muscle invasive bladder cancer. The objective of this study was to assess the relationship between granuloma formation resulting from BCG therapy and histopathological and clinical parameters.

Materials and Methods: This study encompassed 96 patients who underwent intravesical BCG therapy from 1990 to 2003. Post-treatment biopsy specimens were re-evaluated for the presence of granulomas. Cases demonstrating any number of granulomas were classified as positive for granulomatous response. The presence of granulomas was analyzed in relation to various factors including age, sex, pathological tumor stage, tumor grade, and the status of tumor recurrence and progression.

Results: The mean age of the cases was 64.13±10.34 years. The cases were predominantly male (85.4%, n=82) compared to those who were female (14.6%, n=14). Granuloma formation was identified in 39 cases (40.6%). Recurrence occurred in 48 cases (50%). Progression was observed in 11 patients (11.5%). The distribution of pathological stages was as follows: non-invasive tumors (pTa) in 70 cases (72.9%) and pT1 in 26 cases (27.1%). Tumor grading revealed 38 grade 1 cases (39.6%), 45 grade 2 cases (46.9%), and 13 grade 3 cases (13.5%).

Statistical analysis revealed no significant differences between cases with and without granuloma in terms of age (p=0.703), gender (p=0.052), recurrence (p=0.301), progression (p=0.761), time to recurrence (p=0.186), survival (p=0.367) or tumor grade (p=0.353). However, a significant difference was observed in the distribution of pathological stages and the frequency of granulomas was higher in cases with pT1 (p=0.011).

Conclusion: The study revealed a higher prevalence of stage pTa in patients without granulomas, suggesting that granuloma formation might be more likely in tumors that exhibit invasion. This could reflect differences in immune response elicited by BCG therapy or in biological/molecular characteristics of the tumor itself. The presence of granulomas doesn't strongly correlate with the overall prognosis. These results emphasize the need for further research to explore the mechanisms behind granuloma formation and its potential implications for treatment efficacy and patient management in more standardized case series.

Keywords: Bladder cancer, granuloma, BCG, prognosis

Introduction

Bladder cancer ranks as the ninth most common malignancy worldwide in both males and females (1). The majority of these tumors are histologically classified as urothelial carcinomas, where the extent of invasion into the bladder muscle tissue plays a crucial role in determining both the treatment strategy and prognosis. Urothelial carcinomas that do not invade the lamina propria are staged as non-invasive tumors (pTa), while those that have invaded the lamina propria are staged as pT1 (2). These tumors together are categorized as non-muscle-invasive bladder cancer (NMIBC) (3).

Intracavitary Bacillus Calmette-Guérin (BCG) instillation is a treatment modality selected based on the stage of bladder tumors and is used in addition to tumor excision (3). BCG, first introduced as an immunotherapy for NMIBC by Morales et al. (4) in 1976, is an attenuated strain of *Mycobacterium bovis* initially developed as a vaccine for *Mycobacterium tuberculosis*. A key characteristic of chronic inflammation caused by *Mycobacterium* species is granulomatous inflammation, marked by the formation of granulomas. In the context of bladder tumors, an increase in inflammatory cells within the bladder is observed following BCG instillation (5). Histopathologically, this manifests as erosion of

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Address for Correspondence: Yasemen Adalı Ruşen Assoc. Prof, İzmir Democracy University Faculty of Medicine, Department of Pathology, İzmir, Türkiye
E-mail: yasemenadali@hotmail.com **ORCID:** orcid.org/0000-0002-8004-7364
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the surface epithelium, lymphoplasmacytic cell infiltration, and granulomatous inflammation (6). These histological findings contribute to the immune response and are, in some cases, regarded as complications of BCG therapy. Among the most common local complications associated with intravesical BCG therapy, where the optimal number and frequency of applications have yet to be fully established, are cystitis and hematuria (3). BCG therapy can also lead to systemic reactions that may result in multiorgan failure, in addition to local complications such as granulomatous prostatitis and epididymoorchitis (3,7).

One of the primary objectives of administering BCG in bladder cancer, an example of field cancerization, is to prevent tumor recurrence (8). BCG functions as an immunomodulator, and its therapeutic effect is expected to be associated with granulomatous inflammation in the bladder. However, it is noteworthy that granulomas are not observed in some cases where BCG is administered, as seen in routine pathological practice. This absence of granuloma formation may be attributed to an inadequate immune response. Therefore, the aim of this study is to evaluate granuloma presence or absence, particularly focusing on recurrence and progression, with an emphasis on prognostic data.

Materials and Methods

The study was conducted following the approval of the Ethics Committee of İzmir University of Economics for Non-Interventional Research at its 52nd session (approval number: B.30.2.İEÜSB.0.05.05-20-172, date: 19.07.2022). Due to the retrospective design of the study, patient informed consent was waived. Ninety-six cases diagnosed with urothelial carcinoma between 1990 and 2003, who subsequently received intravesical BCG therapy, were included in the study. Cases diagnosed within the same time frame but lacking repeat biopsy, incomplete follow-up, or unavailable biopsy material were excluded. Hematoxylin and eosin stained sections from the repeat biopsy specimens were retrieved from the pathology archive and assessed for the presence of granulomas. Cases were considered positive for granulomas regardless of the number observed. Age and gender data were extracted from the hospital information management system, while recurrence, progression, and survival data were obtained from the records of the Department of Urology.

Statistical Analysis

Statistical analyses were conducted using the SPSS 15.0 software package (SPSS Inc., Released 2006, SPSS for Windows, Version 15.0, Chicago, SPSS Inc.). Analyses were performed using the Mann-Whitney U test and chi-square test, with a 95% confidence interval. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the 96 cases included in the study was 64.1±10.3 years, with the youngest patient being 32 years old and the oldest 89 years old. Of the cases, 82 were male (85.4%) and 14 were female (14.6%), with granuloma formation observed in 39 cases (40.6%). Tumor recurrence was documented in 50% of the cases, with a mean time to recurrence of 8.0±13.8 months. Progression was noted in 11 cases (11.5%). Pathological staging revealed that 70 cases were classified as pTa (72.9%) and 26 as pT1 (27.1%). Tumor grading showed that 38 cases (39.6%) were grade 1, 45 cases (46.9%) were grade 2, and 13 cases (13.5%) were grade 3. During the follow-up period, 5 cases (5.2%) died due to causes unrelated to bladder cancer.

The mean age of the cases with granuloma was 64.5±9.6 years. Regarding the gender distribution, 30 cases (76.9%) were male, and 9 cases (23.1%) were female. Tumor recurrence was detected in 22 cases (56.4%), while progression was noted in 4 cases (10.3%). The pathological stages among these cases were classified as pTa in 23 cases (59.0%) and pT1 in 16 cases (41.0%). Tumor grading revealed that 16 cases (41.0%) were grade 1, 13 cases (33.3%) were grade 2, and 10 cases (25.6%) were grade 3.

The mean age of the cases without granuloma was 63.9±10.9 years. Among these cases, 52 (91.2%) were male and 5 (8.8%) were female. Tumor recurrence was observed in 26 cases (45.6%), while progression was noted in 7 cases (12.3%). In this group, 47 cases (82.5%) were classified as pTa, and 10 cases (17.5%) as pT1. Tumor grading showed that 22 cases (38.6%) were grade 1, 32 cases (56.1%) were grade 2, and 3 cases (5.3%) were grade 3. Clinicopathological characteristics and outcomes in cases with and without granuloma formation following BCG therapy are summarized in Table 1.

In statistical analyses using the Mann-Whitney U test, no statistically significant relationship was found between granuloma formation and age ($p=0.703$), gender ($p=0.052$), or tumor grade ($p=0.353$). Similarly, no significant association was observed between granuloma formation and progression ($p=0.761$), recurrence ($p=0.301$), time to recurrence ($p=0.186$), or survival ($p=0.367$). In gender analyses, which were found to be close to statistical significance ($p=0.052$), it was observed that male dominance was striking in cases where granuloma formation was not observed (91.2% vs. 23.1%). Statistically significant results were obtained in the analysis of granuloma formation in relation to pT stage, indicating that granuloma development is less common in pTa ($p=0.011$).

Discussion

Approximately 25% of bladder cancers are muscle-invasive or metastatic, and treatment modalities for this patient group include neoadjuvant chemotherapy, radical cystectomy, and adjuvant chemotherapy (9). In non-muscle-invasive bladder cancers, intravesical chemotherapy can be administered following tumor resection via transurethral resection of the bladder tumor, which is advantageous, as it avoids the systemic effects of chemotherapy and significantly reduces disease recurrence (3,10). Although non-muscle-invasive bladder cancers generally have a relatively favorable prognosis, with a 5-year survival rate exceeding 85%, they present challenges related to patient quality of life and impose a substantial burden on the healthcare system due to frequent recurrences (11-13).

Intracavitary BCG is utilized as the primary treatment option for non-muscle-invasive bladder cancers at high risk of recurrence (14). Intravesical BCG administration has been shown to reduce recurrence, inhibit tumor progression, and improve

Table 1. Clinicopathological characteristics and outcomes in cases with and without granuloma formation following BCG therapy			
Variable	**Total cases (n=96)**	**With granuloma (n=39)**	**Without granuloma (n=57)**
Mean age (years)	64.1±10.3	64.5±9.6	63.9±10.9
Age range (years)	32-89	-	-
Gender			
- Male	82 (85.4%)	30 (76.9%)	52 (91.2%)
- Female	14 (14.6%)	9 (23.1%)	5 (8.8%)
Granuloma formation	39 (40.6%)	-	-
Pathological stage			
- pTa	70 (72.9%)	23 (59.0%)	47 (82.5%)
- pT1	26 (27.1%)	16 (41.0%)	10 (17.5%)
Tumor grade			
- Grade 1	38 (39.6%)	16 (41.0%)	22 (38.6%)
- Grade 2	45 (46.9%)	13 (33.3%)	32 (56.1%)
- Grade 3	13 (13.5%)	10 (25.6%)	3 (5.3%)
Tumor recurrence	48 (50%)	22 (56.4%)	26 (45.6%)
Mean time to recurrence (months)	8.0±13.8	-	-
Tumor progression	11 (11.5%)	4 (10.3%)	7 (12.3%)
BCG: Bacillus Calmette-Guérin, pTa: Non-invasive tumors, pT1: Low-grade and invasive tumors			

survival rates (15-17). Since Pearl's (18) 1928 article, which noted a lower incidence of tumors in autopsies of patients with tuberculosis, numerous studies have explored the relationship between tumors and tuberculosis (19-22). Early experimental studies evaluating the effects of BCG on tumors suggested that its mechanism of action was not direct cytotoxicity but rather the host's immune response (23,24). Since then, the therapeutic efficacy of BCG has been investigated across various tumor types, including melanoma (25). A significant milestone following the development of the BCG vaccine by Albert Calmette and Camille Guérin in 1921 was the 1976 report by Morales et al. (4), which demonstrated the efficacy of intracavitary BCG in treating non-muscle-invasive bladder tumors.

Since the introduction of BCG in the treatment of bladder cancer, our understanding of its mechanism of action has been continually refined. Tissue and fluid analyses from patients undergoing BCG therapy suggest that intravesical administration induces a multifaceted and complex immune response, involving both innate and adaptive immunity (26). Following BCG administration, inflammatory cells, predominantly granulocytes, macrophages, and lymphocytes, are readily observed in the urine (27). It has been reported that CD4+ T lymphocytes are the predominant cell typewhile similar cells are observed in the tissue response (5). Indeed, some studies have indicated that BCG immunization results in an accelerated T cell response (22). Histopathological examination of tissues reveals granulomatous inflammation, with lymphoplasmacytic inflammatory cells surrounding the granulomas (6).

Following intracavitary BCG administration, cytokine and chemokine secretions from urothelial and antigen-presenting cells are believed to stimulate the cellular components of the immune system (26). Histopathological examinations have demonstrated the presence of macrophages and dendritic cells in the bladder tissues of patients receiving BCG therapy (5) with an increased pre-treatment number of these cells being associated with poor prognosis (28,29). There are relatively few prognostic studies on granulomatous inflammation, the characteristic inflammation type induced by BCG treatment. Two of the few studies available suggest that granuloma formation is not associated with prognosis (30,31). However, Jallad et al. (32), who reported a relationship between granuloma formation and prognosis, evaluated granuloma and inflammation as two separate parameters in their study involving 215 cases. In their analysis, which grouped cases according to the presence or absence of granuloma/inflammation, they found that the absence of granuloma/inflammation was associated with a higher recurrence rate. Additionally, progression-free survival was reported to be higher in the presence of granuloma/inflammation (32).

In this study, no significant relationship was observed between granuloma formation and tumor grade, progression, recurrence, or survival. However, granuloma formation was significantly more common in pT1 tumors than in pTa tumors (p=0.011). This finding suggests that immune response alterations due to tumor invasion may trigger the immune mechanisms necessary for granuloma formation. While this phenomenon may be related to the immune response elicited by BCG, it could also be associated with the expression of different antigens at various pT stages of the tumor or even an increase in tumor mutational burden (TMB). The existence of studies highlighting the central role of the CD4+ T cell response in BCG treatment; the significance of the CD8+ T cell response; and their relationship with the programmed cell death ligand response supports this hypothesis (33,34). Additionally, considering the critical role of T cells in the

antitumor response, including granuloma formation, there is a need for further investigation in homogeneous and larger case series across different pT stages, in which tumor antigen load and TMB are evaluated alongside the depth of invasion.

Study Limitations

The preimmunization status of the cases included in this study with the BCG vaccine is unknown. This limitation, which is also present in many studies in the literature (32), impacts the study's ability to measure the effect of cytokine and T cell responses that could directly develop by bypassing the antigen-presenting cell step (potentially influenced by preimmunization). We believe that future studies should consider the inclusion of distinct groups of preimmunized and non-immunized cases in the selection of case series. This approach could be a significant step toward optimizing study outcomes.

Another limitation of this study is that the tumor grading was derived from the original pathology reports. Grading based on the 1973 World Health Organization criteria was found not to influence granuloma formation. Given that pTa are typically low-grade and invasive tumors (pT1) tend to be high-grade, similar results could be obtained when considering tumor stage (5).

Conclusion

While the roles of innate and adaptive immunity are evident in the mechanism of action of BCG, the precise mechanisms that determine the response to treatment remain incompletely understood. The evaluation of granuloma formation—potentially one of these mechanisms—alongside immune system components and the biological and molecular characteristics of the tumor at different stages, could provide valuable insights for predicting treatment response. Unraveling the mechanisms involved in BCG treatment may also provide information that guides immunotherapy, which has come to the forefront in cancer treatment today.

Ethics

Ethics Committee Approval: The study was conducted following the approval of the Ethics Committee of İzmir University of Economics for Non-Interventional Research at its 52nd session (approval number: B.30.2.İEÜSB.0.05.05-20-172, date: 19.07.2022).

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.A.R., U.M., K.Y., Concept: Y.A.R., K.Y., Design: Y.A.R., U.M., K.Y., Data Collection or Processing: Y.A.R., K.Y., Analysis or Interpretation: Y.A.R., U.M., K.Y., Literature Search: Y.A.R., U.M., K.Y., Writing: Y.A.R., U.M., K.Y.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359-386.
2. College of American Pathologists. Protocol for the examination of specimens from patients with urinary bladder biopsy. 2020. Available from: https://documents.cap.org/protocols/cp-urinary-bladder-biopsy-20-4020.pdf [Accessed 11 Aug 2020].
3. Babjuk M, Burger M, Compérat EM, et al. European association of urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) - 2019 update. Eur Urol. 2019;76:639-657.
4. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116:180-183.
5. Böhle A, Gerdes J, Ulmer AJ, et al. Effects of local bacillus Calmette-Guerin therapy in patients with bladder carcinoma on immunocompetent cells of the bladder wall. J Urol. 1990;144:53-58.
6. Lage JM, Bauer WC, Kelley DR, et al. Histological parameters and pitfalls in the interpretation of bladder biopsies in bacillus Calmette-Guerin treatment of superficial bladder cancer. J Urol. 1986;135:916-919.
7. Kiely B, McLaughlin AM, Lynch TH, Keane J. Intravesical bacille Calmette-Guérin-induced multiorgan failure after treatment for transitional cell carcinoma. Scand J Urol Nephrol. 2011;45:278-280.
8. Curtius K, Wright NA, Graham TA. An evolutionary perspective on field cancerization. Nat Rev Cancer. 2018;18:19-32.
9. Witjes JA, Bruins HM, Cathomas R, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol. 2021;79:82-104.
10. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. JAMA. 2018;319:1880-1888.
11. Berdik C. Unlocking bladder cancer. Nature. 2017;551:34-35.
12. James AC, Gore JL. The costs of non-muscle invasive bladder cancer. Urol Clin North Am. 2013;40:261-269.
13. Abdollah F, Gandaglia G, Thuret R, et al. Incidence, survival and mortality rates of stage-specific bladder cancer in United States: a trend analysis. Cancer Epidemiol. 2013;37:219-225.
14. Álvarez-Maestro M, Guerrero-Ramos F, Rodríguez-Faba O, et al. Current treatments for BCG failure in non-muscle invasive bladder cancer (NMIBC). Actas Urol Esp (Engl Ed). 2021;45:93-102.
15. Malmström PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56:247-256.
16. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168:1964-1970.
17. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:1124-1129.
18. Pearl R. On the pathological relations between cancer and tuberculosis. Exp Biol Med (Maywood). 1928;26:73-75.

19. Old LJ, Clarke DA, Benacerraf B. Effect of bacillus Calmette-Guerin infection on transplanted tumours in the mouse. Nature. 1959;184(Suppl 5):291-292.
20. Davignon L, Lemonde P, St-Pierre J, Frappier A. B.C.G. vaccination and leukaemia mortality. Lancet. 1971;1:80-81.
21. Mathé G, Amiel JL, Schwarzenberg L, et al. Active immunotherapy for acute lymphoblastic leukaemia. Lancet. 1969;1:697-699.
22. Yada Y, Tanaka N, Orita K. Augmentation of anti-tumor activity by immunization with Mycobacterium tuberculosis (Tbc) and tuberculin-coupled tumor cells. Acta Med Okayama. 1985;39:131-141.
23. Rosenthal SR, Crispen RG, Thorne MG, et al. BCG vaccination and leukemia mortality. Natl Cancer Inst Monogr. 1973;39:189-192.
24. Bast RC Jr, Zbar B, Borsos T, Rapp HJ. BCG and cancer. N Engl J Med. 1974;290:1458-1469.
25. Morton DL, Eilber FR, Holmes EC, et al. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. Ann Surg. 1974;180:635-643.
26. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol. 2018;15:615-625.
27. Chevalier MF, Trabanelli S, Racle J, et al. ILC2-modulated T cell-to-MDSC balance is associated with bladder cancer recurrence. J Clin Invest. 2017;127:2916-2929.
28. Takayama H, Nishimura K, Tsujimura A, et al. Increased infiltration of tumor-associated macrophages is associated with poor prognosis of bladder carcinoma in situ after intravesical bacillus Calmette-Guerin instillation. J Urol. 2009;181:1894-1900.
29. Ayari C, LaRue H, Hovington H, et al. Bladder tumor-infiltrating mature dendritic cells and macrophages as predictors of response to bacillus Calmette-Guérin immunotherapy. Eur Urol. 2009;55:1386-1395.
30. Bassi P, Milani C, Meneghini A, et al. Clinical value of pathologic changes after intravesical BCG therapy of superficial bladder cancer. Urology.1992;40:175-179.
31. Pieras-Ayala E, Palou-Redorta J, Tomero-Ruiz JI, et al. Prognostic value of cystoscopically pseudotumoral lesions (inflammation/granuloma) in primary stage T1 grade 3 bladder tumors treated with BCG. Int Urol Nephrol. 2001;33:469-472.
32. Jallad S, Goubet S, Symes A, et al. Prognostic value of inflammation or granuloma after intravesical BCG in non-muscle-invasive bladder cancer. BJU Int. 2014;113:22-27.
33. Antonelli AC, Binyamin A, Hohl TM, et al. Bacterial immunotherapy for cancer induces CD4-dependent tumor-specific immunity through tumor-intrinsic interferon-γ signaling. Proc Natl Acad Sci U S A. 2020;117: 18627-18637.
34. Kates M, Matoso A, Choi W, et al. Adaptive immune resistance to intravesical BCG in non-muscle invasive bladder cancer: implications for prospective BCG-unresponsive trials. Clin Cancer Res. 2020;26:882-891.