Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Orijinal Makale

The Role of Peripheral Blood Inflammation Indices in Patients with a Diagnosis of Endometrial Hyperplasia and Cancer

Endometrial Hiperplazi ve Kanser Tanılı Hastalarda Periferik Kan İnflamasyon İndekslerinin Rolü

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Abstract

Purpose: Endometrial cancer (EC) is an important problem with its increasing incidence, especially in developed countries. There is no generally accepted screening program yet. The management of endometrial hyperplasia (EH), which is the most important risk factor, is complex because it is an invasive process.

Methods: A retrospective study was conducted with a total of 72 patients. Patients between the ages of 35-65 with abnormal uterine bleeding, and increased endometrial thickness on transvaginal sonography were evaluated with pathology results. Sociodemographic characteristics of the patients and laboratory values at hospital admission were obtained from hospital records. White blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and thrombocyte counts ($x10^9$/L); plateletcrit (%), hemoglobin (Hb) (g/dL), and hematocrit (Htc) (%) values were recorded. Neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and thrombocyte lymphocyte ratio (TLR) were obtained. Systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and pan-immune-inflammation value (PIV) were obtained.

Results: Thirty-seven patients diagnosed with EH and 35 patients diagnosed with endometrial malignancy were included. The mean age of the EH was 45.5 years and the mean age of the malignant group was 50.5 years (p=0.027). The sociodemographic characteristics of the patients were found to be similar. There was no significant difference in complete blood count parameters between two groups. Mean values of NLR were 2.33 and 2.52 in EH and EC groups, respectively, p = 0.448. Mean values of MLR were 0.20 and 0.21, respectively, p = 0.498. Mean values of TLR were 0.16 and 0.15, respectively, p = 0.811. Mean values of SII were 720.1 and 812.4 ($x10^9$/L), respectively, p = 0.456. Mean values of SIRI were 943.1 and 1095.6 ($x10^9$/L), respectively, p = 0.257. Mean values of PIV were 312753.6 and 352975.1 ($x10^9$/L), respectively, p = 0.514.

Conclusion: Peripheral blood inflammation indices have recently been used in cancer diagnosis and follow-up. We did not find any statistically significant differences in the investigated parametrers between the EH and EC patient groups. Close follow-up is necessary in the presence of additional risk factors in women with EH.

Keywords: endometrial cancer; endometrial hyperplasia; systemic immune-inflammation index; systemic inflammation response index; pan-immune-inflammation value

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Öz

Amaç: Endometrium kanseri (EK) , özellikle gelişmiş ülkelerde artan sıklığıyla önemli bir sorundur. Henüz genel kabul görmüş bir tarama programı yoktur. En önemli risk faktörü olan endometrial hiperplazinin (EH) yönetimi, invaziv bir süreç olması nedeniyle karmaşıktır.

Gereç ve Yöntem: Toplam 72 hasta ile retrospektif bir çalışma yürütüldü. Anormal uterin kanaması ve transvajinal sonografide artmış endometrial kalınlığı olan 35-65 yaş arasındaki hastalar patoloji sonuçlarıyla değerlendirildi. Hastaların sosyodemografik özellikleri ve hastane yatışındaki laboratuvar değerleri hastane kayıtlarından elde edildi. Beyaz kan hücreleri (WBC), nötrofiller, lenfositler, monositler, eozinofiller, bazofiller ve trombosit sayıları (x10^9/L); plateletcrit (%), hemoglobin (Hb) (g/dL) ve hematokrit (Htc) (%) değerleri kaydedildi. Nötrofil lenfosit oranı (NLO), monosit lenfosit oranı (MLO) ve trombosit lenfosit oranı (TLO) elde edildi. Sistemik immün-inflamasyon indeksi (SII), sistemik inflamasyon yanıt indeksi (SIRI) ve pan-immün-inflamasyon değeri (PIV) elde edildi. Verilerin dağılımı SPSS ile programı ile analiz edildi. Parametrik veriler bağımsız örneklem t-testi ile incelendi. 0,05'ten küçük p değeri anlamlı kabul edildi.

Bulgular: EH tanısı almış 37 hasta ve endometrial malignite tanısı almış 35 hasta çalışmaya dahil edildi. EH grubunun yaş ortalaması 45,5 yıl iken malign grubun yaş ortalaması 50,5 yıl idi (p=0,027). Hastaların sosyodemografik özellikleri benzer bulundu. Tam kan sayımı parametrelerinde iki grup arasında istatistiksel olarak anlamlı fark yoktu. Sistemik inflamatuar indeksler gruplar arasında karşılaştırıldı. EH ve EK gruplarında ortalama NLR değerleri sırasıyla 2,33 ve 2,52 idi, p=0,448. MLO ortalama değerleri sırasıyla 0,20 ve 0,21 idi, p=0,498. TLO ortalama değerleri sırasıyla 0,16 ve 0,15 idi, p=0,811. SII ortalama değerleri sırasıyla 720,1 ve 812,4 (x10^9/L) idi, p=0,456. SIRI'nin ortalama değerleri sırasıyla 943,1 ve 1095,6 (x10^9/L) idi, p = 0,257. PIV'nin ortalama değerleri sırasıyla 312753,6 ve 352975,1 (x10^9/L) idi, p = 0,514.

Sonuç: Periferik kan inflamasyon indeksleri son zamanlarda kanser tanısı ve takibinde kullanılmaktadır. EH ve EK hasta grupları arasında araştırılan parametreler arasında istatistiksel olarak herhangi bir anlamlı fark bulamadık. EH'li kadınlarda ek risk faktörlerinin varlığında yakın takip gereklidir.

Anahtar Kelimeler: endometrial kanser; endometrial hiperplazi; sistemik immün-inflamasyon indeksi; sistemik inflamasyon yanıt indeksi; pan-immün-inflamasyon değeri

1. Introduction

Endometrial cancer (EC) is the second most common gynaecologic cancer and the fourth leading cause of cancer death worldwide (1). The incidence of this disease is increasing rapidly and has become more common in the developed world over the last few decades (2). Previously known as a post-menopausal disease, its incidence in women under 50 has increased in recent years (3). Obesity, metabolic syndrome, advanced age, nulliparity, infertility, unopposed estrogen exposure, diabetes mellitus are some risk factors. Vaginal bleeding is the most common symptom and usually causes symptoms. Therefore, early diagnosis and correct treatment of precancerous lesions is essential for management. The gold standard for diagnosis is endometrial sampling and histopathological examination. There is currently no well-established screening method for EC, except for the recommendation of annual endometrial sampling from the age of 35 for those with a family history of cancer (4). Endometrial hyperplasia (EH) is a common gynaecological endocrine pathology characterised by an increase in the ratio of endometrial glands to strom, as opposed to the normal proliferative endometrium. It's main clinical significance is that it is a known precursor lesion of the endometrioid type, the most common type of EC (5). The differentiation and transition between low- risk and high- risk EH is recognized to be continuous (6). Risk factors include diabetes, advanced age and increased body mass index (BMI) (7). Exposure to unopposed estrogen stimulation is the best identified mechanism of hyperplasia. Early diagnosis and treatment are very valuable for patients with precancerous lesions (8).

Inflammation and the excessive release of pro-inflammatory cytokines in the microenvironment of cancer tissue affect bone marrow cell production. Thus, defects in the immune response mechanism promote cancer development and progression. There is increasing evidence for the use of peripheral blood parameters as alternative markers reflecting the inflammatory status in cancer (9,10). Higher systemic inflammation response index (SIRI) levels were associated with the efficacy of neoadjuvant chemotherapy in breast cancer (11). Pan-immune-inflammation value (PIV) was found to predict recurrence in patients with left-sided colon cancer (12). Histopathological examination is the gold standard for diagnosing endometrial pathology, but systemic inflammatory markers are used clinically as an adjuct to demonstrate tumour aggressiveness and invasiveness. Systemic immune-inflammation index (SII) is a marker that has been evaluated between early and advanced stages of EC (13).

We hypothesised that malignant endometrial pathologies are associated with systemic inflammation, and our primary aim is to compare peripheral blood parameters in EH and cancer.

2. Materials and Methods

Study Population

The retrospective study was conducted on 72 patients who underwent endometrial biopsy and hysteroscopy at Etlik Zübeyde Hanım Women's Gynaecology Training and Research Hospital between 1 January 2024, and 1 September 2024. The study was approved by the institution's education planning committee with decision number 23.08.2024-08/07.

Patients aged of 35-65 years with abnormal uterine bleeding, and increased endometrial thickness on transvaginal sonography were evaluated with pathology results. Those with inflammatory, hematological, rheumatological, thyroid diseases, hyperprolactinemia, steroid and tamoxifen use, and hormone replacement therapy, those diagnosed with secretory, proliferative endometrium, endometrial intraepithelial neoplasia (EIN) as a result of histopathological examination were excluded. The patient's sociodemographic characteristics, preoperative laboratory, and pathology results were obtained from hospital records. White blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophil, basophil, and thrombocyte counts (x10^9/L), plateletcrit (%), hemoglobin (Hb) (g/dL), and hematocrit (Htc) (%) values were recorded before the intervention. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and thrombocyte-lymphocyte ratio (TLR) were calculated. The SII was obtained by dividing the product of neutrophil and thrombocyte counts by the lymphocyte count (x10^9/L); the SIRI was calculated by dividing the product of neutrophil and monocyte numbers by the lymphocyte count (x10^9/L); PIV was calculated by dividing the product of neutrophil, monocyte, and thrombocyte counts by the lymphocyte counts (x10^9/L).

Statistical analysis

The IBM Statistical Package for the Social Sciences software version 25.0; SPSS Inc., Armonk, NY was used for data analysis. The Kolmogorov-Smirnov test was used to examine the distribution of the data. Descriptive statistics were presented as mean ± standard deviation for normally distributed data. Parametric data were compared using the independent sample t-test.

3. Results

A total of 72 patients were enrolled in the study. Thirty-seven participants diagnosed with EH and 35 participants diagnosis with malignancy based on endometrial biopsy and operative hysteroscopy results were included in the study. The mean age of the EH group was 45.5 years and the mean age of the malignant group was 50.5 years (p=0.027). The socio-demographic characteristics of the patients were similar (Table 1).

Complete blood count parameters were compared (Table 2). The mean WBC counts were 7.172 and 7.808 (x10^9/L) respectively, p=0.205. Mean neutrophil counts were 4.530 and 5.059 (x10^9/L) respectively, p=0.208. The mean lymphocyte counts were 2.078 and 2.116 (x10^9/L) respectively, p=0.787. The mean monocyte counts were 0.404 and 0.441 (x10^9/L), respectively, p= 0.331. The mean eosinophil counts were 0.114 and 0.157 (x10^9/L), p= 0.158. The mean basophil counts were 0.031 and 0.041 (x10^9/L), respectively, p= 0.080. The mean thrombocyte counts were 309 and 301 (x10^9/L), respectively, p= 0.770. The mean PCT counts were 0.31 and 0.30 (%), respectively, p= 0.643. The mean Hb values were 11.9 and 11.9 (g/dL) respectively, p= 0.857. The mean Hct values were 36.4 and 37.1 (%), respectively, p= 0.582.

The indices were the compared between groups (Table 3). The mean values of NLR were 2.33 and 2.52 in the premalignant and malignant groups, respectively, p= 0.448. The mean values of MLR were 0.20 and 0.21, respectively, p= 0.498. The mean

Table 1. Comparison of sociodemographic features of hyperplasia and cancer groups

	EH (n=37)	EC (n=35)	p-value
Age (years)	45.5±6.8	50.5±11.1	**.027***
BMI (kg/m^2)	26.2±3.8	27.3±3.4	.724
Gravidity (n)	3±1	3±2	.866*
Parity (n)	3±1	2±1	.395*
Abortus	0±0	1±0	.344*

*Comparison between groups was made with independent t test. Values are given as mean±standard deviation.
EH: endometrial hyperplasia, EC: endometrial cancer, BMI: body-mass index

Table 2. Comparison of laboratory data of the groups			
	EH (n=37)	**EC (n=35)**	**p-value**
WBC (x10^9/L)	7.172±2.067	7.808±2.155	.205*
Neutrophil (x10^9/L)	4.530±1.597	5.059±1.930	.208*
Lymphocyte (x10^9/L)	2.078±0.659	2.116±0.524	.787*
Monocyte (x10^9/L)	0.404±0.169	0.441±0.151	.331*
Eosinophile	0.114±0.077	0.157±0.086	.158*
Basophile	0.031±0.015	0.041±0.020	.080*
Thrombocyte (x10^9/L)	309±91	301±99	.770*
PCT (%)	0.31±0.09	0.30±0.08	.643*
Hb (g/dL)	11.9±2.3	11.9±2.2	.857*
Hct (%)	36.4±5.9	37.1±5.7	.582*
* Comparison between groups was made with independent t test. Values are given as mean±standard deviation. EH: endometrial hyperplasia, EC: endometrial cancer, PCT: plateletcrit			

Table 3. Comparison of peripheral blood inflammation indexes between groups			
	EH (n=37)	**EC (n=35)**	**p-value**
NLR	2.33±1.01	2.52±1.15	.448*
MLR	0.20±0.06	0.21±0.06	.498*
TLR	0.16±0.05	0.15±0.08	.811*
SII (x10^9/L)	720.1±374.5	812.4±641.7	.456*
SIRI (x10^9/L)	943.1±524.1	1095.6±607.1	.257*
PIV (x10^9/L)	312753.6±245588.2	352975.1±274447.9	.514*
* Comparison between groups was made with independent t test. Values are given as mean±standard deviation. EH: endometrial hyperplasia, EC: endometrial cancer			

values of TLR were 0.16 and 0.15, respectively, p= 0.811. The mean values of SII were 720.1 and 812.4 (x10^9/L), respectively, p= 0.456. The mean values of SIRI were 943.1 and 1095.6 (x10^9/L), respectively, p= 0.257. The mean values of PIV were 312753.6 and 352975.1 (x10^9/L), respectively, p= 0.514.

4. Discussion

The presented study investigated the role of inflammatory markers in predicting malignancy in patients with abnormal endometrial findings. The mean age of the EC group was shown to be higher than that of the EH group. Peripheral complete blood count indices showed no difference between hyperplasia and malignant endometrial pathology.

Several pro-inflammatory mediators are released in the tumour milieu, causing impairment of host immunity (14). Oxidative stress leads to haematological changes with the secretion of cytokines, chemokines and various enzymes. The most common are leukocytosis, neutrophilia and lymphopenia. When immunity is suppressed, an increase in the neutrophil-to- lymphocyte ratio is expected. Markers of the systemic inflammatory response have been investigated for diagnosing, prognosis, and predicting metastasis in various types of cancer (9,10,14). In distinction to other cancers, markers that can be used in diagnosis and prognosis will play a valuable role due to the genetic polymorphism and specific molecular structure of EC (15). In a previous study, NLR and TLR were found to be valuable in predicting lymph node metastasis in endometrial adenocarcinoma, but less effective than CA 125 (16). In another study, NLR was found to predict survival in epithelial ovarian cancer (17). In a review investigating the short and long-term prognostic value of SII in EC, increased SII was found to be associated with shorter survival (18). In the present study, the mean SII was found to be similar to the EH group. In a different study, SII was associated with adverse clinicopathological

features but not with recurrence-free survival (19). In the present study, no change in systemic inflammation markers were found in EC cases compared to EH cases. The early stage cancers in the EC group or the possibility of concurrent malignancy in the EH group may play a role in these results.

Although premalignant lesions of the endometrium have been included in various classifications in the past, they are now grouped under two main headings as benign EH and EIN. These two groups differ in their malignant potential, with EINs showing monoclonal growth and being true neoplasms, whereas benign EHs are polyclonal endometrium that develop in response to anovulation and an abnormal hormonal environment. Benign EH that develops due to unopposed estrogen exposure is at risk of EC as the duration of exposure increases (20). It is most common in perimenopausal women, as in this study. It can also be seen in young women with anovulatory cycles. Treatment is medical or surgical, depending on the patient's age, whether hyperplasia is present with or without atypia, and the patient's desire to have children. Hysterectomy is recommended for women with atypical hyperplasia and for women with persistent non-atypical hyperplasia because of the risk of concurrent or future EC if fertility is not desired. Accurate assessment of EC risk plays an important role in optimal clinical management.

The current study showed that women diagnosed with EC were older than those diagnosed with EH. This finding is consistent with studies in the literature. In a study comparing complete blood count parameters in 416 patients, the average age of the EC group was higher than that of the EH group (21). In another study examining platelet indices, the EC group was found to be older (22). Data show that the risk is higher after the age of 60 and that survival decreases (23). This may be due to reduced immune function in the postmenopausal period. Most of the estrogen in the postmenopausal female circulation is formed by peripheral aromatisation (23). The aromatising capacity of adipose tissue is stimulated by pro-inflammatory cytokines. Therefore, older age and obesity are risk factors for EC. In this study, BMI was similar between the groups. Contrary to our results, another study in the literature found that BMI was higher in the EC group (8). According to this study, the risk of EC was higher in EH patients with a BMI above 25 kg/m². In fact, there are recent data suggesting that weight loss prevents EC by reducing systemic inflammation and boosting immunity (24). In adition, nulliparity is also a known as a risk factor for EC. In our presented study, obstetric characteristics were similar between the two groups. Although there is no known screening method for EC, women with established risk factors, such as obesity, advanced age, hyperplasia, diabetes mellitus, and hypertension, may be subjected to closer clinical follow-up.

The strengths of the study are that the SIRI and PIV markers, which have not been previously studied in the EC and EH, were investigated. There are some limitations to our study. The retrospective nature of the research, a single preoperative blood sample, a relatively small number of patients, and the lack of postoperative pathological confirmation of those who underwent hysterectomy are some of the limitations. Studies including EC stages and prognostic markers can be planned.

5. Conclusion

In gynaecology practice, ultrasound and pathological examination are the gold standard for diagnosis. The significance of peripheral blood count parameters in benign, premalignant, and malignant endometrial pathologies is not clearly understood. The importance of early diagnosis has been enhanced by the increasing frequency of EC and the decreasing age of onset. In the presence of a diagnosis of EH, the risk of EC should be accurately assessed and shared decision-making strategies should be developed for patient management.

Author contribution

Study conception and design: MY, HA, EÜ, and YEÜ; data collection: MY, HA, EÜ, and YEÜ; analysis and interpretation of results: MY, HA, EÜ, and YEÜ; draft manuscript preparation: MY, HA, EÜ, and YEÜ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Etlik Zubeyde Hanim Women's Health Education and Research Hospital (Protocol no. 08/23.08.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Araştırma fikri ve tasarımı: MY, HA, EÜ ve YEÜ; veri toplama: MY, HA, EÜ ve YEÜ; sonuçların analizi ve yorumlanması: MY, HA, EÜ ve YEÜ; araştırma metnini hazırlama: MY, HA, EÜ ve YEÜ. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

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