URINARY INFECTION

Case Report

Granulomatous prostatitis diagnosed during intravesical BCG treatment

Sezgin Okçelik¹, Hasan Soydan¹, İsmail Yılmaz², Ömer Yılmaz¹, Ferhat Ateş¹, Kenan Karademir¹

ABSTRACT

The histopathological report of the biopsy material retrieved from hyperemic areas of the bladder during control cystoscopy of a 70-year-old man who had a bladder cancer diagnosis three years previously, indicated the presence of a carcinoma in situ (CIS). Intravesical immunotherapy treatment was initiated. After severe symptoms of dysuria emerging during intravesical immunotherapy with BCG, the immunotherapy treatment dosage was lowered. His treatment was then discontinued due to the progression of symptoms. A biopsy was performed due to higher prostate specific antigen (PSA) and digital rectal examination abnormalities which indicated granulomatous prostatitis. An antituberculosis treatment was initiated because the PPD test result was 25 mm and the QuantiFERON test was positive. After one month, the patient's PSA levels were reduced, and his clinical status improved. The symptoms of severe dysuria, sterile pyuria, abnormal digital rectal examination findings and high PSA levels during intravesical BCG treatment should remind us diagnosis of granulomatous prostatitis. It should not be forgotten that diagnosis of granulomatous prostatitis was established histopathologically, and the patient benefited from medical treatment.

Key words: BCG treatment; bladder cancer treatment; Granulomatous prostatitis.

Introduction

Bacillus Calmette-Guérin is an attenuated live *M. bovis* strain which is used in the treatment of bladder tumor because of its immune modulator effect. Intravesical BCG treatment is the most effective intravesical therapy of carcinoma in situ. Besides it is used in high grade, non-muscle invasive bladder tumors especially with the intention to prevent disease progression. During this treatment granulomatous prostatitis can develop in 1-2% of the cases. Granulomatous prostatitis is an infrequently encountered benign inflammatory disease of the prostate. Its incidence rate was initially reported by Tanner et al. as 3.3% in the year 1943. It is generally seen intraoperatively, following intravesical BCG therapy, and less frequently after resolution of systemic tuberculosis.^[2-4] Treatment of granulomatous prostatitis can start after confirmation of the diagnosis with histopathological evaluation.. Herein, a case with granulomatous prostatitis with a histopathologically established diagnosis, and its treatment after approval of the patient was obtained.

Case presentation

Control cystoscopy performed at first admission of a 70-year-old male patient with a diagnosis of bladder tumor in our outpatient clinic three years ago revealed hyperemic, and velvety areas on old resection areas, lateral, and posterior walls of the bladder which necessitated TUR-bladder biopsy, and resection of suspect areas. All specimens harvested were histopathologically reported as carcinoma in-situ (CIS). Digital rectal examination of the prostate performed at that time was evaluated as grade 1 benign prostatic hyperplasia. According to predetermined schedule intravesical immunotherapy with BCG was started at postoperative 3. week. Then induction therapy was initiated at weekly intervals for 6 weeks, and then administered as a maintenance therapy still at weekly intervals for three weeks at 3., 6., 12., 18., 24., 30, and 36. months. The patient suffered from serious dysuric complaints starting from the third dose. The patient had not any manifestation of fever or systemic infection. Urinalysis revealed the presence of leukocyturia, and microscopic hematuria, but

¹Clinic of Urology, Gülhane Military Medical Academy Haydarpaşa Hospital, İstanbul, Turkey

²Clinic of Pathology, Gülhane Military Medical Academy Haydarpaşa Hospital, İstanbul, Turkey

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Correspondence:
Sezgin Okçelik
Clinic of Urology, Gülhane Military Medical Academy Haydarpaşa Hospital, Üsküdar 34668 İstanbul, Turkey
Phone: +90 543 677 46 04
E-mail: drsezginokcelik@hotmail.com

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any bacterial growth was not observed on his urine cultures obtained. His health condition suggested BCG intolerance, and intravesical application of one third of the previous BCG dose was planned. Despite dose reduction, his complaints persisted which necessitated discontinuation of the BCG therapy. The patient stated that he had not undergo DRE during this interval. During this treatment-free interval his PSA values were evaluated, and DRE was performed. His PSA level risen up to 10.1 ng/dL, and DRE examination revealed a hard left lobe of the prostate with irregular contours which led us to perform 12 quadrant TRUS-guided prostate biopsy. Any additional abnormality was not detected on ultrasonograms. Estimated prostate volume was 32 cc. On histopathological examination, on hematoxylin-eosin stained sections in all quadrants of the field of vision granulomatous aggregates, some of them with central areas of caseification necrosis containing epithelioid histiocytes, lymphocytes, and scattered polymorphonuclear leukocytes were observed (Figure 1). In all biopsy specimens prostatic intraepithelial neoplasia or malignancy was not observed. Its histopathological report indicated granulomatous prostatitis which necessitated discontinuation of intravesical BCG therapy. Acid-fast bacteria were sought in urine samples. Tbc-PCR analyses were performed on formaldehyde fixed, and paraffin-embedded tissue samples to identify mycobacteria. Result of the histopathological analysis was reported as negative for mycobacteria. Erythematous skin lesion of the PPD test was 25 mm in diameter, and evaluated as a positive result. QuantiFERON test result was also positive. QuantiFERON test indicates presence of tuberculous infection, but it can not differentiate between active, and latent disease states. Therefore in cases with test positivity, clinical, and radiological signs should demonstrate active disease in order to establish diagnosis of latent infection. Interpretation of QuantiFERON test results requires consideration of epidemiological, physical, and other diagnostic methods. In our patient, intravesical application of BCG for the treatment of bladder cancer, pathological finding of granulomatous prostatitis, PPD test positivity, and also QuantiFERON test positivity all mandated initiation of triple antituberculostatic therapy (daily oral doses of 600 mg rifampicin, 300 mg isoniazide, and 1000 mg ethambutol). One month later his PSA value was 5.48 ng/dL. At 4. month of the antituberculostatic therapy his PSA level was 2.99 ng/dL, and on DRE disclosed a grade 1 BPH. On his control cystoscopy, two hyperemic regions measuring 1 cm in size on the right, and the left side of the bladder neck were observed. Random biopsy specimens retrieved from these areas, and bladder walls were histopathologically reported as chronic cystitis.AARB, and bacterial cultures of urine samples were unremarkable. From the 2. month of the antituberculostatic treatment, ethambutol was discontinued, and then isoniazide-rifampicin therapy was maintained for 4 more months.

Discussion

In recent years, raised awareness about prostatic abnormalities in the population, and more prevalent use of PSA have lead to an increase in the number of prostatic biopsies. In various series of biopsies performed with the indication of prostate cancer, granulomatous prostatitis has been reported in 0.36-11% of the cases.^[5] Granulomatous prostatitis is more frequently seen in patients who underwent intravesical BCG therapy. Rectal examinations disclose abnormality specific to prostatitis.^[6,7] Diagnosis of prostatitis is made with histopathological examination of the biopsy specimens retrieved because of suspect prostate cancer. In our case, diagnosis was made by histopathological examination of the prostate biopsy specimens harvested because of suspect prostate cancer after detection of increased PSA levels, and abnormal DRE findings. Oates et al.^[8] performed prostate biopsies in 13 patients who received intravesical BCG therapy in 1988, and all pathology reports indicated presence of granulomatous prostatitis. In a study conducted by La Fontaine et al.in 1997, granulomatous prostatitis was detected in 75% of 119 patients who had initially received intravesical BCG therapy, then undergone radical cystoprostatectomy. It is very difficult to differentiate between granulomatous prostatitis, and prostate cancer as a cause of increased PSA levels. However after antituberculostatic therapy, PSA levels decrease in patients with granulomatous prostatitis.^[9] In our patient, measured PSA level at baseline (10 ng/dL) dropped to 5.48 ng/dL at the first, and then down to 2.99 ng/dL at the 4. month of the treatment.

During intravesical BCG therapy, PSA levels can increase. This increase might be related to prostate carcinoma or impact

Figure 1. Granulomatous inflammation consisting of multiple miscellaneous granulomas, some of them with central areas of caseification necrosis containing epithelioid histiocytes, lymphocytes, and scattered polymorphonuclear leukocytes (HE, x 40)

of intravesical BCG application. The best way to differentiate between these two entities is to measure PSA levels before initiation of therapy, and digital rectal examination (DRE). In a study performed by Beltrami et al.^[10] in the year 2008, 106 male patients who had undergone intravesical therapy, following BCG induction therapy, BCG levels increased in 41.6% of the patients, and PSA levels dropped to normal values 12 months after termination of the therapy. Ten patients had undergone prostate biopsies, and the results of the prostatic biopsy were reported as prostate cancer (n=1), and inflammatory process (n=9). In a study by Leibovici et al.^[11] performed in the year 2000, in 41.6% of the patients who had received 36 sessions of intravesical therapy PSA levels increased. These higher PSA levels returned to normal three months after termination of the treatment. Histopathological reports of the biopsy specimens were reported as granulomatous prostatitis in 10, and benign prostatic hyperplasia in 4 patients. Prostate cancer was not detected in any of the biopsy specimens. In our patient we didn't measure PSA levels before intravesical BCG therapy. Digital rectal examination did not reveal any abnormality. PSA was measured during the immunotherapy-free interval which was not long enough for the proper determination of PSA. During intravesical BCG therapy PSA levels can increase despite absence of prostate cancer. If not required absolutely, evaluation of PSA can be postponed. If higher PSA levels were detected, then the patient can be reliably followed up with periodic PSA measurements before scheduling the patient for biopsy.

In conclusion, in patients who consulted with serious complaints of dysuria, detection of sterile pyuria, abnormal DRE findings not previously noted, and increased PSA levels, the diagnosis of granulomatous prostatitis should not be forgotten. It should be also reminded that its diagnosis can be made histopathologically, and the patients benefit from medical therapy.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

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