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Research Article

The Significance of Histological Chronic Prostatitis in Transrectal Prostate Biopsy

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Abstract

Purpose: The histological finding of chronic prostatitis (CP) has been linked to higher levels of prostatic specific antigen (PSA), prostate cancer (PCa) and lower urinary tract symptoms. However, its clinical meaning is still uncertain. We performed a retrospective analysis to determine the role of CP and its relationship to the diagnosis of PCa.

Methods: Patients undergoing prostate biopsy from January 2008 to June 2013 were selected from our database. Those with the histological finding of CP were the focus of this analysis. They were categorized depending on the presence or absence of this feature. We determined the association between CP and PCa diagnosis using univariate and multivariate analyses. Statistical significance was stated as $p<0.05$.

Results: 540 patients were selected. The mean age was 65 ± 7.51 years and median PSA of 7.49 ng/ml. Two groups were defined: 1) 331 patients with chronic prostatitis and 2) 209 without chronic prostatitis. No statistical differences were found between groups regarding age, PSA, IPSS score, prophylactic antibiotic use, comorbidities, alpha-blocker or 5-α-reductase inhibitor therapy, transurethral catheter at biopsy or infectious complications. Significant differences were found for previous hospitalizations, number of previous biopsies, suspicious digital prostate exam, number of cores taken, prostate volume, cancer diagnosis, percentage of positive cores and Gleason score >=7. A multivariate analysis model showed "protective" effect between CP and diagnosis of PCa (HR 0.17, p= <0.01).

Conclusion: Our results suggest that the histological finding of CP is inversely related to PCa diagnosis.

Keywords: Chronic Prostatitis; Prostate Biopsy; Prostate Cancer; Mexico

Abbreviations

ASAP: Atypical Small Acinar Proliferation; CP: Chronic Prostatitis; LUTS: Lower Urinary Tract Symptoms; NIH: National Institutes of Health; PSA: Prostate Specific Antigen; PCa: Prostate Cancer; BPH: Benign Prostatic Hyperplasia; TRPB: Trans-Rectal Prostate Biopsy; DRE: Digital Rectal Exam; MetS: Metabolic Syndrome

Introduction

From a clinical point of view, chronic prostatitis (CP) refers to a condition characterized by pelvic pain and lower urinary tract symptoms (LUTS). When confirmed histologically it is characterized by inflammatory infiltrates within prostate tissue [1]. According to the National Institutes of Health (NIH), prostatitis can be classified as type I: acute-bacterial prostatitis, type II: chronic-bacterial prostatitis, type III: chronic prostatitis/chronic pelvic pain syndrome and type IV: asymptomatic [2]. The latter presents only, as histological diagnosis without symptoms. CP has been linked to nonspecific elevation of prostate specific antigen (PSA) [3], development of prostate cancer (PCa) [4] and progression of benign prostatic hyperplasia (BPH) [5]. A transrectal prostate biopsy (TRPB) is the most common method to obtain prostatic tissue [6]. Although pelvic pain and prostatic enlargement are not indications for this procedure, it has been found that less than 5% of biopsies show significant evidence of inflammation (10 or more leukocytes per high-power field) [7]. However, the diagnosis of CP is found more often than expected in TRPB performed to rule out PCa.

The aim of our study was to assess the association of histologically confirmed CP detected in TRPB advocated to PCa diagnosis and to determine the potential role of this finding.

Material and Methods

A retrospective analysis of our institutional database of TRPB performed from January 2008 to June 2013 was performed. The procedure technique and antibiotic prophylaxis used at our Institution have been previously reported [8,9]. Only patients with complete medical records were included. Information was obtained from clinical charts including perioperative variables, histopathological reports, and follow-up data. Patients were categorized according to the presence or absence of CP on histological reports. CP was defined as "CP type IV" according to the NIH classification of prostatitis syndromes (asymptomatic inflammatory prostatitis). A comparison between groups was made to identify clinical and pathological differences. Student's t-test for independent groups was used for

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continuous variables and Chi square and Mann-Whitney U tests were used for nonparametric variables. A multivariable model was created to analyze the impact of CP on the detection of PCa. A p<0.05 was determined as significant. Statistical analysis was made with the aid of SPSS® v. 17.0 (IBM®, New York) program.

Results

A total of 540 patients were included with a mean age of 65 ± 7.51 years. Median PSA was 7. 49 ng/ml. Indications for TRPB were high PSA in 63%, suspicious digital rectal exam (DRE) in 36.2%, atypical small acinar proliferation (ASAP) in 1 patient and active surveillance in another patient. Two groups were integrated: 1) 331 patients with chronic prostatitis (61.3%) and 2) 209 patients without chronic prostatitis (38.7%). Of these, 172 (31.8%) had PCa and 368 (68.2%) did not. Of the 331 patients with CP, 51 (15.4%) had simultaneous PCa. On the other hand, of the 209 without CP, 121 (57.9%) had a PCa report in pathology.

Clinical characteristics are described in Table 1**.** There were no differences except for previous hospital admissions (p=0.01) and number of previous biopsies (p=0.03) Features concerning indications for TRPB and histological information are summarized in Table 2 & 3, respectively. We found differences regarding suspicious DRE (p<0.01), number of biopsy cores (p<0.01), prostatic volume (p=0.04), positive core percentage (p<0.01) and Gleason score ≥7 (p<0.01). PCa was diagnosed in 57.9% and 15.4% of patients without and with CP, respectively (Table 3; p<0.01).

Table 4 shows multivariate analysis performed with CP, DRE, and number of cores retrieved, prostate volume, age and PSA to determine their association with diagnosis of PCa. Only age, PSA and CP remained independent predictors of PCa. Interestingly, the presence of CP had a protective effect on PCa diagnosis (HR 0.17; 95%CI [0.10–0.29]; p<0.01).

Discussion

Although the influence of inflammation on prostatic architecture is not well understood, different factors have been proposed as potential causes of this association, such as urinary reflux, dietary factors, estrogen or direct infections [10]. Several pro-inflammatory cytokines such as IL-15 [11], IL-18 with T-leukocyte infiltrate [12], TGF-beta [13], IFN-γ [14] and IL-8 [15] have been found to be elevated in biopsies of patients with BPH. However, no study has shown a statistically significant correlation. Some authors have proposed that treating the inflammatory processes may have a preventive role for BPH development. Di Silverio et al. [16] found that the combination of rofecoxib plus finasteride provided better short-term benefit for reducing clinical symptoms of BPH than finasteride alone.

In our series, the histological finding of CP showed a "protective" association with the diagnosis of PCa despite both groups had no statistically significant difference regarding PSA levels (Table 1). Moreover, although group 2 patients were more prone to have suspicious DRE, they had lower frequency of PCa diagnosis. De Nunzio et al. [17] conducted a review of the National Library of Medicine database from 2000 to 2012; they found that patients with chronic inflammation in prostate biopsies developed an increase of prostatic tissue and modification of prostatic architecture due to prostatic dynamic inflammatory mechanisms. Although different hypotheses relating metabolic syndrome (MetS) and BPH development were

Table 1: Clinical variables.

Variable	Units	Without Chronic Prostatitis n=209	With Chronic Prostatitis n=331	*p* Value
Age (mean ± SD)	Years	65.7 ± 7.8	65.8 ± 7.4	0.94
PSA (median)	ng/dL	7.43	8.9	0.52
IPSS (mean ± SD)	Total	7.8 ± 6.0	8.6 ± 5.5	0.38
Diabetes mellitus	Yes No Unknown	62 144 3	103 224 4	0.73
Hypertension	Yes No Unknown	101 105 3	172 155 4	0.71
Dyslipidemia	Yes No Unknown	82 124 3	115 212 4	0.28
Previous/active smoking	Yes No Unknown	111 95 3	153 175 3	0.10
LUTS therapy (alpha-blockers)	Yes No Unknown	129 77 3	223 104 4	0.19
LUTS therapy (5-ARI)	Yes No Unknown	10 196 3	20 307 4	0.54
Transurethral catheter at prostate biopsy	Yes No Unknown	13 193 3	24 304 3	0.66
Hospitalization 1 month before prostate biopsy	Yes No Unknown	20 186 3	14 314 3	0.01
Previous biopsies number	None One or more Unknown	168 38 3	242 85 4	0.04

(± SD): Standard Deviation; PSA: Prostate Specific Antigen; LUTS: Lower Urinary Tract Symptoms; 5-ARI: 5-Alpha Reductase Inhibitors

Table 2: Procedure characteristics.

Variable		Without Chronic Prostatitis n=209	With Chronic Prostatitis n=331	*p* Value
Antibiotic prophylaxis	Piperacillin/ tazobactam Others Unknown	194 12 3	310 17 4	0.76
Number of cores taken (mean±SD)	Total	13.9 ± 3.5	15 ± 3.6	<0.01
DRE suspicious of malignancy	Yes No Unknown	90 112 7	99 221 11	0.02
Prostatic volume (mean±SD)	cm^3	48.2 ± 31.6	53.7 ± 27.3	0.04
Early infectious complications*	Yes No Unknown	12 196 1	14 317 0	0.41

(± SD): Standard Deviation; DRE: Digital Rectal Examination.

** Includes positive urine cultures or acute prostatitis or clinical urinary tract infection*

Table 3: Histological findings.

Variable		Without Chronic Prostatitis n=209	With Chronic Prostatitis n=331	*p* Value
PCa diagnosis	Yes No	121 88	51 280	<0.01
Gleason score ≥ 7	<7 ≥7 Unknown	86 33 2	41 9 1	0.18
Atrophy	Yes No	65 144	218 113	<0.01
Hyperplasia	Yes No	119 90	276 5	<0.01
PIN/ASAP	Yes No	15 194	10 321	0.16

PCa: Prostate Cancer; PIN: Prostatic Intraepithelial Neoplasia; ASAP: Atypical Small Acinar Proliferation of the prostate

Table 4: Multivariable regression analysis. Dependent variable: cancer diagnosis.

Variable	HR	95% CI	*p* Value
Presence of chronic prostatitis	0.17	0.10-0.29	<0.01
Digital prostate exam	1.43	0.80-2.53	0.23
Number of cores taken	0.98	0.90-1.06	0.59
Prostatic volume >50 cc	0.58	0.43-1.00	0.05
Age	1.04	1.00-1.08	0.04
PSA	1.02	1.00-1.03	0.03

HR: Hazard Ratio, CI; 95% Confidence Interval, PSA: specific prostate antigen

proposed, they failed to find any specific evidence to support this association. Conversely, another study found an association between MetS and architectural changes in prostatic tissue [18].

Recently, a meta-analysis [5] including 3 different databases between 2005 and 2012 found that the release of cytokines from stromal prostatic tissue could promote neo-vascularization with the subsequent development of prostatic hyperplasia. This study found a clear association between chronic prostatic inflammation, BPH development, and increasing LUTS severity. Furthermore, chronic inflammation might be a predictor of poor response to medical therapy in patients with BPH.

We also found that patients with histological chronic prostatitis had a lower frequency of PCa. This may be related with a higher frequency of prostatic hyperplasia and higher prostate size, both well-known factors associated with lower incidence of PCa. Our results contrast with recent studies suggesting an association between chronic prostatitis and pre-malignant changes in prostatic epithelium [19] and higher incidence of PCa.

Van Vuuren et al. [4] described that patients with CP had an increased frequency of urinary retention. In the present study, this relationship was not suggested because the prevalence of transurethral catheter was not affected by the presence of CP.

The reduce (Reduction by Dutasteride of prostate Cancer Events) trial [20] found that 77.6% of participants had prostatic inflammation at biopsy and a positive association between inflammation and prostate volume. In the MTOPS (Medical Therapy of Prostatic Symptom) trial, patients with acute or chronic prostatitis symptoms had larger prostates and higher PSA levels with higher progression of LUTS [21].

The interaction between inflammation and PSA levels was evaluated as well. In our series, no significant difference was found. However, previous studies have suggested that prostate inflammation plays a role in PSA elevation in PCa patients with no detectable clinical signs. Opposite results were proposed in a series of 518 patients in whom no significant difference in total to free PSA ratio was found among those with chronic prostate inflammation [22].

Previous hospitalizations are related to a higher frequency of histological chronic prostatitis. This is a novel association supporting a role for exogenous stimulus in relation to prostate inflammation. This leads to the assumption that invasive procedures in patients could increase local inflammation of the prostate. We also found that CP might be an independent factor against PCa diagnosis. This strong association is interesting, although the design of the present series does not allow us to make further conclusions. Our investigation has some limitations, including its retrospective design, which decreases the accuracy of data. Second, biopsies lacked a standardized grading for inflammatory infiltrate; and third, we used histopathological reports instead of a revision of histological slides, representing potential bias. Finally, the associations found cannot be interpreted as a cause-effect association; thus, further investigation is required to determine the impact of chronic histopathological prostatitis on the development of malignancy [23].

Perhaps, more than a protective association of CP against PCa, the former is a differential diagnosis that should be taken in consideration. Currently, type IV Prostatitis (Asymptomatic Inflammatory Prostatitis) has negligible significance. In this analysis, we found that mean PSA values were higher among patients with CP compared to patients without CP who underwent TRPB. Furthermore, an abnormal DRE was more frequent in patients without CP, suggesting that indication for biopsy in patients with CP

is frequently based solely on PSA values. In addition, patients with CP had more subsequent biopsies (with a negative result for PCa), which may be explained by persistently elevated PSA in the absence of cancer.

With the previous considerations, we believe that the decision to perform a second biopsy looking for cancer in patients with CP in the first TRPB should be taken in a more conservative fashion compared to patients without CP. In conclusion, histological CP could be associated to other pathological findings in TRPB. In our series it had a "protective" association to PCa diagnosis; however the presence of CP is not related to the presence of PCa.

Disclosure

Dr. Villeda-Sandoval has nothing to disclosure.

Dr. Herrera-Cáceres has nothing to disclosure.

Dr. Ruiz-Hernández has nothing to disclosure.

Dr. Castillo-de-León has nothing to disclosure.

Dr. Castillejos-Molina reports personal fees from Lilly and GSK, outside the submitted work.

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Villeda-Sandoval C. participated in the design, data analysis and writing of the paper.

Herrera-Caceres JO participated in the design, acquisition of data and writing of the paper.

Ruiz-Hernandez JA participated in the acquisition of data and writing the paper.

Castillo-De-León J participated in the acquisition of data.

Castillejos-Molina R participated in the design and writing of the paper.

Rodríguez-Covarrubias F participated in the design, supervision and writing of the paper.

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