RESEARCH ARTICLE

Subtypes of White Blood Cells in Patients with Prostate Cancer or Benign Prostatic Hyperplasia and Healthy Individuals

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Abstract

Background: This study aimed to evaluate the baseline white blood cell (WBC), neutrophil, lymphocyte, monocyte, basophil, eosinophil count, total prostate-specific antigen (TPSA), free PSA (FPSA) level, neutrophil-to-lymphocyte and neutrophil-to-monocyte ratios among patients with prostate cancer and benign prostatic hyperplasia (BPH), as well as healthy individuals. Materials and Methods: 2005-2012 laboratory files of 160 patients with prostate cancer at Kayseri Training and Research Hospital, Oncology Outpatient Clinic, 285 patients who were pathologically diagnosed with BPH in Urology Outpatient Clinic and 200 healthy individuals who were admitted to Internal Medicine Outpatient Clinic were retrospectively analyzed. Baseline WBC, neutrophil, lymphocyte, monocyte, basophil, eosinophil count, TPSA, FPSA level, neutrophil-to-lymphocyte ratio and neutrophil-to-monocyte ratio were recorded and compared across groups. Results: Patients with prostate cancer had a lower lymphocyte level compared to the patients with BPH and healthy controls ($p<0.001$). The mean monocyte count, leukocyte-to-monocyte ratio, and leukocyte-to-lymphocyte ratio were higher in patients with prostate cancer, but without significance. The mean WBC and leukocyte count were lower in patients with prostate cancer, but again without statistical significance ($p=0.130$). The mean TPSA and FPSA were 39.4 and 5.67, respectively in patients with prostate cancer, while they were 5.78 and 1.28 in patients with BPH. There was a significant difference in the mean TPSA and FPSA levels between the patient groups ($p<0.001$). Conclusions: Our study results showed that patients with prostate cancer had a lower level of lymphocytes, neutrophils and WBCs and a higher level of monocytes with a significant difference in lymphocyte count, compared to healthy controls. We suggest that lymphocyte count may be used in combination with other parameters in the diagnosis of prostate cancer, thanks to its ease of assessment.

Keywords: Prostate cancer - benign prostate hyperplasia - white blood cell - neutrophil - monocyte - lymphocyte

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Introduction

Prostate cancer, which is the most common type of urological cancers, is the third most prevalent cancer in the world (The Committee for Establishment of the Guidelines on Screening for Prostate Cancer, 2010). With the introduction of novel diagnostic tools in recent years, the disease can be highly diagnosed (Dennis and Dawson, 2002). Despite increasing incidence, prostate cancer-related mortality rate has been decreasing. This may be explained by the widely-used prostate-specific antigen (PSA) screening as well as novel management approaches (Nonomura et al., 2010).

Although several studies presenting new insights on prostate cancer are available in the literature, the underlying etiology still remains to be elucidated (Dennis and Dawson, 2002; Cheng et al., 2005; Sfanos and De Marzo, 2012). However, some clues can be obtained from these studies. Inflammation was reported to increase the incidence of prostate cancer, similar to certain types of cancer (Cheng et al., 2005; Nonomura et al., 2010; Fujita et al., 2012; Sfanos and De Marzo 2012). Nelson and Harris (2000) also reported that the prevalence of symptomatic prostatitis was 9% in men above the age of 40 years, although the prevalence of asymptomatic prostatitis was unknown. In addition, prostatic lesion called as proliferative inflammatory atrophy and prostatic intraepithelial neoplasia are considered precursors of prostate cancer. This term includes focal atrophic lesions as well as chronic inflammation. Inflammatory cells release a number of oxidative materials which may lead to genomic and cellular damage. These materials were reported to increase the risk for prostate cancer, leading to infectious gene mutations. Similarly, molecular pathological studies confirmed that inflammation increased the risk for prostate cancer (Nelson and Harris 2000; Shah et al., 2000; Cheng et al., 2005; Sfanos and De Marzo, 2012). Dennis and Dawson (2002) also reported an increased risk for prostate

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cancer due to the presence of inflammation in sexually transmitted diseases. In addition, Nelson and Harris (2000) reported that several anti-oxidants and anti-inflammatory agents reduced the risk for prostate cancer.

Currently, prostate-specific antigen is the most widely adopted biomarker for solid tumors (The Committee for Establishment of the Guidelines on Screening for Prostate Cancer, 2010). This antigen is not cancer-specific, but organ-specific, which remarkably increases in the presence of trauma, inflammation and benign prostatic hyperplasia (BPH). Although free PSA (FPSA) which is widely used in clinical practice has been studied in a number of studies in the literature, it has several disadvantages. On the other hand, total PSA (TPSA) seems to be more effective in the early diagnosis of prostate cancer (Beer et al., 2008; Terakawa et al., 2008). Although no other parameter is reliable than PSA in the diagnosis of prostate cancer today (Beer et al., 2008; Mengus et al., 2011) it may not be a sole method for the definite diagnosis in all patients. As a result, the treatment may be delayed or unnecessary and assays with a high complication rate may be performed. Today, clinicians have been become interested in novel direct or indirect diagnostic methods to overcome such problems. Thus, several molecular, biological and serological studies have been undertaken (Jeromino et al., 2004; Beer et al., 2008; Mengus et al., 2011).

Based on our theoretical review, we aimed to investigate the effectiveness of white blood cells (WBC) and its subtypes, indicators for immunity, in prostate cancer. Within this purpose, we evaluated the baseline white blood cell (WBC), neutrophil, lymphocyte, monocyte, basophil, eosinophil count, total prostate-specific antigen (TPSA), free PSA (FPSA) level, neutrophil-to-lymphocyte ratio and neutrophil-to-monocyte ratio among patients with prostate cancer, BPH and healthy individuals.

Materials and Methods

Since 2005 to 2012 medical data and laboratory files of 160 patients with prostate cancer at Kayseri Education and Research Hospital, Oncology Outpatient Clinic, 285 patients who were pathologically diagnosed with BPH in Urology Outpatient Clinic and 200 healthy individuals who were admitted to Internal Medicine Outpatient Clinic were retrospectively analyzed. Baseline WBC, neutrophil, lymphocyte, monocyte, basophil, eosinophil count, TPSA, FPSA level, neutrophil-to-lymphocyte ratio and neutrophil-to-monocyte ratio were recorded. These values were compared among the patients with prostate cancer, BPH and healthy controls. The study protocol was approved by the Erciyes University, Faculty of Medicine, Ethics Committee on Clinical Studies.

Statistical analysis

The statistical analysis was performed using SPSS for Windows v11.0 software. Univariate analysis of variance (One-way ANOVA) was carried out to compare the means, standard deviations and the lowest and the highest thresholds between the groups. Duncan test was also used to identify the group which differed significantly. T-test was used to compare the test results of TPSA and FPSA among the patients with prostate cancer and BPH. Chi-square test was performed to compare the correlation of categorical variables with a confidence interval (CI) of 95%. The mean values were expressed in mean±standard deviation (SD). A p value of <0.05 was considered statistically significant.

Results

The mean values of blood parameters are shown in Table 1. The mean monocyte count, leukocyte-to-monocyte ratio, and leukocyte-to-lymphocyte ratio were higher in patients with prostate cancer.

The WBC count was 7.99 in patients with prostate cancer and BPH, AND 8.56 in healthy controls. Despite lower level of WBC in patients with prostate cancer and BPH, it did not reach statistical significance (p=0.256). Patients with prostate cancer had the lowest neutrophil count with 5.27, while healthy controls had the highest neutrophil count with 5.41. However, it did indicate any statistical significance (p=0.906).

The mean lymphocyte count was 1.85±1.25 in patients with prostate cancer, 1.84±0.67 in patients with BPH, and 2.29±1.42 in healthy controls. It indicated a highly statistically significant difference in healthy controls, compared to the patients with prostate cancer and BPH ($p<0.001$).

The mean monocyte count was 0.63 in patients with prostate cancer, 0.57 in patients with BPH, and 0.58 in healthy controls. Although the mean value was higher in patients with prostate cancer, it did not indicate any

Table 1. The Mean Values of Blood Parameters in Patients with Prostate Cancer, BPH and Healthy Controls.

Parameter	Prostate cancer group Mean±SD	BPH group Mean±SD	Healthy controls Mean±SD	p (<0.05)
WBC ($\times 10^3\ \mu l^{-1}$)	7.99±3.14	7.99±2.53	8.45±4.25	0.256
Neutrophil($\times 10^3 \mu l^{-1}$)	5.27±2.64	5.35±2.26	5.41±4.00	0.906
Lymphocyte ($\times 10^3\ \mu l^{-1}$)	1.85±1.25[3]	1.84±0.67[3]	2.29±1.42[12]	0.001
Monocyte(μl^{-1})	0.63±0.33	0.57±0.28	0.58±0.30	0.130
Neutrophil/Monocyte	3.72±3.72	3.27±2.76	3.68±5.44	0.395
Neutrophil/Lymphocyte	3.46±2.80	3.33±2.22	3.19±4.49	0.733
Eosinophil (μl^{-1})	0.16±0.17	0.15±0.13	0.16±0.15	0.578
Basophil (μl^{-1})	0.04±0.09	0.05±0.41	0.03±0.05	0.735
TPSA (ng/mL)	39.39±51.43[2]	5.78±9.59[1]	-	0.001
FPSA (ng/mL)	5.67±8.42[2]	1.28±2.31[1]	-	0.001

*Values are expressed in mean±SD

Table 2. The Minimum and Maximum Values in Patients with Prostate Cancer, BPH and Healthy Controls

Parameter	Groups	Minimum	Maximum
WBC	Prostate cancer	2.3	21.6
	BPH	1.5	21.7
	Controls	1.1	37.1
Neutrophil	Prostate cancer	1.4	16.8
	BPH	0.8	18.7
	Controls	0.1	34.9
Lymphocyte	Prostate cancer	0.4	14.75
	BPH	0.4	5.9
	Controls	0.2	18.2
Monocyte	Prostate cancer	0.16	2.02
	BPH	0.2	3
	Controls	0.1	2.1
Eosinophil	Prostate cancer	0	1.4
	BPH	0	0.7
	Controls	0	1
Basophil	Prostate cancer	0	0.86
	BPH	0	6.9
	Controls	0	0.2
TPSA	Prostate cancer	0.05	150
	BPH	0.11	90.3
FPSA	Prostate cancer	0.02	29
	BPH	0.06	25

statistical significance (p=0.130). No significant difference in eosinophil and basophil counts was observed among the groups.

Neutrophil-to-lymphocyte ratio and neutrophil-to-monocyte ratio were 3.72 and 3.46 in patients with prostate cancer, respectively and 3.27 and 3.33 in patients with BPH, respectively, while they were 3.68 and 3.19 in healthy controls, respectively. Patients with prostate cancer had a higher neutrophil-to-lymphocyte ratio (p=0.395) and neutrophil-to-monocyte ratio (p=0.733). However, it did not indicate any statistical significance.

The mean TPSA and FPSA were 39.39 and 5.67, respectively in patients with prostate cancer, while they were 5.78 and 1.28 in patients with BPH. There was a significant difference in the mean TPSA and FPSA level between the patient groups (p<0.001).

Discussion

Despite recent developments in diagnostic and therapeutic approaches, prostate cancer is still one of the leading health problems in the world with a high morbidity and mortality rate. Early diagnosis and management of the disease is of utmost importance to prevent morbidity (Beer et al., 2008; The Committee for Establishment of the Guidelines on Screening for Prostate Cancer, 2010).

It is well-established that cancer has deleterious effects on peripheral blood cells including erythrocytes, leukocytes, and platelets. However, the reason for increased neutrophil and monocyte count is still unknown. This may be partially explained by cytokine and chemokine-releasing cells which lead to leukocyte proliferation (Coussens and Werb, 2002; Mantovani et al., 2008).

It has been also reported that chronic inflammation is responsible for malignant tumors of epithelial origin including gastric, hepatic, colon, lung, pancreatic, esophageal, bladder and gallbladder cancer (Ardies, 2003; Wislez et al., 2003; Margolis et al., 2007). Despite unknown underlying mechanism, it has been suggested that toxic granules in neutrophils lead to inflammation of the neoplastic tissues, activating monocytes (Coussens and Werb, 2002; Nathan, 2006; Fridlender and Albelda, 2012). Also, several reports on inflammation and neutrophils in certain types of cancer are available in the literature.

On the other hand, there is a limited number of studies investigating the possible relationship between inflammation and white blood cells and its subtypes in patients with prostate cancer. So far, a few inflammation biomarkers have been investigated for the potential role in carcinogenesis in prostate cancer. Mengus et al. (2011) evaluated interleukin (IL)-7 levels in patients with localized prostate cancer and BPH. The authors reported that the level of IL-7 was higher in patients with prostate cancer. Similarly, Bear et al. (2008) reported that elevated C-reactive protein (CRP) was associated with poor prognosis in patients with metastatic prostate cancer.

It has been also reported that chronic inflammation is responsible for malignant tumors of epithelial origin. Increased WBC count due to chronic inflammation is responsible for the development and progression of malignant tumors of epithelial origin including lung, breast, colon, hepatic, thyroid, prostate, gastric, bladder, intestine, and esophageal cancer. (Ardies, 2003; Wislez et al., 2003; Mantovani et al., 2004; Walsh et al., 2005; Margolis et al., 2007; Goswami et al., 2008; Cho and Kim, 2009; Cho et al., 2009). Margolis et al. (2007) reported increased neutrophil, monocyte and mean leukocyte count in patients with endometrial cancer compared to healthy controls. The authors also found that cyclooxygenase 2 (COX-2), prostaglandin E2 (PGE2) and nuclear factor kappa B (NF-κB), which played an important role in the inflammatory process, were increased in this patient group. Similar results were obtained from the studies including patients with different types of gynecological cancer (Cho and Kim, 2009; Cho et al., 2009; Fridlender and Albelda, 2012). These studies showed that changes from baseline in neutrophil count were associated not only with the presence of cancer, but also stage and prognosis of the disease. Increased neutrophil counts were present in patients with advanced cancer. In addition, increased neutrophil counts were associated with increased mortality in patients with bronchoalveolar cancer, renal cell carcinoma and malignant melanoma (Wislez et al., 2003; Fridlender and Albelda, 2012). Also, increased neutrophil counts were reported to be a strong and independent prognostic factor for overall survival, recurrence and cancer-specific survival in patients with renal cancer and head and neck tumors (Jensen et al., 2009; Trellakis et al., 2011). Glial tumor grade was also higher in the presence of neutrophil infiltration (Fossati et al., 1999). However, hypothetical relationship between increased neutrophils and poor prognosis in cancer has not been widely adopted. On contrast, increased neutrophils were associated with good prognosis in patients with certain types of cancer, such as gastric cancer (Caruso et al., 2002). Fujita et al.

(2012) found that increased neutrophil count was a good indicator for benign prostate cancer. The authors also reported that biopsy samples were required to be obtained from patients with decreased neutrophils accompanied by high level of PSA and patients with neutropenia were at a higher risk for poor differentiated prostate cancer. In our study, we also obtained similar findings which were consistent with those reported by Fujita et al. (2012). Although the WBC and neutrophil counts were lower in patients with prostate cancer, it did not reach statistical significance. In addition, patients with BPH had a higher level of neutrophils.

In our study, although neutrophil-to-lymphocyte ratio, neutrophil-to-monocyte ratio and monocyte count were higher in patients with prostate cancer, it did not reach statistical significance. Recently, however, it has been largely reported that leukocytosis as well as neutrophil-to-lymphocyte ratio and multiplied neutrophils and lymphocytes may be a diagnostic and prognostic tumor biomarker. Several studies demonstrated that neutrophil-to-lymphocyte ratio was a prognostic factor for colorectal and non-small cell cancer. Other studies showed that neutrophil-to-lymphocyte ratio was associated with poor prognosis (Walsh et al., 2005; Cho and Kim, 2009; Cho et al., 2009). The authors compared multiplied monocyte-to-neutrophil count with neutrophil-to-lymphocyte count in patients with colorectal, cervical or ovarian cancer and found a higher ratio of multipled monocyte-to-neutrophil in these patient groups (Walsh et al., 2005; Cho et al., 2009).

In our study, healthy controls had the highest mean lymphocyte count (2.29±1.42), while patients with BPH had the lowest value 1.84±0.67 There was also a highly statistically significant difference in the mean lymphocyte count among the groups. We also observed a trend for decreased lymphocyte count in patients with advanced cancer or progression. Lymphopenia and neutrophil-to-lymphocyte ratio were found to be a predictor factor for mortality rate and treatment-related response. Several studies also reported that changes from baseline in the subtypes of WBC were prognostic indices for treatment-related response and survival (Wislez et al., 2003; Walsh et al., 2005; Margolis et al., 2007; Fridlender and Albelda, 2012). Reid et al. (2011) observed a correlation between lymphopenia and survival in patients with advanced pancreatic cancer. Similarly, Walsh et al. (2005) found that cancer-related mortality was statistically significantly higher in colorectal cancer patients with a preoperative neutrophil-to-lymphocyte ratio of >5. In addition, Nakahara et al. (2005) reported that neutrophil-to-lymphocyte ratio was an independent prognostic factor in fine needle aspiration biopsy specimen of advanced non-small cell lung carcinoma.

In conclusion, we demonstrated that patients with prostate cancer had a lower value of baseline lymphocytes, neutrophils and WBC with a higher value of monocytes, compared to healthy individuals. Therefore, we suggest that low level of baseline lymphocytes may be useful in clinical practice in patients with prostate cancer. However, further large-scale studies are required to confirm these findings.

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