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# Comparison of nonspecific inflammatory markers in endometrial cancer and hyperplasia

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## SUMMARY

**OBJECTIVE:** This study aims to analyze inflammatory markers among patients with endometrial cancer, hyperplasia with atypia/endometrial intraepithelial neoplasia, hyperplasia without atypia, and normal controls, thus observing the stage at which inflammation becomes the most significant.

**METHODS:** A total of 444 patients who had endometrial sampling were included in the study (endometrial cancer, n=79; endometrial hyperplasia with atypia/endometrial intraepithelial neoplasia, n=27; endometrial hyperplasia without atypia, n=238; and normal controls, n=100). Neutrophil count, lymphocyte count, platelet count, platelet distribution width, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, CA-125, and endometrial thickness of the patients were recorded.

**RESULTS:** Comparing the groups for neutrophil count, the hyperplasia with atypia group had higher values compared with both the hyperplasia without atypia group and the control group (p=0.003). When compared for the lymphocyte count, the hyperplasia with atypia group had lower values compared with the control group (p=0.014). Neutrophil/lymphocyte ratio of the hyperplasia with atypia group was higher than all other groups, and neutrophil/lymphocyte ratio of the cancer group was higher than the control group (p=0.001). Platelet count, mean platelet volume, platelet distribution width, and platelet/lymphocyte ratio values were not significantly different among groups (p>0.05).

**CONCLUSIONS:** Considering the inflammatory markers, the most prominent result was that the hyperplasia with atypia group had neutrophilia, lymphopenia, and increased neutrophil/lymphocyte ratio compared with other groups.

KEYWORDS: Endometrial cancer. Endometrial hyperplasia. Neutrophil/lymphocyte ratio. Platelet/lymphocyte ratio. Endometrial intraepithelial neoplasia.

## INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries[1]. The prevalence of EC is expected to increase with increasing elderly population and obesity[2]. The major risk factor is excess estrogen without adequate opposition by progesterone. Majority of ECs are endometrioid-type adenocancers and have a background of endometrial hyperplasia (EH)[3]. Hyperplasia without atypia has a low progression rate to cancer whereas hyperplasia with atypia/endometrial intraepithelial neoplasia (EIN) has a higher progression rate to cancer, one-third of these actually have concurrent EC[4].

The link between inflammation and cancer was first suggested by Virchow in the 19th century after observing leukocyte influx to cancers developing in tissues with chronic inflammation[5]. Two pathways describing the link have emerged. The extrinsic

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pathway hypothesis suggests that inflammatory conditions promote cancer development[6]. The intrinsic pathway hypothesis suggests that the activation of different oncogenes leads to carcinogenesis which later increases inflammatory markers[7].

Inflammatory mediators such as cytokines, prostaglandins, and leukocytes play role in inflammation that can be observed as thrombocytosis, neutrophilia, and lymphocytopenia[3]. Neutrophils produce angiogenic factors and proteases contributing to tissue remodeling[8]. Platelet count is increased with hypoxic tumor microenvironment, protecting tumor cells from lysis[9]. We aimed to compare the inflammatory markers among patients with EH, cancer, and controls, thereby observing the stage when inflammation becomes evident.

## METHODS

This retrospective cross-sectional study was conducted with the data of patients having endometrial sampling between 2011–2017 in Haydarpaşa Numune Training and Research Hospital, Istanbul. Ethical approval was obtained (HNEAH-KAEK 2017/75). Pathology results of EC and hyperplasia were selected. Having an infection, rheumatological, inflammatory, collagen vascular, cardiovascular, hepatorenal or hematological disease, other malignancy, and using hormonal or corticosteroid therapy were the exclusion criteria. Out of 380 patients with EC and hyperplasia, 344 were suitable for the study. Another 100 women among the most recently biopsied patients who had physiological endometrium results were included as the control group (Group 4). Having a complete blood count tested no later than two weeks and having the pathological examination at the same hospital were required.

Full blood count data of the patients such as neutrophil, lymphocyte, platelet counts, and platelet distribution width (PDW) were recorded. The neutrophil/lymphocyte ratio (NLR) was defined as the neutrophil count divided by the lymphocyte count, and platelet/lymphocyte ratio (PLR) was defined as the platelet count divided by the lymphocyte count. CA-125 levels were measured using radioimmunoassay. Transvaginal ultrasonography was performed prior to biopsy. The main outcome measure was the difference of neutrophil count, lymphocyte count, platelet count, NLR, PLR, and PDW among groups.

Statistical analysis was performed using MedCalc Statistical Software version 12.7.7. The Kruskal–Wallis test was used to compare the nonparametric variables. The Mann–Whitney U test with Bonferroni correction was used to assess differences among the groups. The chi-square test and the Fisher's exact test were used to analyze the relation of categorical variables. $p<0.05$ was considered statistically significant.

## RESULTS

A total of 344 patients with cancer/hyperplasia results were included, of whom 79 were presented with EC (Group 1), 27 with EH with atypia/EIN (Group 2), and 238 with EH without atypia (Group 3). Mean ages were 60±11 (Group 1), 54±8 (Group 2), 47±7 (Group 3), and 52±10 (Group 4). Patients with EC were older. There was no difference among groups for gravidity and parity. The percentage of premenopausal patients was higher in Group 3 than other groups (Table 1). CA-125 level and endometrial thickness were both significantly higher in Group 1 compared with other groups. Endometrial thickness was significantly lower in controls than Groups 1–3 (Table 2).

Neutrophil count was significantly different among groups. The *post hoc* analysis revealed that neutrophil count was higher in Group 2 compared with Groups 3 and 4 (p=0.003). Lymphocyte count was also significantly different among groups. The *post hoc* analysis revealed that lymphocyte count was lower only in the hyperplasia with atypia/EIN group than the control group (p=0.014). When the groups were compared for NLR, the values of Group 2 were significantly higher than all other groups. NLR of the cancer group was higher than the control group (p=0.001). There was no significant difference among groups for PLR, platelet count, and PDW (Table 3).

Table 1. General characteristics of the patients.

| | Group 1 (Cancer) | Group 2 (Hyperplasia with atypia/EIN) | Group 3 (Hyperplasia without atypia) | Group 4 (Control) | p-value |
|---|---|---|---|---|---|
| Age[a] | 60.2±11.1 | 53.9±8.1 | 47.3±7.2 | 52.4±9.5 | 0.05 |
| Gravidity | 4.8±3.7 | 3.4±2.2 | 3.8±2.4 | 3.9±2.6 | 0.167 |
| Parity | 3.3±2.2 | 2.6±1.8 | 2.8±1.8 | 2.6±1.8 | 0.271 |
| Postmenopausal (n %)[b] | 57 (72) | 14 (52) | 48 (20) | 63 (63) | 0.001 |

[a]Group 1 was significantly older than other groups (p<0.05). [b]The percentage of premenopausal women was significantly higher in Group 3 when compared with other groups (Fisher's exact test; p<0.001). EIN, endometrial intraepithelial neoplasia;

Table 2. CA 125 levels and endometrial thickness.

| | Group 1 | Group 2 | Group 3 | Group 4 | p-value |
|---|---|---|---|---|---|
| CA 125 level[a] (U/mL) | 79.6±23.9 | 16.08±5.8 | 18.02±10.8 | 13.8±6.6 | 0.001 |
| Endometrial thickness[b] (mm) | 21.2±13.05 | 15.9±6.1 | 14.5±6.2 | 8.9±3.5 | 0.001 |

[a]CA 125 level was significantly higher in Group 1 (p<0.001). [b]Endometrial thickness was significantly higher in Group 1 (Kruskal–Wallis test; p<0.001).

Table 3. Comparison of hematological inflammatory markers.

| | Group 1 (Cancer) | Group 2 (Hyperplasia with atypia/EIN) | Group 3 (Hyperplasia without atypia) | Group 4 (Control) | p-value |
|---|---|---|---|---|---|
| Neutrophil (1´/µL)[a] | 5,109.6±2,034.5 | 6,562.2±3,266 | 4,808.9±1,853 | 4,398.9±1,467.2 | 0.003 |
| Lymphocyte (1´/µL)[b] | 2,354.8±777.4 | 1,988.6±1,003.7 | 2,384.0±759.6 | 2,516.7±909.9 | 0.014 |
| NLR[c] | 2.4±1.4 | 4.9±5.5 | 2.5±1.8 | 1.97±1.03 | 0.001 |
| PLR | 127.9±68.9 | 163.9±110.2 | 132.2±61.6 | 120.9±45.04 | 0.256 |
| Platelet (1´/µL) | 273,228±76,503 | 255,222±58,016 | 288,431±80,237 | 276,960±74,573 | 0.093 |
| PDW | 17.2±2.1 | 17.2±2.6 | 16.9±2.3 | 17.5±1.3 | 0.293 |

[a]Neutrophil count (p=0.003), [b]Lymphocyte count (p=0.0014) and [c]NLR values were significantly different among groups. EIN: endometrial intraepithelial neoplasia; NLR: NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; PDW: platelet distribution width.

## DISCUSSION

The relation of inflammation and ECs is well established. The majority of publications focus on the relation of markers to prognosis. High NLR and PLR are the predictors of poor prognosis[10,11].

However, there is limited research on hematological inflammatory markers and EH. One of these is a study by Açmaz et al.[12] Subjects were grouped as EC, EH, and control, and atypia was not differentiated. NLR was higher in the EC group compared with the EH and control groups. PLR was higher in the EC and EH groups compared with controls[12]. Another study grouping the subjects similarly reported higher neutrophil count, higher NLR, and lower PDW in the EC group compared with the control group. There was no difference between EC and EH groups. PLR was not different among the groups[13]. A similarly designed study reported that NLR was significantly higher in the cancer group than the hyperplasia and control groups. There was no significant difference between their PLR values[14]. The study by Kurtoğlu et al.[15] grouped their patients according to the hysterectomy results as benign and malignant. They did not observe a difference between NLR and PLR whereas MPV was higher and PDW was lower in the malignant group[15]. In our study, we did not observe a significant difference between groups in terms of platelet count, PLR, and PDW.

Prior studies comparing hyperplasia, cancer, and controls did not differentiate between the types of hyperplasia. Up to our knowledge, there is only one study in the literature grouping the subjects as EH group with atypia, EH group without atypia, and normal controls. This study did not include EC. The hyperplasia with atypia group had significantly higher NLR and PLR than other groups[16]. This study is the first in the literature comparing all the four groups up to our knowledge. The intuitive expectation would be a gradual increase in NLR as the situation proceeds from normal to hyperplasia without atypia to with atypia to EC. In our study, NLR was significantly higher in the EC group compared with the control group, which was an expected finding compatible with the literature. NLR was significantly higher in the hyperplasia with atypia group compared with hyperplasia without atypia and control groups. NLR was also higher in the hyperplasia with atypia group compared with the EC group. PLR was highest in the hyperplasia with atypia group, but a statistically significant difference was not seen. The finding of higher inflammation in the hyperplasia with atypia compared with cancer was supported by a recent study aiming to investigate the inflammatory marker differences between complex atypical hyperplasia (CAH)/EIN and endometrioid-type grade 1 cancer using the pathological results of hysterectomy. Both NLR and PLR were higher in the CAH/EIN group than the cancer group[17].

Information about the inflammation status of precancerous lesions can be valuable in the investigation of the etiopathogenesis of EC. Hormonal and genetic changes are the important risk factors in ECs. We know the role of genetic mutations such as PTEN and Kras, and these genetic

changes occur in the presence of increased cell proliferation caused by unopposed estrogen. There is a complex interaction between sex steroid hormones and cytokines/growth factors in the endometrium[7]. Proinflammatory milieu further increases estrogen *via* aromatase expression. Nasier et al. demonstrated the increasing expression of COX-2 from EH to invasive EC and suggested that COX-2 inhibition could potentially stop the progression of precursor lesions[18]. Sanderson et al. reported in their review that COX-2 needs to be further investigated as a potential biomarker of the progression of EH to EC[2]. The inhibition of inflammation could be a therapeutic intervention for endometrial adenocarcinoma[7].

The retrospective design is a limitation of our study since all confounding factors could not be excluded. Another limitation is not having compared the body mass index (BMI). Adipose tissue increases both estrogen and proinflammatory cytokines. The previously mentioned study compared the BMI and nonspecific inflammatory markers of the groups, and no correlation was present[16].

## CONCLUSIONS

Considering the link between inflammation and EC, EH is worthy of investigation. Complete blood count being easily accessible and cheap would be a practical guide to reveal the systemic inflammatory condition of the patient. This study suggests that inflammation plays a role in the progression to EC, especially from the stage of hyperplasia with atypia/EIN. Future large-scale studies are needed to support this suggestion.

## AUTHORS' CONTRIBUTIONS

**ECDA:** Conceptualization, Data Curation, Writing – Original Draft. **ADEC:** Conceptualization, Formal Analysis, Writing – Original Draft. **FV:** Supervision, Writing – Review & Editing.

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