

Original Article

Investigation of granulomatous prostatitis incidence following intravesical BCG therapy

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Abstract: In the present manuscript, we studied the incidence of granulomatous prostatitis in the prostatectomy specimen of the patients who underwent transurethral resection of the prostate (TURP) after superficial bladder cancer treatment with intravesical Bacillus Calmette-Guerin (BCG) and were diagnosed with benign prostate hyperplasia (BPH). The clinical data and histopathological specimen records of 472 patients who underwent TURP due to BPH diagnosis, obtained over a period of 6 years in the urology department of Private Konya Hospital, Konya, Turkey, were studied retrospectively. The cases were divided into two groups as (Group I) who did not undergo any treatment and as (Group II) who underwent BCG treatment. The frequency and the clinical course of the cases with granulomatous prostatitis were studied histopathologically. There were in total 472 patients who underwent TURP. Out of the 459 patients who did not undergo BCG treatment (Group I), the histopathological specimen records of 262 (57%) was BPH, of 197 (43%) BPH + chronic prostatitis. Of the second group, 13 cases underwent intravesical BCG treatment before surgical intervention due to superficial bladder CA diagnosis. In this group 4 of the cases were diagnosed as (30%) BPH, 9 as (70%) chronic prostatitis + BPH. 6 out of the 9 chronic prostatitis cases were chronic prostatitis, 2 caseous granulomatous prostatitis, 1 non-caseous granulomatous prostatitis. Granulomatous prostatitis cases should require no specific therapy. Conclusion: In patients with obstruction complaints following intravesical BCG treatment, granulomatous prostatitis should also be considered and treatment plans should be made accordingly.

Keywords: Granulomatous prostatitis, intravesical BCG immunotherapy, TUR-P

Introduction

One of the rare disorders of the prostate, granulomatous prostatitis was first described by Tanner and Mc Donald in 1943 [1]. Granulomatous prostatitis, caused by bacteria, fungi, parasites, and viruses is an inflammatory condition of prostate that histologically features the presence of granulomas. Nowadays, infectious granulomatous prostatitis occurs after BCG therapy for superficial bladder cancer [2].

Incidence of granulomatous prostatitis following intravesical BCG treatment has been reported as 0.8-3.3% [3, 4]. As it is rarely observed, it can be identified in many cases after the histopathological analysis of the prostatectomy

specimen. The aim of the present study is to identify to histopathological diagnosis, and the incidence, and clinical course of granulomatous prostatitis in patients who underwent intravesical BCG treatment by analyzing their TURP specimen.

Material and methods

The study was carried out at the urology department of Private Konya Hospital between February 2004 and October 2010 in Konya, in Turkey. 472 patients who admitted to the urology department with storage symptoms include urinary frequency, urgency, urgency incontinence, and voiding at night (nocturia) and diagnosed benign prostate hypertrophy (BPH) were included in the study. All patients prostate spe-

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Table 1. Histopathological diagnoses according to groups

HISTOPATHOLOGICAL DIAGNOSIS	Group I (n:459)	Group II (n:13)
BPH	262	4
BPH + chronic prostatitis	197/197	6/9
BPH + caseous granulomatous prostatitis	0/197	2/9
BPH + non-caseous granulomatous prostatitis	0/197	1/9

specific antibodies were normally and the prostates were bigger than normal prostate size with made ultrasonography. The surgery underwent with TUR-P (24 Fr, Storz) for each patients. The prostates were resected with TUR-P operation, and resected specimens were analyzed histopathologically. Patients' stories, all symptoms, and the entire process before operations and after operations were recorded. 13 patients of 472 patients had received bacillus Calmette-Guérin (BCG) therapy to the urinary bladder for treatment of bladder cancer. We also analyzed the role of BCG therapy in the etiology of granulomatous prostatitis.

The data were analyzed retrospectively. The obtained data are summarized relative in percent. The relation between the variables was analyzed using Chi-square test (χ^2). The level of statistical significance was determined as $p = 0.05$.

Results

472 specimens were analyzed histopathologically. 459 patients who did not receive BCG treatment formed the first group. In this group, 262 specimens identified as BPH (57%) and 197 specimens identified (43%) as BPH and chronic prostatitis histopathologically. None had granulomatous prostatitis in this group.

The second group was formed 13 patients specimens who underwent intravesical BCG treatment within a mean time of 18 months (13-30 months). 4 of 13 patients (30%) were identified BPH, 9 of 13 patients (70%) were identified chronic prostatitis and BPH. The chronic prostate cases could be divided as the following; 6 chronic prostatitis, 2 caseous granulomatous prostatitis, 1 non-caseous granulomatous prostatitis (**Table 1**). Granulomatous prostatitis frequency of the group who underwent intravesical BCG treatment was higher and statistically significant ($P = 0.0001$, $\chi^2 = 3.56$, $SD = 2$).

Only in two cases caseous granulomatous prostatitis was determined. Among the prostatic tissue, granulomatous structures with calcification necrosis in the center were observed (**Figure 1**). Red colored bacillus was observed with histochemical EZN staining of the granulomatous prostatitis specimen (**Figure 2**). In the case with non-caseous granulomatous prostatitis, no bacillus was observed in the EZN staining (**Figure 3**).

The incidence of chronic prostatitis and granulomatous prostatitis was higher in the group receiving intravesical treatment compared to the other group and statistically significant ($P = 0.0001$, $\chi^2 = 3.56$, $SD = 2$).

Discussion

Granulomatous prostatitis is categorized into 4 subgroups as specific infectious granulomatous prostatitis, nonspecific granulomatous prostatitis (NSGP), post-biopsy granulomas, and as systemic granulomatous prostatitis according to the underlying cause. Earlier, most cases of granulomatous prostatitis were categorized as NSGP (50% to 77%) [2, 3, 5, 6]. NSGP etiology is considered to be based on reactions to bacterial toxin, cell debris, and secretions spilling from blocked ducts or refluxed urine into the stroma [2, 7].

The underlying cause of infectious granulomatous prostatitis may be bacteria, viruses, fungi, and parasites [8] with fungi and mycobacterium tuberculosis as the usual causes. The most common forms of mycotic prostatitis are blastomycosis, coccidioidomycosis, and cryptococcosis [2].

BCG therapy for superficial bladder cancer is nowadays considered to be the most common cause of infectious granulomatous prostatitis [2]. Mycobacterial prostatitis does not require any therapy as it is clinically insignificant. Yet, tuberculous prostatitis which is clinically significant may occur in patients with systemic tuberculosis at a rate of 3% to 12% incidence [9].

Morale et al applied in 1976 for the first time Bacillus Calmette-Guérin (BCG), a live attenuated strain of Mycobacterium bovis, intravesically which is now the standard adjunctive therapy for superficial bladder cancer [10-13].

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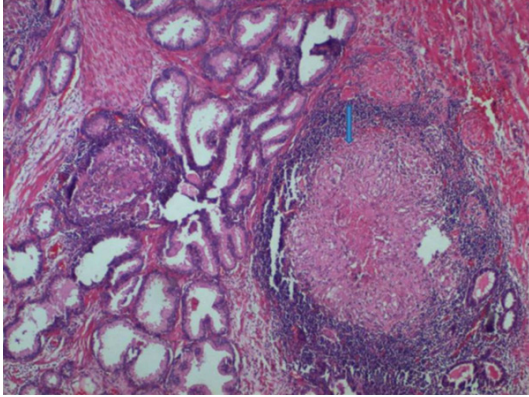


Figure 1. Granuloma structure with caseous necrosis in the center (arrow), ×100, H.E.

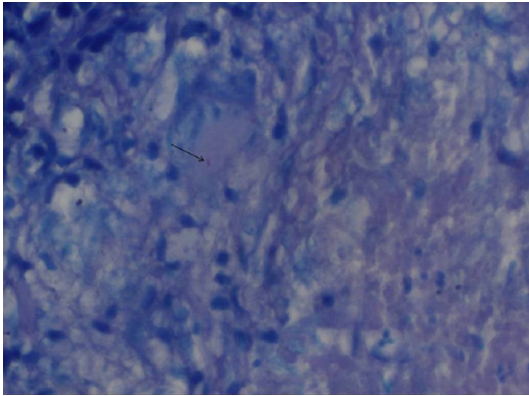


Figure 2. Red colored basils in Lang Hans type giant cells (arrow), ×400, EZN staining.

Although it is well tolerated at large, local and systemic infectious complications might arouse.

Bladder biopsy during BCG therapy, transurethral resection of the bladder tumor or of the prostate, traumatic catheterization, simultaneous cystitis presence, diabetes, and genetic factors are among the factors increasing the systemic side effects [21].

BCG mechanisms leading to infectious complications are yet not completely understood. Its action mechanism as an immunotherapeutic agent in cancer is not known completely; yet, recently the elaboration of a particular helper T cell cytokine profile, the “Th1 response”, is suggested as an integral part of it [15, 16].

Local instillations of BCG do not cause severe adverse effects. The overall rate of serious

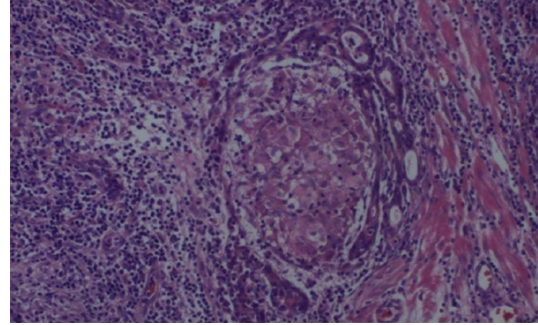


Figure 3. Granuloma necrosis without calcification in prostate stroma, ×100, H.E.

complications was less than five percent as reported in a retrospective study made with a series of 2602 patients in 1989 [17].

Current literature presents debates about whether BCG driven infectious complications due hypersensitivity reaction or ongoing active infection represent the underlying reason for the presence of granulomas. The former hypothesis was widely accepted due to the presence of granulomas and the lack of recoverable organisms. Yet several case reports indicated the lack of acid-fast bacilli and organisms growth despite a high clinical suspicion of BCG infection [17, 18].

A series of 13 patients who underwent prostate biopsy at some time after receiving intravesical BCG, was reported by Oates et al. Granulomatous prostatitis was detected in all of them [19]. LaFontaine PD et al reported about 119 men who underwent radical cystoprostatectomy for invasive bladder cancer. 12 of them had received intravesical BCG therapy before undergoing cystoprostatectomy. Granulomatous prostatitis was identified in 9 of 12 patients (75%) [20]. Another study claimed that 40% of patients undergoing prostate biopsy after intravesical BCG had developed granulomatous prostatitis [21]. In the presents study, 3 (23%) out of 13 the patients who underwent TURP had granulomatous prostatitis. 2 of them had developed caseous granulomatous prostatitis, and 1 non-caseous granulomatous prostatitis.

Although it might lead to negative outcomes in some patients, specimens should be obtained for staining for acid-fast bacilli, culture, and PCR testing for mycobacterial DNA in patients with suspected disseminated BCG infection

[16]. In the present study, red bacillus were observed in the histochemical EZN staining in the caseous granulomatous prostatitis specimen. However, no bacillus was observed in the non-caseous granulomatous prostatitis specimen. No specific treatment was administered in all cases with granulomatous prostatitis. Patients received only symptomatic treatment.

Conclusion

In this study, incidence of granulomatous prostatitis was found high after intravesical BCG therapy. In patients with obstruction complaints following intravesical BCG treatment, granulomatous prostatitis should also be considered and treatment plans should be made accordingly.

Disclosure of conflict of interest

None.

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