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Evaluation of the Relationship between Prostate Cancer and Serum Inflammation Markers

Mustafa Aldemir*, Kemal Ener, Deniz Dehni, Koray Ağras, Önder Kayıgil

Department of Urology, Second Urology Clinic, Atatürk Teaching and Research Hospital, Ankara, Turkey

Abstract

Background and Aims: In this study, we aimed to examine possible relationship between the serum inflammation markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimantation rate (ESR), ceruloplasmin; and the stage of prostate cancer (Pca), serum prostate specific antigen (PSA) level and the Gleason score in patients with Pca.

Methods: Fourtyone patients diagnosed with prostate cancer, and 46 patients forming the control group, and diagnosed as having benign prostatic hyperplasia (BPH) were included in this study. The prostate cancer group was divided into subgroups according to the following parameters; PSA ≤20 ng/ ml and >20 ng/ ml, Gleason scores of ≤6 and >6, and further the cases with and without bone metastasis.

Results: It was detected that serum levels of CRP, ceruloplasmin and ESR were significantly higher in prostate cancer group, compared with the control group ($p<0,05$). Serum levels of CRP, ceruloplasmin, LDH and ESR were significantly higher in the Pca group with Gleason score of >6 compared with the Pca patients Gleason score ≤6 ($p<0.05$). Also, CRP, ceruloplasmin, alkaline phosphatase (ALP), LDH and ESR were significantly higher in the patients with PSA>20 ng/ ml, compared with the ones with serum PSA levels≤20 ng/ ml in the Pca group, as well ($p<0.05$).

Conclusions: We conclude that the serum inflammation markers are elevated significantly higher in patients with prostate cancer, especially for the ones with higher PSA and Gleason score.

Keywords: C-Reactive Protein, Ceruloplasmin, İnflammation, Prognostic Factors, Prostate Cancer

Introduction

Chronic inflammation has been associated with infection based cancers for a long time. For instance; stomach, liver and intestine cancers are seen more widely in the patients who already have inflammatory intestinal diseases (1). Common existence of inflammation process seen in radical prostatectomy specimens, prostatic tissues resected during the treatment of benign prostate hyperplasia and tissue samples obtained from prostate needle biopsy, suggests that inflammation may play a role in prostate carcinogenesis. Histologically, inflammatory cells are commonly found within and around the atrophy centre that is characterized as increased proliferative index. This centre, which is also known as proliferative inflammatory atrophy, may be the early precursor of Pca or the indicator of the suitable environment

*Correspondence:
Mustafa Aldemir, MD
Aydınlıkevler Mahallesi Arılık Sokak No: 5/5 06130, Ankara, Turkey.
Tel: +90-533-6309102
Fax: +90-312-2912705
E-mail: drmaldemir@yahoo.com.tr
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where intraprostatic cancer develops (1).

C-reactive protein (CRP) is a general indicator for systemic inflammation. It is reported that high serum levels of CRP indicates poor prognosis in Pca patients, and it is observed with the existence of bone metastasis (2, 3). Physiological functions of ceruloplasmin include transport of copper, organic amine oxidation, ferro-oxidase activity, cellular iron regulation, glutathione peroxidase and ascorbate oxidase activities, and anti-oxidant activity. Additionally, ceruloplasmin also binds reactive oxygen species such as superoxide and hydroxide radicals (4).

The aim of this study was to investigate the relationship between the serum inflammation markers such as CRP, ceruloplasmin, Lactate Dehydrogenase (LDH) and erythrocyte sedimantation rate (ESR) and the stage of prostate cancer (Pca), serum prostate specific antigen (PSA) level and Gleason score.

Materials and Methods

From January 2008 to March 2009, 41 male patients diagnosed with prostatic adenocarcinoma in our clinic and 46 patients diagnosed with benign prostatic hyperplasia (BPH) by prostate needle biopsy as the control group were included in the study. Based on history, patients with chronic hepatitis, inflammatory bowel disease, systemic inflammatory diseases, pyelonephritis, prostatitis syndromes, urinary tract infection, pyuria, hematuria and the ones using anti-inflammatory or immunosupressive drugs were excluded from the study.

In addition to the routine biochemical blood testing, complete blood count, total PSA and physical examinations; serum CRP, ceruloplasmin, LDH levels, ESR and a radionucleotide bone scan have been checked. The prostate volumes of the patients were measured by transrectal ultrasound using the ellipsoid formula. Post-voiding residual urine volumes were determined by using pelvic ultrasonography. Statistical significance of the laboratory variables were compared between subgroups of Pca patients such as; PSA ≤20 ng/ ml and PSA>20 ng/ ml, Gleason score ≤6 and Gleason score >6, and bone metastatic and not non-metastatic patients. The patients were informed of nature of the study and their approvals were taken.

CRP (N: 0-4.99 mg/L) (CardioPhase hs kit, Dade Behring BN 2, Germany), Alkaline phosphatase (ALP) (N: 25-136 U/L) and LDH (N: 100-190 U/L) (flex reagent cartridge kits, Dade Behring Dimension RXL MAX, USA) were measured after collection of serum samples from the study participants. Ceruloplasmin (20-60 mg/dl) was measured by nephelometry kit, (Dade Behring Prospec, Germany).

Statistics

SPSS version 11.5 was used for statistical analysis. All of the data are expressed as mean ± standard deviation (SD). The statistical analysis between Pca and BPH groups were conducted with the parametric Independent Samples Test, t-test for Equality of Means. Analyses between subgroups were conducted with non-parametric Mann-Whitney U test. $P<0.05$ was accepted as statistically significant.

Results

The mean age of the 41 patients within the Pca group was 68.6±7.8 years and the mean age of the 46 patients within the BPH group was found to be 57.7±6 years.

When the Pca and BPH groups were compared without taking the stage of the cancer and Gleason score into consideration, it was found that CRP, ceruloplasmin and ESR levels are significantly higher in the Pca group (Table 1).

The Pca patients were evaluated into two separate groups according to their PSA levels with a cut-off value of 20 ng/ ml. Serum CRP, ceruloplasmin, ALP, LDH and ESR values were observed to be higher in the PSA>20 ng/ ml group; and this difference was

Table 1. The comparison of Pca and control (BPH) groups

	Prostate Cancer (n=41) Mean±SD	BPH (n=46) Mean±SD	P Value*
Total PSA (ng/mL)	38.2±46.6	1.2±0.9	<0.001
Prostate volume (mL)	48.5±23	40.8±7.7	>0.05
PSA density	0.9±1.3	0.4±0.3	<0.001
CRP (mg/dl)	8.2±10.5	4.8±3.3	0.41
Platelet (x103)	234.2±61.9	218.7±38.2	>0.05
Hgb (g/dl)	14.6±1.7	15.2±1.4	>0.05
ESR (mm/hr)	27.5±28.6	16.1±14	0.19
Ceruloplasmin (mg/dl)	33.1±13.8	25.4±5.1	0.01

* Independent Samples Test, t-test for Equality of Means test, p<0.05

found to be statistically significant (Table 2).

In Pca patients with the values of Gleason score ≤6, the serum CRP, ceruloplasmin, LDH levels and ESR have been found to be significantly higher in those with Gleason score >6. However, serum ALP levels were found higher in the Gleason ≤6 subgroup (Table 3).

The Pca patients with and without bone metastasis no statistically significant difference was observed for the values of inflammation markers. Blood hemoglobin (Hgb) and creatinine values were found significantly higher within the non-metastatic Pca patients (Table 4).

Table 2. The data of the Pca patients with the values of serum PSA ≤ 20 ng/ ml and > 20 ng/ ml

	Total PSA ≤ 20 ng/ml (n=22) Mean±SD	Total PSA > 20 ng/ml (n=19) Mean±SD	P Value*
CRP (mg/dl)	4.5±3.5	12.5±14	<0.01
Platelet (x103)	230±46.2	239±77.3	>0.05
Hgb (g/dl)	15.1±1.5	14±1.9	>0.05
Ceruloplasmin (mg/dl)	26.9±7.6	40.2±15	0.01
ALP (U/L)	68.9±29.9	125.2±77.2	<0.01
LDH (U/L)	143.1±30.3	176.9±38.5	0.04
Urea (mg/dl)	33.4±10	53.7±74	>0.05
Creatinine (mg/dl)	1±0.2	1±0.1	>0.05
Prostate volume (ml)	47.2±15.8	49.8±29.7	>0.05
PSA density	0.2±0.2	1.7±1.6	<0.01
Post-voiding residual urine	47±27.4	61.6±53.8	>0.05
ESR (mm/hr)	15.6±9.5	41.4±36.5	0.02

* Non-parametric Mann-Whitney U, p<0.05

Table 3. The data of the Pca patients with Gleason score≤6 and >6

	Gleason score ≤ 6 (n=20) Mean±SD	Gleason score > 6 (n=21) Mean±SD	P Value*
CRP (mg/dl)	8.1±13.7	8.3±6.5	<0.001
Platelet (x103)	226.2±47.5	241.8±73.5	>0.05
Hgb (g/dl)	14.9±1.7	14.3±1.7	>0.05
Ceruloplasmin (mg/dl)	27.3±11.3	38.7±13.8	0.01
ALP (U/L)	95.4±82.2	94.7±38.8	<0.001
LDH (U/L)	155.7±38	161.7±38.6	0.04
Urea (mg/dl)	33.7±9.9	51.5±70.7	>0.05
Creatinine (mg/dl)	1±0.2	1±0.2	>0.05
Prostate volume (ml)	47.4±15	49.5±29	>0.05
PSA density	0.7±1.7	1±0.8	<0.001
Post-voiding residual urine	47.2±35.2	60±47.3	>0.05
ESR (mm/hr)	21.7±25	33.2±31.2	0.24

* Non-parametric Mann-Whitney U, p<0.05

Discussion

Although it is not proven that chronic or recurrent inflammation causes prostate cancer to develop, there are some reports about the possible role of inflammation in prostate cancer through various potential interrelated mechanisms (5). The quite common existence of the chronic inflammatory process, including the epithelial and stromal

Table 4. The data of the bone metastatic and non-metastatic Pca patients

	None metastatic (n=22) Mean±SD	Metastatic (n=19) Mean±SD	P Value*
CRP (mg/dl)	6±5.7	10.8±13.9	>0.05
Platelet (x103)	226±45.4	242.8±77.2	>0.05
Hgb (g/dl)	15.1±1.3	13.9±2	0.04
Ceruloplasmin (mg/dl)	29±9.5	37.8±16.5	>0.05
ALP (U/L)	82.5±38.5	109.4±81.6	>0.05
LDH (U/L)	153.8±37.5	164.5±38.7	>0.05
Urea (mg/dl)	34.8±9.8	52.2±74.5	>0.05
Creatinine (mg/dl)	1±0.2	1±0.1	0.02
Prostate volume (ml)	43.1±15.8	54.6±28.4	>0.05
Total PSA (ng/ml)	24.1±33.5	54.6±54.6	0.02
ESR (mm/hr)	20.8±20.7	35.3±34.5	>0.05

* Non-parametric Mann-Whitney U, p<0.05

infiltration of lymphocytes and hystiocytes within the peripheral zone, which is the most common region for prostate cancer to occur, also supports this hypothesis (5). In addition, the release of several pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF), that start CRP synthesis from the micro environment of the tumour, liver and other tissues, leads us to consider the possible relationship between tumour and inflammation (6).

Several studies report that, acetyl salisilic acid and paracetamol have prophylactic effect against the risk of prostate cancer development, and long term use of non-steroidal anti inflammatory (NSAI) medicines reduce this risk (7, 8). The most prominent mechanism of acetyl salisilic acid and other NSAI medicines regarding cancer prevention is their inhibition of cyclooxygenase-2 (COX-2). This enzyme is responsible for the release of various inflammatory prostaglandines. Prostaglandines play a key role in the acceleration of the tumoral tissue growth (9). In addition, it is known that COX-2 is found in increased quantity within prostate cancer tissue, and there is a positive correlation between COX-2 levels and prostatic tumour grade (10).

In our study, when the variables of Pca patients are compared with the patients in the control group, without taking the tumour grade or Gleason values into consideration; serum inflammation indicators such as CRP, ceruloplasmin and ESR were found to be significantly higher in the Pca group. These results demonstrate that there is a correlation between inflammation and prostate cancer, as also indicated in the literature. In a previous study, conducted on prostate cancer, the writers suggest that in case of the serum PSA level is higher than 20 ng/ml and/ or the Gleason score over 6, it should be considered as an advanced stage and the necessity of bone scintigraphy is emphasized (11). Therefore, we arranged our study by dividing the Pca patients into subgroups, that comprise of PSA ≤20 ng/ml and >20 ng/ ml, Gleason score ≤6 and >6, bone metastasic or non-metastatic, in order to investigate the relationship of these variables with Pca stage and grade.

Copper plays an important role in angiogenesis with various mechanisms. In addition, tumour growth may be downgraded by decreasing the copper levels (12).

In a related study that involved 20 cases of patients with prostate and colon cancers, it has been found that serum copper and ceruloplasmin levels had statistically significant increase in these patients, compared to the control group.

It is known that trace elements and free radicals play a certain role in cancer etiology. Therefore, it is usually suggested that the levels of specific anti-oxidants such as ceruloplasmin and trace elements including copper should be determined for the early diagnosis of prostate and colon cancers (13).

In our study, CRP, ALP, LDH, ceruloplasmin levels and ESR are found significantly higher in the Pca patients with PSA >20 ng/ ml, compared to the subjects with PSA ≤20. CRP, LDH, ceruloplasmin levels, and ESR are also found significantly higher in patients with Gleason score >6, compared to the patients with Gleason score ≤6. Elevated levels of these variables in patients with advanced Gleason score and high PSA value demonstrate their diagnostic value in advanced stage prostate cancer.

In conformation with our findings, in another study, it has been determined that in patients having locally advanced prostate cancer with extracapsular expansion beyond the organ, serum CRP, PSA and ALP levels show significant increase, while Hgb levels decrease significantly. The writers suggest that there is a significant correlation in regards to disease specific survival, between the tumour extension beyond the organ and CRP, PSA, ALP, Hgb levels and tumour histology. In the same study, the authors emphasize the 'level of serum CRP'

and 'extension of tumour beyond the organ', as two important prognostic factors (14). In another study, 62 metastatic prostate cancer patients receiving androgen abstinence treatment were evaluated. It has been determined that increased CRP levels may foresee a shorter disease-specific survival as an independent variable in this study (15). Similarly, it has been observed that increased CRP levels in metastatic prostate cancer patients may foresee a worse prognosis, independent from PSA (16).

In our study, the data of the Pca patients who had bone metastasis were compared with those from non-metastatic patients. The PSA value is found to be significantly higher in the metastatic group, as expected. However, when other markers such as CRP, ceruloplasmin and ESR were investigated, we find no statistically significant difference, which may be attributed to the less total number of patients involved in our study. In another study, Lehrer and colleagues have reported no statistically significant difference in serum CRP levels between patients with local Pca and BPH, while in cases with bone metastasis, the serum CRP levels were found to be significantly higher, compared with the non-metastatics (17).

The results of this study conclude that levels of the serum inflammatory markers such as CRP, LDH and ESR, and the anti-oxidant ceruloplasmin are elevated significantly higher in Pca patients. There is also a statistically significant correlation between these indicators and Pca. We suggest long-term studies involving higher number of patients that examine the effects of these indicators on the Pca prognosis.

Conflict of Interest

None declared.

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