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Letter to the Editor

Serum and tissue monocyte differentiation in PSA value 4–10 ng/mL prostate cancer and benign prostatic hyperplasia

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Abstract

Increased serum prostate-specific antigen (PSA) level is closely associated with prostate cancer; however, there is still no reliable method for distinguishing prostate cancer from benign prostatic hyperplasia (BPH) when the PSA level is between 4 and 10 ng/mL. In this study, we detected the inflammatory cell counts in serum and prostate tissues in prostate cancer and BPH patients. The results showed that the monocyte counts in both serum and prostate tissues were obviously less in patients with prostate cancer than that in those with BPH, which indicates that monocyte may be associated with development of prostate cancer and it is possible to increase positive finding for prostate cancer with 4–10 ng/mL PSA concentration by detecting and analyzing monocyte count in serum and tissue simultaneously.

Keywords

benign prostatic hyperplasia, inflammation, monocyte, prostate cancer, prostate-specific antigen

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Introduction

Prostate cancer has been the most common cancer accounting for almost 20% of new diagnoses and the second leading cause of cancer death accounting for almost 10% of estimated cancer mortality in men in the United States until 2018.[1] The majority of patients with prostate cancer are primarily diagnosed through prostate-specific antigen (PSA) screening, though pathological finding is critical for the final diagnosis. However, it is difficult to distinguish prostate cancer from benign prostatic hyperplasia (BPH) so that unnecessary repeat biopsies and over-treatment are often performed when the total prostate-specific antigen (tPSA) level ranges from 4 to 10 ng/mL.[2] On the other hand, some patients with low tPSA level present with discordant high-grade diseases. So it is important to find an effective method for diagnosing early prostate cancer with a PSA level of 4–10 ng/mL.

Inflammation has been considered as a potential risk factor which is associated with many cancers, including those in the liver, urinary bladder, gastric mucosa, lung, colon, and pancreas.[3–5] Some studies have demonstrated that either local inflammation or systemic inflammation was involved in the development and progression of prostate cancer.

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Platz et al.[6] showed that inflammation in prostate tissue was positively associated with prostate cancer by leveraging two trials, Prostate Cancer Prevention Trial (PCPT) and Selenium and Vitamin E Cancer Prevention Trial (SELECT). Furthermore, Arthur et al.[7] found that serum inflammatory markers, such as C-reactive protein (CRP), albumin, and white blood cell (WBC), were associated with prostate cancer severity and progression. However, it is unclear whether the local and/or systemic inflammation could distinguish prostate cancer from BPH when the PSA levels range between 4 and 10 ng/mL.

In this study, we analyzed the systemic and local inflammation in prostate cancer and BPH patients with PSA levels of 4–10 ng/mL and found that the monocyte count was obviously less in serum as well as prostate tissues in prostate cancer patients than that in BPH patients.

Patients and methods

Patients

A total of 6 prostate cancer patients who underwent radical prostatectomy and 13 BPH patients who underwent transurethral resection of the prostate (TURP) at our department between October 2014 and January 2018 were enrolled for retrospective analysis. The patients were diagnosed by multi($\geqslant$12)-core transrectal ultrasound (TRUS)-guided biopsy before surgery and confirmed by tissue samples after radical prostatectomy or TURP. The blood was collected from all 19 patients with the initial PSA level range of 4–10 ng/mL for detecting PSA concentration and peripheral blood cell counts before biopsy or drug therapy. The following situations before collecting blood were excluded for all patients: (1) digital rectal examination (DRE), urinary retention, and catheterization within 1 week; (2) hematuria, bladder stones, urinary tract infections, and inflammation; (3) prostate drug therapy before collecting blood and biopsy; (4) systemic inflammatory and immune diseases; and (5) abnormal peripheral WBCs $< 4 \times 10^9$/L or $> 10 \times 10^9$/L. All subjects gave informed and signed consent to participate in the study. This study protocol was approved by the Ethics Committee of Bengbu Medical College.

Peripheral blood cell examination

Peripheral blood cell counts, including WBC, neutrophil, lymphocyte, and monocyte, were performed prior to the prostate biopsy and drug therapy, and obtained using standard clinical testing as part of routine clinical examination. Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and neutrophil-to-monocyte ratio (NMR) were calculated.

Immunohistochemical staining

The prostate samples from radical prostatectomy and TURP were fixed and embedded. Sections were made to a thickness of 4 μm. Immunohistochemistry (IHC) was performed according to the manufacturer's instructions. Briefly, the slides were deparaffinized, rehydrated, and blocked. Then, the slides were incubated with primary antibodies: anti-MPO antibody (1:100) and anti-CD15 antibody (1:100) for neutrophil, anti-CD14 antibody (1:100) for monocyte, and anti-CD3 antibody (1:100), anti-CD4 antibody (1:100), and anti-CD8 antibody (1:100) for lymphocyte, respectively. The sections were added with the secondary antibody (Boster, Wuhan, China) for 40 min at room temperature overnight at 4°C. After washing, the sections were incubated with an SABC solution according to the manufacturer's instruction. The sections were observed under light microscopy (Nikon Ti-S, Tokyo, Japan). Staining was evaluated by two independent researchers.

Statistical analysis

The data are presented as mean $\pm$ standard deviation (SD). The data were analyzed by Student's t test. All analyses were performed using GraphPad Prism software (version 5.0). Results were considered significant when $P < 0.05$.

Results

The subject characteristics are shown in Table 1, and the mean ages of the patients with prostate cancer and benign prostate hyperplasia were 67.33 ± 8.26 and 72.38 ± 5.59 years, respectively. The mean body mass index (BMI) values were 22.44 ± 2.46 and 22.15 ± 2.11, and the mean

Table 1. Characteristics of patients with prostate cancer or BPH.

	Prostate cancer	BPH	*P* value
Number of patients	6	13	
Age (years)	67.33 ± 8.26	72.38 ± 5.59	0.215
BMI (kg/m^2)	22.44 ± 2.46	22.15 ± 2.11	0.810
Prostate volume (mL)	54.31 ± 22.41	68.98 ± 19.53	0.202
tPSA (ng/mL)	8.04 ± 1.40	7.21 ± 2.01	0.319
fPSA (ng/mL)	1.47 ± 1.23	1.82 ± 0.78	0.534
f/tPSA ratio (%)	0.19 ± 0.18	0.25 ± 0.07	0.449

BPH: benign prostatic hyperplasia; BMI: body mass index; tPSA: total prostate-specific antigen; fPSA: free prostate-specific antigen.

Table 2. The mean values of blood parameters in patients with prostate cancer or BPH.

	Prostate cancer	BPH	*P* value
WBC ($\times 10^9$/L)	6.53 ± 1.31	6.28 ± 1.35	0.702
Neutrophil ($\times 10^9$/L)	4.11 ± 0.81	3.71 ± 0.84	0.349
Monocyte ($\times 10^9$/L)	0.35 ± 0.08	0.46 ± 0.13	0.029
Lymphocyte ($\times 10^9$/L)	1.77 ± 0.39	1.79 ± 0.80	0.945
LMR (%)	5.23 ± 1.58	4.11 ± 2.28	0.240
NMR (%)	12.10 ± 3.12	8.38 ± 2.54	0.036
NLR (%)	2.37 ± 0.42	2.50 ± 1.31	0.746

NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; NMR: neutrophil-to-monocyte ratio.

prostate volumes were 54.31 ± 22.41 and 68.98 ± 19.53 mL, respectively. The tPSA values, free prostate-specific antigen (fPSA) values, and f/tPSA ratios in the prostate cancer and benign prostate hyperplasia groups were 8.04 ± 1.40 ng/mL, 1.47 ± 1.23 ng/mL, 0.19 ± 0.18% and 7.21 ± 2.01 ng/mL, 1.82 ± 0.78 ng/mL, 0.25 ± 0.07%, respectively. We observed no statistically significant difference between the two groups.

To verify whether the numbers of inflammatory cells in peripheral blood are different between prostate cancer and BPH patients, we detected the WBC, neutrophil, lymphocyte, and monocyte counts and analyzed the values of LMR, NMR, and NLR. As shown in Table 2, despite the fact that the mean WBC and neutrophil counts were more in prostate cancer patients (WBC 6.53 ± 1.31 and neutrophil 4.11 ± 0.81) than those in BPH patients (WBC 6.28 ± 1.35 and neutrophil 3.71 ± 0.84), there was no significant difference ($P > 0.05$). The mean lymphocyte counts in peripheral blood in prostate cancer and BPH patients were 1.77 ± 0.39 and 1.79 ± 0.80, respectively, and there was also no significant difference ($P = 0.945$). Interestingly, the mean monocyte count was obviously less in the prostate cancer group than that in the BPH group (0.35 ± 0.08 vs 0.46 ± 0.13, $P = 0.029$). In addition, the values of LMR and NLR have no significant differences between the two groups; however, the value of NMR was evidently higher in patients with prostate cancer than that in patients with BPH (2.10 ± 3.12 vs 8.38 ± 2.54, $P = 0.036$).

Furthermore, we performed the IHC staining to observe the expressions of inflammatory cells in prostate cancer and BPH tissues, including lymphocyte (CD3, CD4, CD8), monocyte (CD14), and neutrophil (CD15, MPO). As shown in Figure 1, the expressions of CD3, CD4, and CD8, which were markers of lymphocyte, had no significant differences between prostate cancer and BPH tissues. On the other hand, we did not observe any difference in the expressions of two neutrophil markers, CD15 and MPO. All the above data demonstrated that the lymphocyte and neutrophil counts were not different in prostate cancer and BPH tissues. However, the increased expression of CD14 resulted in increased monocyte count in BPH compared to prostate cancer tissues. Similar results were observed for the monocyte count in peripheral blood and prostate tissues in prostate cancer and BPH patients.

Discussion

PSA is the most widely used biomarker of prostate disease, the level of which could elevate in some conditions, including prostate cancer, BPH, prostatitis, prostate biopsy, and transurethral intervention. The men with PSA level ⩾ 10 ng/mL are considered possibly suffering from prostate cancer and may need prostate biopsy for further diagnosis. However, it remains controversial whether the prostate biopsy is necessary for the men with a PSA level of 4–10 ng/mL.

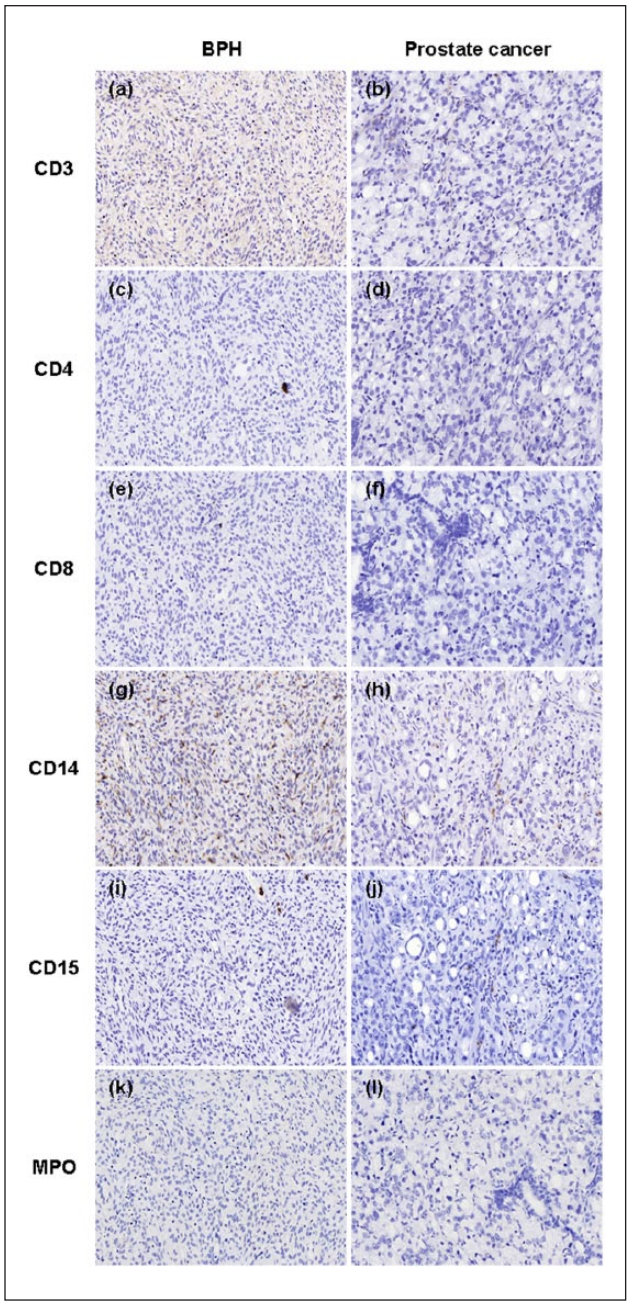


Figure 1. The monocyte count in prostate cancer tissue is less than that in BPH tissue. IHC was performed with CD3, CD4, CD8 antibodies to detect lymphocyte counts in tissues from prostate cancer (a,c,e) and BPH (b,d,f). IHC was performed with CD14 antibody to examine monocyte counts in prostate cancer (g) and BPH (h) tissues. CD15 and MPO antibodies were used to detect neutrophil counts in prostate cancer (i,k) and BPH (j,l) tissues. Brown staining represents positive cells (magnification, 200×).

Emerging evidence has demonstrated that inflammation is closely related to the development and progression of prostate cancer. Gurel et al.[8] detected the inflammatory cells using hemotoxylin and eosin (H&E) staining and found that inflammation in prostate tissue was positively associated with prostate cancer, especially high-grade, although the type of inflammatory cell was not verified. On the contrary, Vasavada et al.[9] performed a comprehensive literature review and meta-analysis and confirmed that inflammation on prostate needle biopsy is associated with lower prostate cancer risk. The discrepancy in findings may be a result of difference in the evaluation. In addition, the different inflammation expressions in low and high PSA levels are not considered in most of the studies. Ceylan et al.[10] found that NLR and NMR were lower in the serum of BPH patients than that in the serum of prostate cancer patients, both of which had a PSA level of 2.5–10 ng/mL. However, the NLR and NMR evaluations were performed after prostate biopsy in that study, which could affect the systemic inflammation. Furthermore, inflammation in prostate tissue was not evaluated.

In this study, we detected the inflammatory reaction in serum and prostate tissue in patients with a PSA level of 4–10 ng/mL. The results demonstrated that the mean monocyte count was significantly decreased in patients with prostate cancer than that in those with BPH, which indicated that inflammatory reaction could be not only associated with PSA level, other factor, for example, type of disease, maybe affected the monocyte count when the PSA level was same, although the mechanism of the effect of prostate cancer or BPH on monocyte remain unclear.

Declaration of conflicting interests

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