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ORIGINAL ARTICLE

Can Prostatic Calcifications in the Peripheral Zone be Predictors of Prostate Cancer During Diagnostic Transrectal Ultrasound-Guided Needle Biopsy of the Prostate?

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Abstract

Introduction: Prostatic calculi are generally associated with benign prostatic hyperplasia and chronic inflammation of the gland. Many studies have reported that prostatic calcifications (PCs) and inflammatory processes are involved in the pathogenesis of prostate cancer (PCa). In the present study, we evaluated the frequency of finding PCs in the peripheral prostatic zone during transrectal ultrasound (TRUS) and its relationship with histologic results of the biopsy.

Methods: In total, 156 patients with prostate-specific antigen (PSA) levels >2.5 ng/ml and/or abnormal digital rectal examination findings who presented in the urology policlinics of the Bağcılar Training and Research Hospital underwent TRUS-guided prostate needle biopsy. PCs were considered to be positive in patients with the presence of more than one hyperechoic foci in the peripheral zone with their largest diameter >3 mm. All TRUS biopsies were performed by the same physician.

Results: Of 156 patients, PCs were observed in 41 patients. Between patient groups with and without concomitant PCs, there was no significant difference in PSA levels, prostate volume, and patient age. PCa frequency was 41.4% among PC-positive patients and 15.6% among PC-negative patients (p=0.001). Patients diagnosed with PCa were also categorized according to Gleason score, and PCs were observed in all the patients with Gleason score ≥8 without any exception (p<0.05). Higher Gleason scores showed positive correlation with the presence of PCs.

Discussion and Conclusion: In the present study, we revealed the involvement of chronic inflammation and PCs in the pathogenesis of PCa. At the same time, we found a positive relationship between higher Gleason scores and the presence of PCs. Further high-volume prospective studies are needed to confirm this hypothesis.

Keywords: Prostate cancer; prostatic calcifications; transrectal ultrasonography.

Prostatic calcifications (PCs) are ovoid structures found in various shapes and sizes in the prostate gland alveoli and are formed by the accumulation of calcium salts in the corpora amylacae [1,2]. It is thought that the incidence of PCs increases after adolescence and with age [3,4]. PCs are generally considered to be associated with benign prostatic hyperplasia (BPH) or chronic inflammation [5]. However, many studies have demonstrated the involvement of PCs and inflammation in the pathogenesis of prostate cancer (PCa) [6-8]. In this study, we investigated the relationship between the frequency of occurrence of PCs in the prostatic peripheral zone detected using transrectal ultrasound (TRUS) and the histological findings of biopsy results.

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Materials and Methods

Between June 2017 and January 2018, patients referred from the Urology Polyclinic of the Bağcılar Training and Research Hospital who underwent TRUS-guided prostate needle biopsy were included in this study. Patients with a history of biopsy, prostatitis, prostate surgery and/or radiotherapy were excluded from the study. All the patients included in the study were informed about study procedures, and a written informed consent was obtained from them after they signed the World Medical Association Helsinki Declaration of Ethical Principles Concerning Medical Research on Human Beings Form. A total of 156 patients with abnormal findings on digital rectal examination and/or prostate-specific antigen (PSA) levels >2.5ng/ml underwent 12-core TRUS-guided prostate needle biopsy performed by a single physician, with the patient in the left lateral decubitus position. Three minutes before the procedure, local anesthesia in the form of lidocaine gel (Cathejell Lidocaine C, Pharmazeutische Fabrik Montavit, Tirol, Austria) was applied to each patient. BK Medical Ultrasound Pro Focus 2202 Color (Herlev, Denmark) type biplane 8818 (4–12 MHz) probe was used for TRUS.

Before the biopsy was initiated, the prostate volume was measured and the presence of PCs and their morphological characteristics were evaluated and recorded for each patient. The prostate volume was calculated using the formula "0.52 × length × width × height." PCs were considered to be positive in patients with the presence of more than one hyperechoic foci in the peripheral zone with their largest diameter >3 mm. Prostate sampling was performed using an 18-gauge Tru-Cut disposable needle working with an automatic spring-loaded gun (Bard Magnum Biopsy Systems, Tempe, AZ, USA). Twelve prostate biopsy specimens were mapped as described in the European Society of Urology Transrectal Ultrasonography 2011 Guideline for Prostate Needle Biopsy and were evaluated according to the recommendations of the International Society of Urological Pathology 2005 Consensus by a pathologist specializing in the evaluation of genitourinary pathologies.

Statistical methods (mean, standard deviation) and independent t test were used to compare the patient groups. Chi-square and Fisher's exact tests were used for the comparison of qualitative data using Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) package program. $P<0.05$ was set for significance.

Results

Mean age of the patients included in the study was 62.36±7.61 (44–84) years, mean PSA levels were 8.17±13.26 (2.2–60.3) ng/dl, and mean prostate volume was 52.05±26.07 (10–183) ml. PCs were detected in 41 (26.2%) of the 156 studied patients. PSA levels, prostate volumes, and patient ages were not significantly different between the patients with and without PC (Table 1).

When biopsy results were examined, PCa was detected in 17 (41.4%) of 41 patients with PCs and 18 (15.6%) of 115 pa-

Table 1. Demographic characteristics and biopsy results of the patients included in the study

	Prostate Cancer	*BPH	Total	P
Age (year), Mean±SD (max–min)	64.59±8.91(47-84)	61.67±7.24 (44-78)	62.36±7.61 (44-84)	0.02
PSA (ng/ml), Mean±SD (max–min)	12.01±18.7 (3.14-60.3)	7.08±4.25 (2.2-22.63)	8.17±13.26 (2.2-60.3)	0.386
BMI kg/m^2, Mean±SD (max–min)	30.31±3.10 (25-37)	29.77±3.04 (24-37)	29.89±3.01 (24-37)	0.449
TRUS volume (ml), Mean±SD (max–min)	42.6±17.95 (10-71)	54.81±27.35 (20-183)	52.05±26.07 (10-183)	0.263
Number of biopsied cores, n, Mean±SD (max–min)	11.05±1.99 (5-14)	11.09±1.22 (10-14)	11.08±1.42 (5-14)	0.258
Chronic Prostatiti, n (%)				
Yes	3 (2.04)	23 (15.8)	26 (17.9)	0.177
No	28 (19.3)	91 (62.7)	119 (82.06)	
TRNB-related infection, n (%)	2 (1.28)	4 (2.56)	6 (3.84)	>0.05
Abnormal DRE, n (%)	22 (14.1)	14 (8.97)	34 (21.79)	<0.001

PSA: prostate-specific antigen; BMI: body mass index; TRUS: transrectal ultrasound; TRNB: transrectal needle biopsy; DRE: digital rectal examination.

tients without PCs; thus, PCa was found in 35 (22.4%) of all study patients (p=0.001). Grading results based on Gleason scores in patients with established diagnosis of PCa were as follows: n=24 (15.4%) Gleason scores: 3+3; n=3 (1.9%) Gleason scores: 3+4; n=2 (1.3%) Gleason scores: 4+3; n=2 (1.3%) Gleason scores: 4+4; and n=4 (2.6%) Gleason scores: 5+4. All patients with Gleason score ≥8 were shown to have synchronous PCs. Higher Gleason scores were found to be significantly associated with the concurrent presence of PCs (p=0.001) (Table 2).

Discussion

PCs are assumed to be the calcifications of accumulated prostate secretions in layers around a calcium apatite nidus [9]. Formation of PCs is thought to involve multiple etiologic factors, such as infections, dietary factors, trauma, hormonal changes, urinary reflux, and intraprostatic duct obstruction secondary to desquamation of the prostatic epithelial cells [3, 8, 10]. The prostate gland is an immune system organ; epithelial and stromal cells as well as immune system cells known as prostate-associated lymphoid tissue (lymphocytes, macrophages, and granulocytes) are present in the prostate [11]. Vignozzi and Maggi have shown that prostate stromal cells can act as antigen-presenting cells by stimulating alloreactive $CD4^+$ T cells to produce inflammatory cytokines, chemokines, and growth factors [interleukin (IL)-8, IL-6, and basic fibroblast growth factor] in response to a variety of inflammatory stimuli [12].

To date, no study has investigated the incidence of PCs in the general population. However, reportedly, the incidence of PCs increases with age [13]. In a study with 612 patients, 47.2% patients aged under 50 years and 86% patients aged above 50 years were found have chronic inflammation [14]. It has been shown that chronic inflammation is more likely to be detected in patients having PCs of larger sizes [15]. The link between chronic inflammation and carcinogenesis was first revealed by Virchow in 1863 [16]. Today, it is accepted that 25% of cancers are associated with chronic inflammatory diseases. Concomitancies between *Helicobacter pylori* infection and gastric cancer and between Crohn's disease and colon cancer are the classical examples [17]. In recent years, the causal link between PCa and inflammation has been investigated [18]; however, the role of chronic prostate inflammation in carcinogenesis has not yet been elucidated. A relationship has been suggested between PCs and PCa in epidemiological, genetic, molecular, and experimental animal model studies. Concomitant inflammation and PCs are frequently seen in the PCa specimens of elderly patients [4]. In a study conducted by Griffiths et al., correlation was seen between PCs and PCa in 63% of the patients [19]. Chronic inflammation in pathologic specimens has been found to be more localized in the proximal peripheral and transitional zones. In a study conducted by Carmelo et al., [20] PCa was found to be associated with PC in the prostatic peripheral zone, but no correlation was found between higher Gleason scores and PCs. In our study, we showed a correlation between PCs and PCa in the prostatic peripheral zone and showed that higher Gleason scores also correlated with the presence of PCs.

Our study had few limitations. First, we did not know the ethnicity of the patients included in the study, but the vast majority of patients were Turkish and Caucasians. We believe that this limitation does not affect the study outcome because of the fact that different ethnic groups of patients did not even reach 1% of our patient population and that these patients did not carry a high risk for PCa. Second, PCs were only visually assessed and the dimensions and localization characteristics of hyperechoic prostate images were recorded. The general acceptance of PCs as an indicator of inflammation has left a subjective area in evaluating the results [21,24]. Many molecular investigations require evaluation of inflammatory markers such as cytokines and interleukins to clarify the true role of PCs in the development of PCa. There is no evidence to confirm the temporal relationship between chronic inflammation and carcinogenesis. Long-term follow-up of patients having PCs will help understand the correlation between inflammation and PCa.

Table 2. Correlation between pathology results and presence of PCs

	PC		Total	P
	Yes	No		
Gleason Grade (%)				
3+3	8 (5.12)	16 (10.25)	24 (15.38)	0.001
3+4	1 (0.64)	2 (1.28)	3 (1.92)	
4+3	2 (1.28)	0 (0)	2 (1.28)	
4+4	2 (1.28)	0 (0)	2 (1.28)	
5+4	4 (2.56)	0 (0)	4 (2.56)	
BPH	24 (15.38)	97 (62.17)	121 (77.56)	
Prostate Cancer (%)				
Yes	17 (10.89)	18 (11.53)	35 (22.43)	0.001
No	24 (15.38)	97 (62.17)	121 (77.56)	
Prostatitis (%)				
Yes	13 (8.33)	17 (10.89)	30 (19.23)	
No	28 (17.94)	98 (62.82)	126 (80.76)	
Total	41 (26.3)	115 (73.7)	156 (100)	

PC: prostatic calcification; BPH: benign prostatic hyperplasia.

Conclusion

Chronic prostate inflammation can result from an immunological response to different pathogenic causes that create vulnerability to a tissue injury and subsequent cancer. The role of PCs, thought to be related to chronic inflammation, in the development of BPH and PCa has not been fully understood. We could not show the correlation between PCs and PCa in the prostate peripheral zone in this study; prospective, randomized studies are needed to better explain this association.

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