

Predictive value of neutrophil-to-lymphocyte ratio before the second biopsy while detecting atypical small acinar proliferation

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Abstract

Aim: In this study, we aimed to detect of predictive value of neutrophil-to-lymphocyte ratio before the second biopsy while detecting atypical small acinar proliferation (ASAP) in high prostate-specific antigen (PSA) level.

Material and Methods: Two thousand two hundred ninety five patients underwent 10-12 quadrant TRUSBP between January 2008 and January 2016 have been evaluated retrospectively. Seventy six patients, whose data were reached, are taken into the study. Before the first biopsy, total PSA (tPSA), free PSA (fPSA), rate of percentage of free to total prostate specific antigen (f/tPSA) rate, PSA density (PSAD), blood neutrophil count (NC) and neutrophil-to-lymphocyte ratio (NLR) were measured. Second biopsy results and changes in the data are compared.

Results: Benign prostate hyperplasia in 44 patients (57.89%), ASAP in 16 (21.05%) and prostate adenocarcinoma (PCa) in 16 patients (21.05%) was detected. The patient's age, tPSA, fPSA, t/fPSA, PSAD, NC and NLR were 63.29 years, 8.68 ng/mL, 1.87 ng/mL, 21.34%, 18.15 ng/ml², 5.2710³/μL and 2.95 in group 1 and 64.31 years, 8.62 ng/mL, 1.58 ng/mL, 21.01%, 20.18 ng/ml², 7.5310³/μL and 2.84 in group 2, respectively. Patient's age, tPSA, fPSA, f/tPSA, PSAD, NC and NLR were not statistically significant between in two groups (p > 0,05).

Conclusions: We think that inflammation is a stimulant factor for PCa in patients with ASAP. So, before the first biopsy, it may be able to predict a cancer by considering NC and NLR in patients with ASAP. Although not significant, NC and NLR values were found to be higher in ASAP/malign than benign cases in the evaluation of ASAP patients before the second biopsy.

Keywords: Prostate Cancer; Atypical Small Acinar Proliferation; Neutrophil-To-lymphocyte Ratio.

INTRODUCTION

ASAP is suspicious for, but not diagnostic of, adenocarcinoma and first defined by Bostwick (1), represents suspicious glands without histologic atypia for a prostate adenocarcinoma. It is thought to be a period of travel towards prostate cancer (PCa). ASAP can be found 1.5% to 9.0% of prostate biopsy specimens in the literature (1,2). Optimal repeat biopsy (ORB) strategy may result in the diagnosis of prostate cancer by 30-40% (3,4). ORB recommend within 3-6 months after the initial diagnosis of ASAP in current guidelines.

NC and NLR are usually considered as an indicator of sub-clinical inflammation. Inflammation-related mutations and increased angiogenesis are thought to contribute

to the formation of carcinogenesis (5). NLR is a very successful parameter for predicting tumor progression (6) as well as estimating morbidity and mortality.

We aimed to assess the relationship between ASAP and inflammation status in patients with suspicious biopsy results (DRE) and determine the predictive value of NC and NLR for decision of second biopsy in our prostate biopsy cohort.

MATERIAL and METHODS

Study Population

Two thousand two hundred ninety five patients with prostate biopsy performed due to high PSA or significant DRE findings in our clinics between January 2008 and January 2016 were enrolled retrospectively. On 228 of

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2295 prostate biopsy patients ASAP was diagnosed, and the second biopsy was performed in 120 cases. Seventy six patients were reached taken into the study.

The criteria for inclusion in the study were as follows: DRE results suggestive or non-suggestive of neoplasia and elevated PSA (>2,5ng/mL in men). Disease of coagulopathies, patients with urinary tract infections, individuals who have had surgery in the past year, total number of cores less or more than 10, and patients who had previous anti-androgen and 5- α reductase inhibitory treatment were also excluded from the study. The patient's medical records were reviewed, patients with inadequate data were not included the study. Individual's age, grading and findings of digital rectal examination, TRUS calculated PVs with the ellipse method (length X depth X width X $\pi/6$), tPSA and fPSA, f/tPSA, PSA density (PSAD) that was calculated as total PSA (ng/mL) divided by prostate volume (ml), NC and NLR were evaluated before the initial biopsy in all patients.

One day before the TRUSBP, oral administration of 500-mg levofloxacin and 400-mg etodolac was started and it was continued until the end. The day of biopsy a rectal enema (250 mL) was performed before the biopsy. The procedure was performed while the patient was in the left lateral position with the thighs flexed. The procedure was performed under the guidance of ultrasound device with a 7.5 MHz biplanar probe.

The biopsy was performed on an outpatient basis in a room equipped with all material necessary for emergency intervention. Sedation and anesthesia were not achieved. 10 minutes before the procedure, periprostatic nerve blockade was performed in addition to perianal intrarectal lidocain gel. Injections were delivered at the angle between the seminal vesicle and prostate on each side using 5 cc of 2% lidocain. The biopsies were performed by multiple experienced urologists. Standard 10-12 (both lateral and medial biopsies from the base, medial and apex on the right and left side of the prostatic peripheral zone) core biopsy was performed in initial biopsies. For the patients with ASAP, a second prostate biopsy is performed after 3-6 months from the initial biopsy. 12,14, 16 or 18 samples were taken from the patients in second prostate biopsy.

Study Design

Pathological specimens were reviewed by a single genitourinary pathologist based on the 2005 International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma (7). Cases with ASAP were divided into groups according to the pathology by benign (group 1) or ASAP/Malign (group 2).

Statistical Analysis

All data was analyzed with SPSS 16 and Windows package (SPSS Inc. Chicago, IL, USA) and Microsoft excel computer programs. In the analysis of the data, the normality hypothesis was first investigated using the kolmogorov-smirnov test, followed by Mann-Whitney U test, chi-square and Fisher's exact as the statistical method. Relation was

studied by Ordinal-Spearman's Correlation. $P < 0.05$ was accepted as statistically significant.

RESULTS

The patient's age, tPSA, fPSA, t/fPSA, PSAD, neutrophil count (NC) and neutrophil lymphocyte ratio (NLR) were 63.29 years, 8.68 ng/mL, 1.87 ng/mL, 21.34%, 18.15 ng/ml², 5.27 10³/ μ L and 2.95 in group 1 and 64.31 years, 8.62 ng/mL, 1.58 ng/mL, 21.01%, 20.18 ng/ml², 7.53 10³/ μ L and 2.84 in group 2, respectively. Patient's age, tPSA, fPSA, t/fPSA, PSAD, NC and NLR were not statistically significant between in two groups ($p > 0,05$).

Benign prostate hyperplasia was detected in 44(57.89%), ASAP in 16 (21.05%) and PCain 16 patients (21.05%) was detected. The mean ages were not statistically significant between two groups: 63.29 \pm 7.83 for group 1, 64.31 \pm 7.33 for group 2. The tPSA, fPSA, f/tPSA, PSAD, NC and NLR were not statistically significant between two groups 8.68 ng/mL, 1.87 ng/mL, 21.34%, 18.15 ng/ml², 5.27 10³/ μ L and 2.95 in group 1 and 8.62 ng/mL, 1.58 ng/mL, 21.01%, 20.18 ng/ml², 7.53 10³/ μ L and 2.84 in group 2, respectively. ($p > 0,05$) (Table 1). In group 2, prostate adenocarcinoma was most common detected with Gleason score 3+3 in 11 of 16 patients (68.75%) (Table 2). 63,63% of patients (n=28/44) with benign pathology results were not detected abnormal digital rectal examination findings, but 34,37% of patients (n=11/32) with malign pathology results were had the digital rectal examination findings such as prostatic asymmetry, nodule and hard prostate (10,5%, 9,6% and 14,3% respectively).

Table 1. Evaluation of descriptive characteristics according to the groups

	Group 1 (mean)	Group 2 (mean)	P
Patients (n)	44	32	
Age (years)	63.29 \pm 7.83	64.31 \pm 7.33	0.57
PV (ml)	56.45 \pm 30.74	52.56 \pm 27.03	0,57
tPSA (ng/mL)	8.68 \pm 6.2	8.62 \pm 6.49	0,97
fPSA (ng/mL)	1.87 \pm 1.43	1.58 \pm 1.39	0,41
f/tPSA (%)	21.34 \pm 7	21.01 \pm 15	0,91
PSA Density(ng/ml ²)	18.15 \pm 15	20.18 \pm 18	0,59
Neutrophil Count (10 ³ / μ L)	5.27 \pm 2.69	7.53 \pm 2.45	0,48
Neutrophil-Lymphocyte Ratio	2.95 \pm 2.9	2.84 \pm 2.44	0.86

Table 1. Number of patients according to Gleason scores

Gleason Score (Group 2)	n (Overall)	%
3+3	11	68,75
3+4	2	12,5
4+3	1	6,25
4+4	1	6,25
5+5	1	6,25

DISCUSSION

Prostate cancer is the most common cancer in men (8). ASAP is considered a progression to cancer tissue from a normal prostatic tissue. There are arguments that inflammatory processes can change this alteration. Inflammation has been shown to induce fibroblast activation, immunocyte infiltration and stromal remodeling in the prostate (9). Neutrophils are activated after tumor formation in prostate tissue and active neutrophils cause the release of molecules such as reactive oxygen radicals, vascular endothelial growth factor. These factors have influence the development of tumor tissue (10). Lymphocytes inhibits the tumor cell proliferation and migration, on the contrary, activates tumor cell apoptosis and antibody-dependent cell cytotoxicity (11,12). Studies have shown that the prognosis is good as the amount of lymphocytes increases (13). NC and NLR values may be useful to clarify this issue because that is a cheap and easy parameter to use.

The normal ranges of NC and NLR vary by age. Mean NC and NLR values for 40-49, 50-59, 60-69 and >70 years are 1.94, 2.16, 2.41 and 2.96, respectively (14). The mean NLR values of patients in our study consistent with literature. This suggests that the inflammation process is less than expected.

ASAP is seen in 5% of the patients applied prostate biopsy due to high PSA or abnormal finding during DRE (15,16). In the literature, studies have suggested that 17-70% of patients with ASAP have PCa present on subsequent prostate biopsies (3,4). In our cohort, ASAP rate was 9,93%. PCa was found 21.05% in all patients with ASAP. We attribute two major factors to our higher than expected results; the first factor is performing more prostate biopsy compared to previous years and the second reason is early diagnosis due to the fact that patients are more conscious. Up to 80% of the patients with ASAP who are found to have PCa on repeat biopsy have low risk (Gleason score < 7) (17). In our patients, this rate was close the literature. We think that early diagnosis is also effective at this point. We believe that active surveillance for patients with PCa can be performed as an appropriate treatment protocol in suitable patients. More importantly, early detection of patients outside the low-risk group. We believe that we should focus on this issue in the coming years. If predictive factors are detected for diagnosis of intermediate or high risk PCa in patients with ASAP, we do not expect to wait for 3-6 months to perform of second prostate biopsy.

CONCLUSION

ASAP is a histopathologic stimulant result regarding to PCa and one of the problems in the early diagnosis of PCa. Another problem that needs to be solved is that tPSA, fPSA, f/tPSA rates and PSA density cutoffs are not sufficient for a proper diagnosis of prostate cancer. We do not think that NC and NLR should be routinely evaluated before the second biopsy in patients with ASAP. However, we believe that it may be useful to evaluate the PSA change at the same time. To explain that there is a need to further study

the routine assessment of NC and NLR values in ASAP patients in the current proven findings between PCa and NLR.

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