Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2024; 41(1): 92-96
doi: 10.52142/omujecm.41.1.15

Can a complete blood count test predict coexisting adenocarcinoma in patients with atypical endometrial hyperplasia?

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Received: 20.11.2023 • **Accepted/Published Online:** 11.01.2024 • **Final Version:** 29.03.2024

Abstract

To assess the role of inflammatory markers in preoperative prediction of a coexisting endometrial adenocarcinoma (EC) in patients with atypical endometrial hyperplasia (AEH). Patients with a preoperative diagnosis of AEH based on endometrial sampling and who underwent surgical treatment were retrospectively assessed. Ratios of platelet-to-lymphocyte, neutrophil-to-lymphocyte and lymphocyte-to-monocyte, systemic immune-inflammation index and systemic inflammation response index were calculated. Patients were grouped based on the definitive postoperative pathological diagnosis as benign and endometrial adenocarcinoma groups. The cell counts and inflammatory markers were compared between these two groups. ROC curves were constructed for independent predictors of the diagnosis of coexisting endometrial adenocarcinoma to establish diagnostic cut-off values. There were 54 patients. Coexisting EC was detected in 30 patients (55.6%). All of the adenocarcinomas were endometrioid adenocarcinomas in stage 1. Among components of complete blood count (CBC) test monocyte counts, nucleated red blood cell (NRBC) percentage and immature granulocyte (IG) percentage were found to be significantly higher in the adenocarcinoma group. No significant difference was observed with respect to the inflammation indices. ROC curve analysis was performed in order to find cut-off values for monocyte count, NRBC percentage and IG percentage with significant sensitivities and specificities to predict coexisting adenocarcinoma, however, none of these parameters reached a significant area under the curve value. Monocytes, NRBCs and IGs tend to rise in AEH patients with coexisting EH; however, in endometrial biopsy-based AEH diagnosed patients, the prediction of coexisting EC with a simple CBC seems not to be possible.

Keywords: complete blood count, atypical endometrial hyperplasia, immature granulocyte, monocyte, inflammatory index, endometrial adenocarcinoma

1. Introduction

Endometrium carcinomas are the most common gynecologic malignancies in the developed countries and atypical endometrial hyperplasias are considered to be precancerous lesions or intraepithelial neoplasias associated with them (1, 2). It is estimated that about 25% of atypical endometrial hyperplasias progress to cancer (3, 4). In fact in about up to half of the cases of complex atypical hyperplasia there is coexistent endometrial adenocarcinoma (5, 6). The diagnosis is made by the histopathological examination of the endometrial sampling obtained with an endometrial biopsy, however the histological distinction between atypical hyperplasia and adenocarcinoma may be difficult (7). Almost 40% of the cases diagnosed to have precancerous endometrial hyperplasia by endometrial biopsy are found to have a postoperative concurrent endometrial carcinoma in the hysterectomy specimen (8). Due to the high risk of concurrent EC and or progression to endometrial aden0carcinoma, hysterectomy is the recommended choice of treatment for the postmenopausal women and women who do not desire pregnancy. Progesterone therapy oral or in the form of intrauterine device are the management in women who wish to preserve their fertility or in whom surgery has substantial risks (9). These women should be counseled about the risks of coexistent EC and or progression to invasive disease, metastases, and death. Therefore, any non-invasive method that may predict presence of concurrent endometrial adenocarcinoma in patients diagnosed to have atypical hyperplasia would be of great value.

It has been known that inflammation is a feature of cancer and is associated with initiation, promotion, progression, metastasis and clinical features (10). Some components of peripheral blood cells including monocytes, lymphocytes and neutrophils are considered as biomarkers of tumor immunity,

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reflecting cancer-related inflammatory microenvironment (11). These inflammatory markers have recently been shown to have a prognostic role in some solid organ malignancies including endometrial adenocarcinomas (12–14). NLR, PLR, MLR, neutrophil /monocyte ratio (NMR), systemic immune-inflammatory index (SII) and systemic inflammation response index (SIRI) are the most commonly assessed markers calculated with lymphocytes, neutrophils and monocytes (15). In addition to these cells immature granulocytes are immature cells compromising myelocytes, metamyelocytes and promyelocytes and indicate bone marrow activation as a response to inflammation (16). There is no data with respect to the prognostic value of immature granulocytes in endometrial cancer.

The aim of this study is to assess the role of these inflammatory markers including immature granulocytes in preoperative prediction of the presence of a coexisting endometrial adenocarcinoma in patients with atypical endometrial hyperplasia.

2. Materials and methods

All the patients admitted to Mersin University Faculty of Medicine Department of Gynecological Oncology with a preoperative diagnosis of atypical endometrial hyperplasia based on an endometrial sampling and who underwent surgical treatment in this clinic between January 2020 and January 2022 were retrospectively assessed. Patients with a known concomitant malignancy or a history of another malignancy, with inflammatory diseases, hematological and or autoimmune diseases, showed non-endometrioid histopathology or had no preoperative compete blood count test in our laboratory within two weeks before the surgery were excluded. A total of 54 patients were enrolled.

All the data were obtained from the electronic database of the hospital. Data included patients' demographic characteristics, preoperative pathological WHO class of endometrial hyperplasia, postoperative definitive pathological diagnosis and the CBC which was analyzed with a SYSMEX-XN-1000/23797 hemogram device of the hospital's laboratory (Supplementary file). Platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), neutrophil to monocyte ratio (NMR), lymphocyte to monocyte ratio (LMR), systemic immune-inflammation index (calculated by multiplication of absolute neutrophils and platelet counts, divided by lymphocyte count), and systemic inflammation response index (SIRI) calculated by multiplication of absolute neutrophil and monocyte counts divided by lymphocyte count) were calculated,

Patients were grouped based on the definitive postoperative pathological diagnosis as benign and endometrial adenocarcinoma groups. The cell counts and inflammatory markers were compared between these two groups.

Statistical analyses were accomplished using IBM SPSS Statistics 22 package software (IBM Corp, New York, USA). Normality of the distribution of the data was tested with Kolmogorov-Smirnov Test and Q-Q graphs. Data were expressed as percentages, means ± standard deviation if normally distributed and medians with interquartile ranges (IQR) if not normally distributed. For comparisons of two groups independent samples t test or Mann-Whitney-U test were used. ROC curves were constructed for independent predictors of the diagnosis of coexisting endometrial adenocarcinoma to establish diagnostic cut-off values. The sensitivity, specificity values with positive and negative predictive values were calculated based on the obtained cut-off values. A value of ≤ 0.05 was considered to be significant.

3. Results

All 54 patients underwent total hysterectomy (44.4% laparoscopic) and salpingectomy with or without salpingo-oophorectomy. 48.1 % (n:26/54) of the patients were in menopause. Coexisting endometrial adenocarcinoma was detected in 30 patients (55.6%). All of the adenocarcinomas were endometrioid adenocarcinomas in stage 1. Twenty-five of them were in grade 1, 2 were in grade 2 and grade was not determined in 3 patients.

The comparison of the age, CBC parameters and inflammatory indices was depicted in table 1. Patients with coexisting adenocarcinoma were significantly older compared to the patients with only atypical hyperplasia (55.6±10.6 vs 49.2±7.1 years, p:<0.01). Among components of complete blood count test monocyte counts, nucleated red blood cell percentage and immature granulocyte percentage were found to be significantly higher in the adenocarcinoma group (Table 1). No significant difference was observed with respect to the inflammation indices between the groups.

Table 1. Comparison of complete blood count parameters and inflammation indices between atypical endometrial hyperplasia patients with and without coxisting adenocarcinoma

	EAC present (n:30)	No EAC (n:24)	p
Age (years)	5.6 ± 10.6	49.2 ± 7.1	0.01
Hemoglobin	12.8 ± 1.7	12.3 ± 1.4	0.288
Hematocrit	38.8 ± 4.8	37.9 ± 3.2	0.458
Lymphocyte	2310 (710)	2065 (790)	0.113
Monocyte	580 (182.5)	485 (120)	0.039
Platelet	279966.7 ± 73230.6	301958.3 ± 80257.5	0.298
Neutrophil	5141 ± 1894	4610 ± 1690	0.288
PDW	12.87 ± 2.2	14.1 ± 6	0.308

Table 1. Comparison of complete blood count parameters and inflammation indices between atypical endometrial hyperplasia patients with and without coexisting adenocarcinoma (Continue)

	EAC present (n:30)	No EAC (n:24)	p
Mean platelet volume	10.7 ± 0.9	10.6 ± 1.1	0.605
Nucleated red blood cell %	0 (0.1)	0 (0)	0.029
Immature granulocyte %	0.3 (0.2)	0.2 (0.1)	0.045
Platelet to lymphocyte ratio (PLR)	116.5 (72.3)	138.6 (56.9)	0.058
Neutrophil to lymphocyte ratio (NLR)	2.3 (1.3)	2.02 (1.1)	0.807
Neutrophil to monocyte ratio (NMR)	8.7 ± 2.7	8.9 ± 4.1	0.728
Lymphocyte to monocyte ratio (LMR)	3.87 (2.26)	3.77 (2.28)	0.931
SII	572060.3 (486358.6)	627276.1 (419236.3)	0.497
SIRI	1413.6 (1374.9)	1155.0 (597.9)	0.520

EAC: endometrial adenocarcinoma, SII: Systemic immune-inflammatory index, SIRI: Systemic inflammation response index

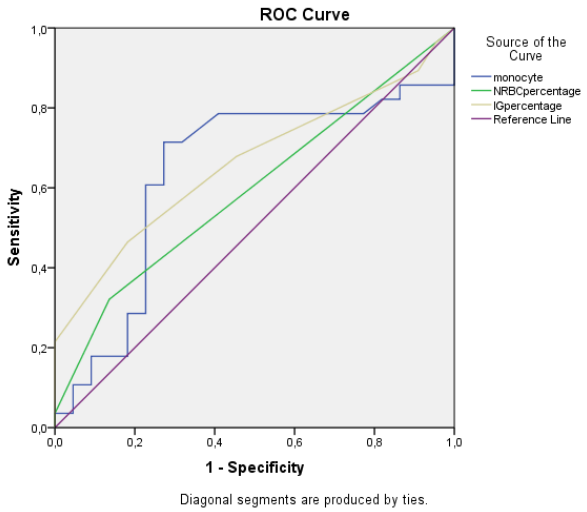

Fig. 1. ROC Curve analysis results of monocyte, nucleated red blood cell percentage and immature granulocyte percentage for the prediction of concurrent adenocarcinoma in patients with atypical endometrial hyperplasia

ROC curve analysis was performed in order to find cut-off values for monocyte count, NRBC percentage and IG percentage with significant sensitivities and specificities to predict coexisting adenocarcinoma (Fig. 1, Table 2). Although IG percentage had an area under the curve value of 66.2% which had a p value close to statistical significance (p:0.052), none of these parameters reached a significant area under the curve value (Table 2). Therefore, these parameters did not come out to be significant predictors of coexisting adenocarcinoma in the setting of atypical endometrial hyperplasia.

Table 2. ROC Curve analysis results of monocyte, nucleated red blood cell percentage and immature granulocyte percentage for the prediction of concurrent adenocarcinoma in patients with atypical endometrial hyperplasia

	Area	Std. Error	p	95% CI	
				Lower	Upper
Monocyte	0.640	0.084	0.091	0.476	0.805
NRBC percentage	0.595	0.080	0.253	0.437	0.752
IG percentage	0.662	0.077	0.052	0.511	0.812

CI: Confidence Interval, NRBC: nucleated red blood cell, IG: immature granulocyte

4. Discussion

The risk of concurrent EC in AEH has always been of great concern and inaccurate diagnosis is mostly due to insufficient sampling or diagnosis by pathologists (5, 17, 18). The under diagnosis of EC in AEH is utmost important especially in women who desire future fertility and or refuse hysterectomy. Any modality that increases the chance of accurate diagnosis would be very beneficial. In this study the role of systemic inflammatory markers and immature granulocytes in the diagnosis of concurrent EC in AEH was assessed and it was found that none of the assessed systemic inflammatory indices could predict the presence of concurrent EC. Although monocytes, nucleated red blood cells and immature granulocytes are significantly higher in AEH patients with concurrent EC compared with the AEH patients without EC, these markers did not come out to be significant predictors of concurrent EC in ROC curve analysis.

The current evidence shows that inflammation has a very critical role in carcinogenesis (19). Inflammation is associated with cellular changes and immune responses that may lead to sustained tissue damage, damage-induced cellular proliferation, and mutation when becomes chronic. Chronic inflammation is associated with transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis stages of carcinogenesis (20, 21). Cancer associated inflammation occurs in the tumor microenvironment and in the systemic circulation. Neutrophilia, thrombocytosis, and lymphocytopenia may be observed in complete blood counts due to secreted inflammatory mediators (22). From this point numerous indices that reflect inflammatory response in the setting of cancers have been developed and assessed in various solid organ tumors including female genital organ malignancies (15). Many studies reported that NLR, PLR and LMR are predictors of disease-free survival and overall survival in endometrium adenocarcinoma (13, 22). These markers have also been assessed in EH. Cakmak et al reported a higher NLR and PLR in patients with atypical endometrial hyperplasia compared with women with no hyperplasia or hyperplasia without atypia (23). SII is reported to be an independent risk factor for lymph node metastasis and myometrial invasion in EC patients (24). Huang et al reported that postoperative, but not preoperative, SII was associated

with prognosis (25). SIRI was reported to be correlated with prognosis in cervix cancer (26). In the present study none of the assessed inflammation markers were found to be significantly different in patients with AEH who had concurrent EC and without concurrent EC.

These markers assess inflammation and the intensity of the inflammation is associated with the progression of malignancy. In the present study all of the concurrent endometrial adenocarcinomas were in the earliest stages of malignancy. This may explain why inflammatory markers could not detect concurrent EC.

Although inflammation markers did not yield any significant difference, some single blood components were found to be significantly higher in patients with concurrent EC. Monocytes, nucleated red blood cells and immature granulocytes were found to be significantly increased in AEH patients with coexisting EC. Monocytes are components of mononuclear phagocyte system and are involved in the regulation of cancer development and progression. These cells are composed of heterogeneous populations and have different responses. In cancer they display many functions including phagocytosis, secretion of tumoricidal mediators, promotion of angiogenesis, remodeling of the extracellular matrix, recruitment of lymphocytes, and differentiation into tumor-associated macrophages and dendritic cells (27). NRBCs were also found to be significantly increased in coexisting EC patients. NRBC are progenitor cells that are usually not present in the peripheral blood of the healthy adults. Its presence has been shown to be associated with some serious conditions including hematologic and solid organ malignancies, cardiovascular, respiratory diseases and severe infections (28–31). Increased levels of pro-inflammatory cytokines are suggested to be associated with the presence of NRBCs in the peripheral blood (32). There is no data of NRBC in endometrial adenocarcinomas. Immature granulocytes are promyelocytes, myelocytes and metamyelocytes that are shown to be released from bone marrow during severe infection (33, 34). Recently they are shown to be increased in the peripheral blood in cases with systemic inflammation (35). The increase in IGs are accompanied by an increase in the absolute neutrophil count. Like NRBCs, there is no data with respect to IG in endometrial adenocarcinomas. All these three parameters that are components of cheap and easily obtainable CBC test are found to be significantly increased in AEH patients with coexisting EC compared to the AEH patients without EC. The possible explanation lies under the mechanisms related with oncogenesis, in which inflammation plays a critical role. Although these markers are found to be elevated, no significant cut-off values could be calculated. However, these markers may be promising markers for the prediction of concurrent EC in the setting of AEH.

The main limitation of this study is its retrospective design. The main strength is this was a single center study. All the patients were operated and managed by the same team and all the samples were analyzed by the same device in the same laboratory.

In conclusion in endometrial biopsy-based AEH diagnosed patients, the prediction of coexisting EC with a simple CBC seems not to be possible. None of the systemic inflammatory response indices which have already been shown to be increased especially in the advanced stages of many different malignancies including endometrial adenocarcinomas and closely associated with the prognosis, have no significant role in the prediction of coexisting EC in AEH patients. The main reason for this may be that the coexisting EC are usually in the very early stages of the carcinogenesis; however, monocytes, NRBCs and IGs tend to rise in AEH patients with coexisting EC.

Ethical Statement

Ethical approval was obtained from the Mersin University Clinical Research Ethics Committee (Date: 26.04.2023, Decision No: 09/274). Informed consent was obtained from each patient.

Conflict of interest

The authors declare no conflict of interest.

Funding
Inonu University Scientific Research Unit financially supported this work.

Acknowledgments
None to declare.

Authors' contributions
Concept: S.G.G., P.A., H.A., Design: S.G.G., P.A., H.A., Data Collection or Processing: S.G.G., P.A., H.A., Analysis or Interpretation: S.G.G., T.T.I., P.A., H.A., A.Y., M.C.K., K.A., Z.K.C., G.U., Literature Search: S.G.G., T.T.I., P.A., H.A., Writing: S.G.G., T.T.I., P.A., H.A.

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