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Comparison of Abnormal Prostate MRI and Histopathology of Prostatic Biopsy after Intravesical BCG Therapy for Non-Muscle Invasive Bladder Cancer

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1. Abstract

1.1. Aims: The MRI appearance of the prostate after intravesical bacillus Calmette–Guerin (BCG) therapy is known to be affected by granulomatous prostatitis. However, abnormal findings on MRI can also indicate prostatic invasion by urothelial carcinoma or prostate cancer. We examined the cases of abnormal prostate findings on MRI after intravesical BCG therapy, and considered the necessity of prostate needle biopsy for these cases.

1.2. Methods: We retrospectively evaluated the radiological and pathological findings in 17 males with non-muscle invasive bladder cancer who underwent prostate biopsy after intravesical BCG therapy.

1.3. Results: In MRI of the prostate performed prior to biopsy, 16 of the 17 patients had a PI-RADS v2 score of 4 or 5. The pathological findings were granulomatous prostatitis (n=14), prostate cancer (n=2), and urothelial carcinoma (n=1).

1.4. Conclusion: Most abnormal prostate MRI findings after intravesical BCG therapy are due to granulomatous prostatitis; however, in some patients abnormal findings indicate cancer. Needle biopsy of the prostate should be performed if the clinical findings suggest malignancy.

2. Introduction

There is wide consensus that immunotherapy is a valid choice in the adjuvant treatment of intermediate or high-risk non-muscle invasive bladder cancer (NMIBC) because of its ability to reduce disease recurrence and/or progression [1, 2]. However, the risk of bacillus Calmette–Guerin (BCG)-related complications, which include hematuria, cystitis, bladder contracture, BCG prostatitis, pneumonitis, and other life-threatening adverse events, must always be considered [3, 4]. Although the complications of intravesical BCG therapy are known, to the best of our knowledge few studies have examined the association between the radiological and pathological findings of the prostate after intravesical BCG therapy. Although several case studies have reported changes in the prostate on magnetic resonance imaging (MRI) following intravesical BCG therapy [5, 6], there is no clear consensus whether they warrant prostatic biopsy (PBx).

The aim of this study was to assess the effect of intravesical BCG on

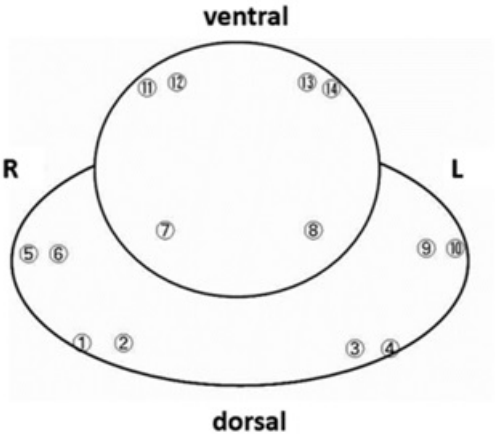
the prostate by reviewing changes in the radiological and pathological findings before and after therapy, and to determine the necessity for PBx after intravesical BCG therapy.

3. Materials and Methods

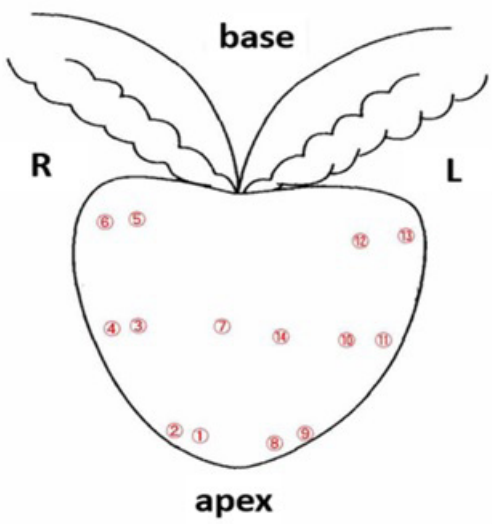
This retrospective study was approved by our Institutional Review Board (approval number S20028). We reviewed the radiological and pathological findings of 17 male NMIBC patients who underwent prostate needle biopsy between April 2010 and September 2019, after intravesical BCG therapy. BCG therapy was scheduled for weekly administration for 8 weeks in 13 patients, and for 6 weeks and a maintenance treatment in 4 patients.

The median interval from BCG therapy to PBx was 7.0 months (range, 3.4–17.1 months). Transperineal ultrasound-guided 14-core systematic PBx was performed in 8 patients, and transrectal ultrasound (TRUS)-guided 14-core systematic PBx was performed in 9 patients. In all patients, prostate MRI obtained before PBx was analyzed by a genitourinary radiologist (N.Ki., 10 years experiences in prostate MRI [>200 prostate MRIs read per year]) using the Prostate Imaging Reporting and Data System (PI-RADS) v2. Histopathologic evaluation of the PBx specimens was performed by a genitourinary pathologist (N.H.). To confirm the relationship between the imaging and pathological findings, a urologist (T.M.) assigned a biopsy specimen number to each abnormal finding seen on MRI, using the biopsy sampling positions marked on the templates shown in Figure S1. All specimens were examined histologically by a genitourinary pathologist (N.H., more than 20 years of experience in prostate cancer pathology using the International Society of Urological Pathology - modified Gleason score classification).

Figure S1:



(a) Positioning template used for transperineal ultrasound-guided 14-core systematic biopsy



(b) Positioning template used for transrectal ultrasound-guided 14-core systematic biopsy

4. Results

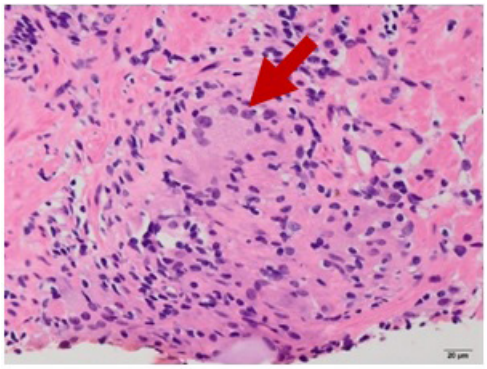
Table 1 summarizes the clinicopathological features of the 17 evaluated patients. Mean age at PBx was 70.8 ± 9.8 years, mean PSA before intravesical BCG therapy was 2.9 ± 3.6 ng/dl, mean PSA before PBx was 7.9 ± 7.0 ng/dl, mean prostate volume was 26.9 ± 15.4 cm^3, and mean PSA density was 0.32 ± 0.26 ng/dl/cm^3. Digital rectal examination (DRE) was positive in 6 patients, negative in 7, and unknown in 4. PI-RADS v2 score was 3, 4, and 5 in 1, 12, and 4 patients, respectively.

Table 1: Clinical characteristics in overall patients (n=17) and pathological diagnoses

Age at prostate needle biopsy, years	**70.8 ± 9.8**
PSA before intravesical BCG therapy, ng/dl	**2.9 ± 3.6**
PSA before prostate needle biopsy, ng/dl	**7.9 ± 7.0**
Prostate volume, cm^3	**26.9 ± 15.4**
PSA density, ng/dl/cm^3	**0.32 ± 0.26**
DRE, n (%)	
positive	**6 (35.3)**
negative	**7 (41.2)**
unknown	**4 (23.5)**
PI-RADS score, n (%)	
3	**1 (5.9)**
4	**12 (70.6)**
5	**4 (23.5)**
Pathological diagnosis, n (%)	
adenocarcinoma	**2 (11.8)**
urothelial carcinoma	**1 (5.9)**
epithelioid cell granuloma	**15 (88.2)**
caseous necrosis	**4 (23.5)**

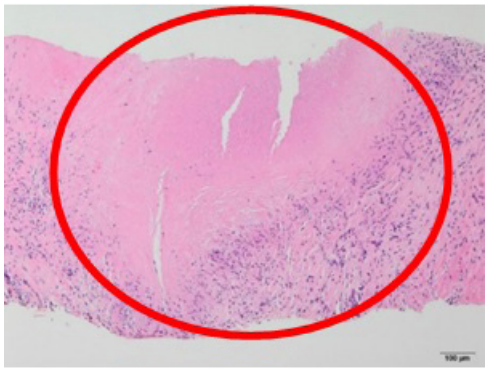
The indications for PBx were abnormal MRI findings in 16/17 and increase in PSA in 10/17 cases. The pathological results revealed cancer in 3 patients (17.6%): adenocarcinoma of prostate in 2 and urothelial carcinoma (UC) in 1. Of the cases of prostate cancer (PC), one was cT2aN0M0 with Gleason score 4+3, and the other was cT3aN0M1b with Gleason score 4+3. Epithelioid cell granuloma was detected in 15 patients (88.2%), and caseous necrosis in 4 (23.5%) (Figure 1). No cancer was detected in 14/17 cases (82.4%). In addition, as a result of examining the positional relationship between diagnostic imaging and pathological findings, epithelioid granuloma cells, PC, or UC was detected in biopsy specimens by the urologist in all cases (Table 2). These results suggest that abnormal imaging findings before biopsy were due to epithelioid granuloma cells, PC, or UC. However, it was difficult to distinguish these abnormalities because the MRI findings were very similar (Figure 2).

(a)



(a)Epithelioid cell granuloma (the part indicated by the arrow) was frequently observed in cases of granulomatous prostatitis (H.E.)

(b)



(b) Granulomatous prostatitis with caseous necrosis (circled part). (H.E.)

Figure 1. Pathological findings.

Table 2: Comparison of the positional relationship between the imaging and pathological findings.

Patient No.	Biopsy method	Designated biopsy specimen number (see Figure S1)	Pathological findings positive number	Pathological findings
1	transrectal	2,3,4,9,10,11	2,3,4,10,11	epithelioid cell granuloma, caseous necrosis
2	transperineal	1,2,3,4,9,10,11	1,2,3,11	urothelial carcinoma, epithelioid cell granuloma
3	transperineal	2,3,4,9,10,13,14	2,4,9,10,13,14	epithelioid cell granuloma
4	transrectal	1,2,3,8,9,10	1,2,3,8,9,10	adenocarcinoma, epithelioid cell granuloma
5	transperineal	3,4,7,9,10,11,12	3,4,9,10	epithelioid cell granuloma, caseous necrosis
6	transrectal	9,10,11,12,13,14	9,10,11,12,13,14	epithelioid cell granuloma, caseous necrosis
7	transperineal	1,2,5,6,8,13,14	1,2,5,6,8,13,14	epithelioid cell granuloma
8	transrectal	8,9,10,11,14	8,9,11,14	adenocarcinoma, epithelioid cell granuloma
9	transperineal	1,2,3,4,8,9,10	3,8,9,10	epithelioid cell granuloma
10	transrectal	2,3,4,5,7	2,3,4,5,7	epithelioid cell granuloma
11	transrectal	1,2,5,6,11,12	5,6,11,12	epithelioid cell granuloma, caseous necrosis
12	transperineal	1,2,5,6,11,12	1,5,6,11,12	epithelioid cell granuloma
13	transrectal	2,3,4,5,6,7	2,3,4,5,6	epithelioid cell granuloma
14	transperineal	1,2,5,6,7,11,12	1,2,7	epithelioid cell granuloma
15	transrectal	1,2,3,4,11,12,13	1,2,3,4,12	epithelioid cell granuloma
16	transperineal	1,2,5,6,7	7	epithelioid cell granuloma
17	transrectal	8,9,10,11,12,13	9,10,11,12,13	epithelioid cell granuloma

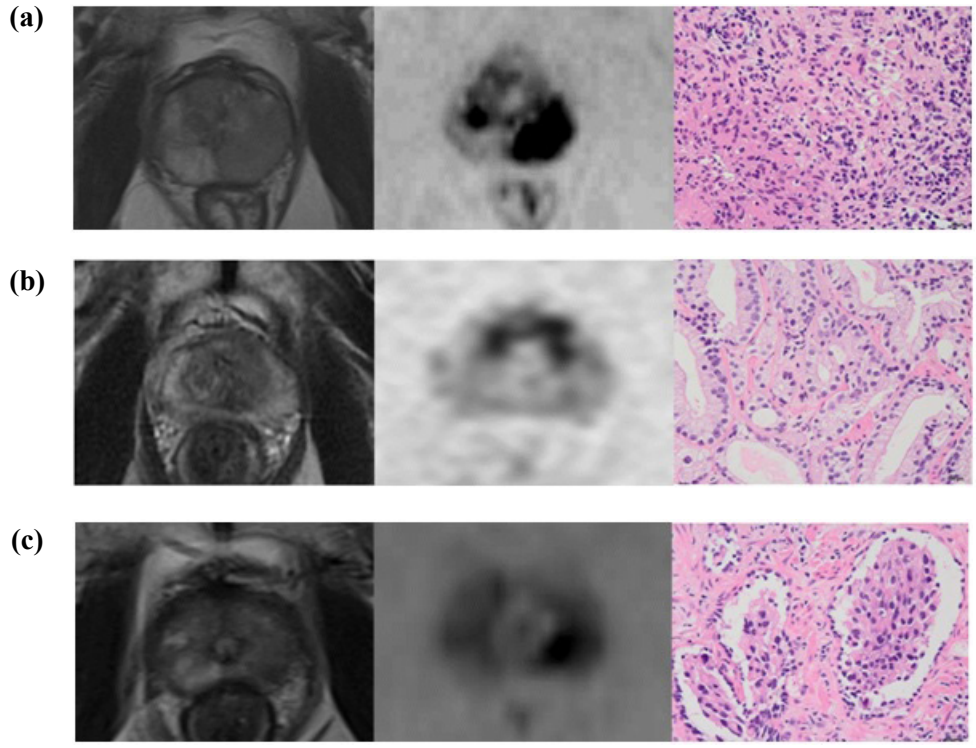
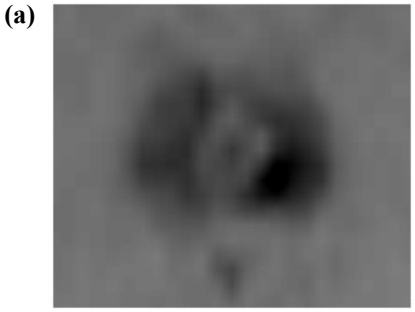
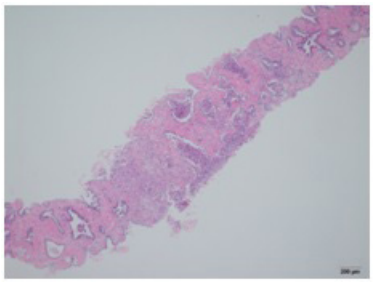


Figure 2: MRI T2WI, DWI, and pathological slides (H.E.) of (a) granulomatous prostatitis with PI-RADS score 5, (b) prostate cancer with PI-RADS score 5, and (c) urothelial carcinoma with PI-RADS score 4. Note the differences in pathological findings despite the similarity in imaging appearances.

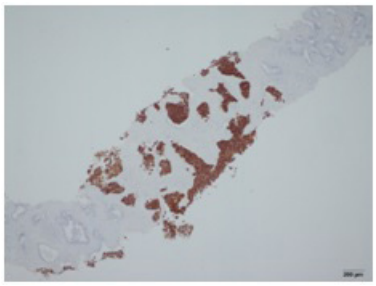
The detailed clinical course of the case of prostatic invasion by UC was as follows. The patient was diagnosed with carcinoma in situ (CIS), and received intravesical BCG therapy seven times (the eighth was discontinued due to an adverse event). Urinary cytology 12 months after the first transurethral resection of the bladder tumor was class V, and cystoscopy examination revealed a reddish site in the bladder suspicious of recurrent bladder cancer. Contrast-enhanced MRI revealed no gross lesions on the bladder mucosa, but the prostate MRI findings were abnormal, suggestive of PC (Figure 3a). We performed random bladder biopsy and TRUS-guided PBx. None of the bladder specimens showed evidence of malignancy; however, the PBx specimen revealed invasion by UC (Figure 3b-1, 2), and findings of UC were also observed in the prostate urethral biopsy. After diagnosis, neoadjuvant chemotherapy was performed with a course of Gemcitabine plus Cisplatin, followed by total cystectomy and ileal conduit construction.



(a) Diffusion-weighted MRI is suggestive of prostate cancer.



(b-1): Biopsy specimen of the prostate shows prostatic invasion by urothelial carcinoma (H.E.)



(b-2): Biopsy specimen of the prostate shows CK20-positive urothelial carcinoma (CK-20).

Figure 3: Prostatic invasion by urothelial cancer following intravesical BCG therapy.

Of the 14 patients in which no cancer was found at the first PBx, re-PBx was required in 3/14 (21.4%) during subsequent follow-up. The clinicopathologic features of these patients are shown in Table 3. The reasons for re-PBx were abnormal MRI findings (n=2) and

increase of PSA in (n=1). Average PSA was 2.4 ± 1.5 ng/dl before the start of intravesical BCG therapy and 4.0 ± 2.5 ng/dl before re-PBx. Mean interval from the start of BCG to re-biopsy was 29.5 ± 11.6 months. DRE was positive in 1 patient and negative in 2, and the PI-RADS v2 score was 2, 4, and 5 in these three patients. The pathological findings of re-PBx were prostatic adenocarcinoma in 1 patient (33.3%) and negative findings in 2 (66.7%). Epithelioid cell granuloma was found in all 3 patients (100%) and caseous necrosis in 1 (33.3%).

Table 3: Clinical characteristics and pathological diagnoses of the three patients who underwent re-biopsy.

Age at prostate needle re-biopsy, years	65.3 ± 4.7
PSA before intravesical BCG therapy, ng/dl	2.4 ± 1.5
PSA before prostate needle re-biopsy, ng/dl	4.0 ± 2.5
Prostate volume, cm³	25.6 ± 8.0
PSA density, ng/dl/cm³	0.16 ± 0.06
DRE, n (%)	
positive	1 (33.3)
negative	2 (66.7)
PI-RADS score, n (%)	
2	1 (33.3)
4	1 (33.3)
5	1 (33.3)
Pathological diagnosis, n (%)	
adenocarcinoma	1 (33.3)
epithelioid cell granuloma	3 (100.0)
caseous necrosis	1 (33.3)

5. Discussion and Conclusion

There is a wide consensus that immunotherapy is a valid choice in the adjuvant treatment of intermediate or high-risk NMIBC [1, 2]. However, it is also known that adverse events such as granulomatous prostatitis are associated with intravesical BCG therapy [3, 4]. In the pathological study of Balasar et al. [7], in which transurethral resection of the prostate was performed for benign prostate hyperplasia (BPH) after intravesical BCG therapy, granulomatous prostatitis was found in 23% of cases [7].

Polanec et al. [8], reported that clinically significant PC (Gleason score >6) was significantly associated with higher PI-RADS v2 scores [8], and Faiena et al. [9] reported that in patients with Gleason score of 3+4 at biopsy, lesions with a PI-RADS v2 score of 5 predicted adverse pathology features and biochemical recurrence-free survival [9]. These reports indicate the importance of PI-RADS v2 score in the treatment of PC, and PBx should be performed if the PI-RADS v2 score is 4 or 5. Garrido-Abad et al. [6], reported granulomatous prostatitis in PBx performed after intravesical BCG therapy in a patient with PI-RADS v2 score of 4. [5] Gottlieb et al. [6], reported that acute BCG-induced granulomatous prostatitis can have similar findings to PC on multi-parametric MRI. They considered that patients with known BCG exposure and a PI-RADS v2 score ≤3 may not require PBx [6]. However, Beltrami et al. [10], detected PC in 1 of 10 patients who underwent PBx due to elevated PSA after intravesical BCG therapy [10], similar to the present study in which we found prostatic invasion by UC and PC.

As shown in confirmation of the positional relationship between the imaging and pathological findings undertaken by the urologist, the abnormal imaging findings identified prior to biopsy indicated epithelioid granuloma cells, PC, or UC. However, as shown in Fig. 1, because the MRI findings of granulomatous prostatitis and prostatic invasion by UC and PC are very similar, a differential diagnosis by MRI is difficult. Therefore, despite the high possibility of granulomatous prostatitis, PBx should be performed if the clinical findings are suspicious of malignancy.

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