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ORIGINAL INVESTIGATION

Prostatic inflammation is associated with benign prostatic hyperplasia rather than prostate cancer

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Background and aims. The relationship between prostatic inflammation, benign prostatic hyperplasia and prostate cancer is controversial. The present study aimed to determine the relationship between grade and aggressiveness of prostatic inflammation and the risk of being diagnosed with prostate cancer.
Methods. Grade and aggressiveness of prostatic inflammation were assessed by Irani G and A scores, respectively, in prostate biopsy specimens of men having undergone this procedure because of increased serum PSA and/or digital rectal examination. We also assessed the correlation between Irani G and A scores and clinical variables related to benign prostatic obstruction.
Results. Of the 1178 eligible patients, 615 (52.2%) were diagnosed with PCa; they were older, had greater PSA, suspicious digital rectal examination and peak flow rate but lower post-void residual urine volume, prostate volume and international prostate symptoms score than those without cancer. High-grade inflammation (Irani G 2-3) was significantly more common in patients with benign prostate than in those with PCa and the same applied to highly aggressive inflammation (Irani A 2-3). Indeed, patients with high-grade inflammation had greater PSA, prostate volume, post-void residual and international prostate symptoms score, suggesting high-grade inflammation to correlate with benign prostatic obstruction. Highly-aggressive inflammation conversely correlated only with prostate volume.
Conclusions. Prostatic inflammation seems to be associated with benign prostatic hyperplasia rather than prostate cancer, with benign prostatic obstruction being strictly linked to the degree of inflammation.

Key words: IRANI score, Prostatic inflammation, Benign prostatic hyperplasia, Prostate cancer

INTRODUCTION

Benign prostatic hyperplasia (BPH) and Prostate cancer (PCa) are chronic diseases with a long period for their development and progression. BPH develops from a simple micronodular hyperplasia to a macroscopic volume enlargement and then to clinical expression. Similarly, PCa evolves through early and late precancerous modifications [1].
The prostate is an immunocompetent organ populated by T and B lymphocytes, macrophages and mast cells. Regulatory T cells (CD-4) are located into the fibromuscolar stroma whereas Cytotoxic T cells (CD-8) are more distributed around periglandular area creating the so-called Prostate associated Lymphoid Tissue (PALT).
Recent studies pointed out a potential relationship between prostatic inflammation and development and progression of BPH and PCa, but question remains if there is a trend towards one or the other disease [2-5].
The present study aimed to determine the relationship between inflammation grade and aggressiveness, as assessed by the Irani G and A score respectively, and

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the diagnosis of benign prostate or PCa at prostate biopsy (PBx).

PATIENTS AND METHODS

Data of patients scheduled for transrectal ultrasound (TRUS)-guided PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database.

All patients underwent PSA measurement before DRE and TRUS. Uroflowmetry (UFM) was carried out before PBx, waiting for the patient to report a strong sensation to void. Following local non-infiltrative anesthesia [6 7], TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme [8]. Men with PSA > 20 ng/ml, men receiving 5 alfa-reductase inhibitors (5-ARIs), or who had previously undergone invasive treatment for benign prostatic hyperplasia, or with dwelling urethral catheters were excluded from the present study.

A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate [9], and PCa. Clinically significant PCas (CSPCa) included those with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus [10]. Prostatic inflammation was assessed using the Irani score [11]. Specifically, the grade (G) of inflammatory infiltrate was scored as 0-no inflammatory cells, 1-scattered inflammatory cells infiltrate within the stroma without lymphoid nodules, 2-nonconfluent lymphoid nodules and 3-large inflammatory areas with confluence of infiltrate. Inflammatory aggressiveness (A) was graded as 0-no contact between inflammatory cells and glandular epithelium, 1-contact between inflammatory cell infiltrate and glandular epithelium, 2-interstitial inflammatory infiltrate associated with a clear but limited (< 25% of the examined material) glandular epithelium disruption, and 3-glandular epithelium disruption on more than 25% of the examined material. Irani G score 0-1 represented low-grade inflammation, whereas G score 2-3 represented high-grade inflammation. Similarly, Irani A 0-1 represented low-aggressiveness inflammation, whereas G score 2-3 represented high-aggressiveness inflammation. Grading did not include the types of inflammatory cells (polymorpho nuclear leukocytes, lymphocytes, monocytes or plasma cells).

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

Statistical analysis

Continuous variables were reported as median and interquartile range and compared by the Mann-Whitney U-test. Rates were tested by Fisher's exact test or chi-square test, as appropriate. Statistical significance was set at $p < 0.05$. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

RESULTS

Patients characteristics are summarized in Table I. Of the 1178 eligible patients, 615 (52.2%) were

Table I. Patients characteristics.

Variable	Benign (n = 563)	Prostate cancer (n = 615)	P-value
Age (y)*	65 (60, 69)	68 (63, 73)	< 0.0001
PSA (ng/mL)*	6.07 (4.68, 8.40)	6.45 (4.75, 10.00)	0.008
Suspicious DRE, n (%)	140 (28.5%)	249 (50.1%)	< 0.0001
Prostate volume (mL)*	61.00 (46.50, 81.00)	45.00 (34.00, 60.00)	< 0.0001
PFR (mL/s)*	12.00 (8.80, 16.00)	13.00 (9.10, 18.00)	0.010
PVR (mL)*	30.00 (1.00, 60.00)	20.00 (1.00, 50.00)	< 0.0001
IPSS*	10 (6, 18)	9 (5, 15)	0.001
Irani G, n (%)			
0-1	341 (60.6%)	444 (72.2%)	< 0.0001
2-3	222 (39.4%)	171 (27.8%)	
Irani A, n (%)			
0-1	427 (75.8%)	541 (88.0%)	< 0.0001
2-3	136 (24.2%)	74 (12.0%)	

*Data are expressed as medians (interquartile range).

diagnosed with PCa; they were older, had greater PSA, suspicious DRE and peak flow rate (PFR), but lower prostate volume (PVol), post-void residual (PVR) and international prostate symptoms score (IPSS) than those without cancer. Interestingly, high-grade inflammation (Irani G 2-3) was significantly more common in patients with benign prostate than in those with PCa and the same applied to highly aggressive inflammation (Irani A 2-3).

In view of this, we looked at the correlation between Irani scores and BPO-related parameters (Tab. II). Interestingly, patients with high-grade inflammation (Irani G2-3) had greater PSA, PVol, PVR and IPSS but lower PFR than those with low-grade inflammation; thus a strict correlation with BPO-related parameters. Conversely, highly-aggressive inflammation was associated only with PVol (Tab. III).

Finally, there was no correlation between Irani scores and GGG in patients with PCa.

DISCUSSION

The present study pointed out that high-grade inflammation (Irani G 2-3) was significantly more common in patients with BPH than in those with PCa and the same applied to highly-aggressive inflammation (Irani A). A novel finding of our study was that inflammation grade strictly correlated with BPO-related parameters. Specifically, patients with high-grade inflammation had greater PSA, PVol, PVR and IPSS but lower PFR than those with low-grade inflammation.

Our findings are in agreement with those by Nickel et al. [12] who evaluated the relationship between prostatic inflammation, prostate volume and the degree of LUTS. They evaluated 8224 men aged 50-75 years with BPH undergoing prostate biopsy and included in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial. Prostatic inflammation, scored as none, mild, moderate, or marked, was found in 77.6% of patients. Patients with chronic inflammation had higher prostate volumes than those without inflammation (46.5 *vs* 43.4 mL, respectively; $p < 0.001$) as well as higher IPSS (8.8 *vs* 8.2, respectively; $p < 0.001$).

In a cohort study of 282 patients, Robert et al. [13] found a significant association among the degree of prostatic inflammation, prostate volume, and urinary symptoms. Specifically, mean prostate volume was 62 ml in patients with low-grade inflammation and 77 ml in those with high-grade ($p = 0.002$); similarly, mean IPSS score was 12 and 21 in low-grade and high-grade inflammation ($p = 0.02$), respectively.

The correlation between prostatic inflammation and serum PSA levels has been highlighted by Irani et al. [11] who concluded that the inflammatory aggressiveness (Irani A), defined as rupture of the prostatic epithelium, was the morphological-diagnostic parameter that correlates most with the rise of the PSA. Accordingly, Song et al. [14] showed that, in patients undergoing surgery for

Table II. Association between Grade of inflammation (Irani G) and patients' clinical and pathological features.

	Irani G0-1 (n = 785)	Irani G2-3 (n = 393)	P-value
Age (y)*	66.0 (60.0, 72.0)	67.0 (62.0, 72.0)	0.073
PSA (ng/mL)*	6.01 (4.60, 9.03)	6.59 (4.81, 9.60)	0.027
Prostate volume (mL)*	50.00 (37.00, 68.00)	57.00 (42.00, 78.00)	<0.0001
PFR (mL/s)*	13.00 (9.00, 18.00)	12.00 (9.00, 15.70)	0.002
PVR (mL)*	20.00 (1.00, 50.00)	30.00 (1.00, 57.50)	0.003
IPSS*	9.5 (5.0, 16.0)	11.0 (6.0, 17.0)	0.032

*Data are expressed as medians (interquartile range).

Table III. Association between aggressiveness of inflammation (Irani A) and patients' clinical and pathological features.

	Irani A0-1 (n = 968)	Irani A2-3 (n = 210)	P-value
Age (y)*	66 (61, 72)	66 (61, 72)	0.6
PSA (ng/mL)*	6.20 (4.68, 9.06)	6.70 (4.80, 10.00)	0.2
Prostate volume (mL)*	52.00 (38.00, 70.00)	57.00 (41.00, 77.00)	0.009
PFR (mL/s)*	12.50 (9.00, 17.00)	13.00 (9.20, 17.00)	0.9
PVR (mL)*	30.00 (1.00, 50.00)	20.00 (1.00, 50.00)	0.3
IPSS*	10 (5, 16)	10 (5, 17)	0.9

*Data are expressed as medians (interquartile range).

BPH, the aggressiveness of inflammatory infiltration was a significant contributor to elevated PSA levels. Thus, patients with BPH with high levels of serum PSA might be considered at higher risk of harbouring chronic inflammation. In clinical practice this leads many patients with BPH and prostatic inflammation to undergo PBx because of increased serum PSA levels. Indeed, we demonstrated [15-17] that BPO-related parameters were independent predictors of the risk of being diagnosed with PCa; specifically, the more the BPO the less the risk of being diagnosed with PCa. Based on these findings, we developed a novel BPO-related parameters nomogram [18] that may help reducing the number of unnecessary PBxs, thus exposing patient to the risk of overdiagnosis and consequent overtreatment.

Another front of research is assessing the role of inflammation in conjunction with novel molecular markers [19 20]. Recently, Pentraxin 3, a marker potentially related to prostatic inflammation and immune-response has been shown to significantly outperform PSA (AUC 0.92 *vs* 0.55) in predicting the risk of being diagnosed with PCa [21]; these findings however await validation in a large series of patients scheduled for first PBx.

Fujita et al. [22] found that increased monocyte chemotactic protein-1 (MCP-1) levels in prostatic secretions correlated with prostate volume, and hypothesised that MCP-1 and macrophages might play a role in the development of prostatic inflammation and in the pathogenesis of BPH. An *in vitro* study by Latil et al. [23] elegantly reported that phytotherapeutic agents, such as the hexanic lipidosterolic extract of *Serenoa Repens*, inhibit MCP-1 expression by human prostate cells blocking key steps of the inflammation process.

More controversial is the relationship between prostatic inflammation and non-steroidal anti-inflammatory drugs (NSAID). While previous studies [24 25] pointed out a protective association between NSAID use and measures of BPH, more recent ones [26 27] pointed out a close relationship between NSAID usage and increase in BPH risk and the probability of BPH progression to a stage requiring surgical management.

In conclusion, prostatic inflammation correlates to BPH more than to PCa, with BPO playing a key role. If and how this clinical factor may impact on treatment outcome, like smoke in bladder cancer [28], remains to be determined. For sure, the role of inflammation and therefore of modulators of the immune response, which are opening new pathways in several urological cancers [29 30], deserves attention.

Conflict of Interest

The authors declare no conflict of interest.

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