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Relation of Preoperative Thrombocytosis between Tumor Stage and Grade in Patients with Endometrial Cancer

Endometriyum Kanserlerinde Preoperatif Trombosit Sayısının Tümör Grade ve Evre ile İlişkisi

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Abstract

Objective: We aimed to evaluate the predictive value of preoperative thrombocytosis for postoperative tumor stage and tumor grade in patients with endometrial cancer.

Materials and Methods: This was a retrospective study carried out in our gynecologic oncology department between January 2000 and December 2011. We reviewed the medical charts of 190 patients diagnosed with endometrial carcinoma and underwent complete staging procedure. The clinicopathologic characteristics of the patients such as; age, gravidity, parity, menopausal status, body mass index, co-morbidities (diabetes, hypertension etc.), stage, grade, histological subtype, depth of myometrial invasion, peritoneal washing cytology and preoperative platelet count were recorded. Endometrioid adenocarcinomas were graded according to the FIGO classification. Blood samples for the measurement of platelet count were obtained 3 days prior to the surgery. Thrombocytosis was defined as a platelet count of 300×10^9/L. P values less than 0.05 derived from two-tailed tests were considered statistically significant.

Results: The mean age of the study population was 55.4 (range 33-80) years. The mean gravidity was 3.8 (range 0-12) and the mean parity was 3.32 (range 0-11). 108 (56,8%) patients were with body mass index of >30 kg/m^2. The mean platelet count among women was 288, $6\pm90.7\times10^9$/L (range 105-772×10^9/L). The majority of the patients were with early stage diseases during the surgeries. 170 (89.5%) of the patients had stage I to II disease, and 20 (10.5%) of them had stage III to IV disease. There were no statistical significance between thrombocytosis and age, gravidity, parity, BMI, cancer grade and stage, histological subtype of the tumor, depth of invasion, cervical involvement, intrauterine tumor volume and peritoneal washing cytology.

Conclusion: We found that preoperative platelet count was not correlated with the stage or grade of endometrial cancer.

Key Words: Endometrial cancer, prognosis, thrombocytosis

Özet

Amaç: Endometrium kanseri olan hastalarda preoperatif trombositozun postoperatif tümör evre ve derecesini tahmin etmedeki değerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma ocak 2000 ve aralık 2011 yılları arasında jinekoloji onkoloji birimimizde retrospektif bir çalışma olarak yapılmıştır. Tam bir cerrahi evreleme yapılan endometrial karsinoma tanılı 190 hastanın medikal kayıtları incelendi. Hastaların yaş, gravida, parite, menapozal durum, vücut kitle indeksi, eşlik eden morbiditeleri (diyabet, hipertansiyon vb.), evre, derece, histolojik alt tip, miyometriyal invazyon derinliği, periton yıkama sitolojisi ve preoperatif trombosit sayısı gibi klinik ve patolojik özellikleri kayıt edildi. Endometrioid adenokarsinomalar FİGO klasifikasyonuna göre derecelendirildi. Trombosit sayısı cerrahi işlemden 3 gün önce elde edildi. 300×10^9/L'in üzerindeki trombosit değerleri trombositozis olarak değerlendirildi. 0,05'in altındaki p değerleri istatistiksel olarak anlamlı olarak kabul edildi.

Bulgular: Çalışma grubundaki hastaların ortalama yaşı 55,4 (dağılım 33-80) idi. Ortalama gravide 3.8 (dağılım 0-12) ve ortalama parite 3,32 (dağılım 0-11) idi. 108 (%56,8) hastanın vücut kitle indeksi >30 kg/m^2 idi. Ortalama platelet sayısı 288, $6\pm90,7\times10^9$/L (dağılım 105-772×10^9/L) idi. Cerrahiler sırasında hastaların çoğunu erken evre hastalığı olanlar oluşturuyordu. Hastaların 170 (%89,5)'i evre 1-2 iken, 20 (%10,5)'si evre 3-4 idi. Trombositoz ile yaş, gravida, parite, BMI, kanser derecesi, evresi, histolojik alt tipi, invazyon derinliği, servikal tutulum, intrauterin tümör hacmi ve peritoneal yıkama arasında istatistiksel anlamlılık saptanmadı.

Sonuç: Çalışmamızda endometrium kanserinin evre ya da derecesi ile preoperatif trombosiztoz arasında ilişki olmadığını saptadık.

Anahtar Kelimeler: Endometrial kanser, prognoz, trombositozis



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Introduction

Prevalence of endometrial cancer tends to higher in developing countries [1, 2]. Because of the increasing trend of this malignancy, physicians are forced to develop new diagnostic and treatment modalities for this cancer. There are some reports investigating the relation between malignant tumors and thrombocytosis in the literature [3]. Several studies have also documented that thrombocytosis is a poor prognostic factor in gynecological malignancies, such as ovarian, cervical, vulvar, and endometrial carcinoma [3-7]. Some of these studies pointed out that thrombocytosis may reflect tumor burden, however other studies suggest that platelets may contribute to tumor growth and metastases [8, 9]. The main hypothesis in these studies was that the tumor cells induce cytokines such as interleukins, interferon gamma, and tumor necrosis factor [10]. Furthermore, various hematopoietic proteins may have effect on angiogenesis, metastasis, and proteolysis [3, 11]. Platelets release both platelet-derived growth factor (PDGF) and thrombospondin [12]. PDGF functions as a potent mitogen for different cell types, including ovarian surface epithelium [12]. Thrombospondin is an adhesive glycoprotein that may cause the adhesion of tumor cells and promote metastases [13]. Nevertheless, there is still a lack of information on how platelets are involved in tumor dissemination.

In this study, we evaluated the relation between preoperative thrombocyte level and tumor stage and grade in patients with endometrial cancer.

Materials and Methods

After obtaining ethical committee approval from the local ethics committee of Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey (24.06.2009. 244), a retrospective study carried out in our gynecological oncology department between January 2000 and December 2011.

We reviewed the medical charts of 190 patients diagnosed with endometrial carcinoma who underwent a complete staging procedure after informed consent was obtained from each participant. The data were extracted from the medical records after the approval of the local ethics committee. The clinicopathologic characteristics of the patients such as age, gravidity, parity, menopausal status, body mass index, co-morbidities (diabetes, hypertension etc.), stage, grade, histological subtype, depth of myometrial invasion, peritoneal washing cytology, preoperative peripheral blood platelet count were recorded. Exclusion criteria were a diagnosis of cancer within the past 5 years, a history of splenectomy, myeloproliferative disorders, or prior treatment with neoadjuvant chemotherapy or radiotherapy. The surgical procedures for endometrial cancer in our institution are extended surgical staging consisting of a washing peritoneal cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy with full pelvic and/or para-aortic lymphadenectomy. The pelvic and periaortic lymphadenectomy involves systemic dissection of all pelvic and periaortic nodes, including the periaortic and common iliac nodes, from the below of renal vein to the deep circumflex vein distally. The obturator fossa is entered removing all obturator nodes above the obturator nerve. The tumors were surgically staged according to the FIGO staging system [14]. Endometrioid adenocarcinomas were also graded according to the FIGO classification. According to this classification, grade 1 was defined as 5% or less nonsquamous and nonmorular cell proliferation, grade 2 was defined as 6%-50% solid growing pattern and grade 3 was defined as solid growing pattern greater than 50%. The histological classification was based on the classification of tumors by the World Health Organization Classification [15]. Formalin-fixed hematoxylin and eosin-stained slides of 4μ were prepared again from the tumor tissue of the same patients and revised by a senior pathologist to verify the diagnosis. Myometrial invasion was evaluated by assessing the percentage of myometrial thickness of the deepest tumor extension. Presence or absence of vascular invasion, cervical stromal invasion, omental metastasis, lymph node metastasis and adnexal involvement from endometrial cancer were evaluated. Tumor size was measured taking its maximum diameter. Peritoneal cytology was studied in order to determine the presence or absence of cancer cells. Vascular invasion, adnexal involvement, cervical involvement, omental metastasis, and positive washing cytology were dichotomized based on the presence or absence of each factor. Blood platelet counts of the patients were obtained 3 days prior to the surgery. Thrombocytosis was defined as platelet count of greater than 300×10^9/L [16]. Statistical analyses were performed using the "SPSS 19 software program. Mean values, and standard deviation are used for the descriptive analyses. The Kolmogorov Smirnov test is used for defining distribution of data, ANOVA was used for parametric data and Kruskal-Wallis was used for non-parametric data. P values less than 0.05 derived from two-tailed tests were considered statistically significant**.**

Results

The mean age was 55, 4 (range 33-80) years. 53 (27.9%) women were in premenopausal period and 137 (72.1%) of them were in postmenopausal period. The mean gravidity was 3.8 (range 0-12) and the mean parity was 3.32 (range 0-11). 108 (56.8%) patients were with body mass index of >30 kg/m^2. There were 86 (45.3%) patients with hypertension, 56 (29.5%) patients with diabetes mellitus and 42 (11.5%) patients were with a medical history with both of these diseases. The postoperative surgical staging of the patients is listed in Table 1. The mean platelet count among women was 288.6±90. 7×10^9/L (range 105-772×10^9/L). Clinicopathologic parameters and their associa-

tion with preoperative thrombocytosis are shown in Table 2. The majority of the patients were with an early stage disease during the surgeries. 170 (89.5%) of the patients had stage I to II disease, and 20 of them (10.5%) had stage III to IV disease. There were no statistical significances between thrombocytosis and age, gravidity, parity, BMI, tumor grade and stage, histological subtype of the tumor, depth of invasion, cervical involvement, intrauterine tumor volume and peritoneal washing cytology.

Discussion

Endometrial cancer is one of the most common cancers in women in developing countries [1]. Therefore it is important to define some predictive factors to identify patients at high risk of the disease [3, 7]. In some published articles in the literature, thrombocytosis and anemia is speculated as a marker in predicting prognosis of patients with advanced endometrial cancer [3, 7, 17]. According to the theory, platelet activation may play a role in releasing various kinds of growth factors, cytokines and modulators [3]. There are also some other hypotheses that try to explain the mechanisms, such as secretion of interleukin 6 (IL-6), interleukin 1(IL-1) and leukemia inhibitory factor [3,18]. These released cytokines may stimulate megakaryocytes and their precursors.

IL-6 plays a major role in production of Thrombopoietin (TPO) that leads releasing platelets [19]. Additionally, platelets contribute to tumor angiogenesis by promoting growth factors such as vascular endothelial growth factor (VEGF) [20]. Another growth factor, called fibroblast growth factor, plays a role in endothelial cell migration and differentiation [21]. In a study from Graz, Austria,

Table 1. The postoperative surgical staging of the patients with endometrial cancer

Surgical stage	n	%
1a	115	60.5
1b	45	23.7
2	10	5.3
3-4	20	10.5

Table 2. Clinicopathologic parameters and their association with preoperative thrombocytosis

		Plt <300198[3]		Plt >300198[3]		
		n	%	n	%	p
Grade 1		35	31.0	21	27.3	0.458
Grade 2		47	41.6	39	50.6	
Grade 3		31	27.4	17	22.1	
Peritoneal washing cytology		20	17.7	8	10.5	0.173
Cervical invasion	<7 mm	12	10.6	7	9.1	0.473
	>7 mm	7	6.2	2	2.6	
Myometrial invasion	<1/2	75	66.4	54	70.1	0.586
	>1/2	38	33.6	23	29.9	
Tumor volume	<2 cm	41	36.3	29	38.2	0.794
	>2 cm	72	63.7	47	61.8	
Stage	1a	63	55.8	52	67.5	0.171
	1b	27	23.9	18	23.4	
	2	7	6.2	3	3.9	
	3-4	16	14.2	4	5.2	
Tumor type	Endometrioid	93	82.3	70	90.9	
	Clear Cell	3	2.7	2	2.6	
	Adenosquamous	1	0.9	1	1.3	
	Serous Papillary	15	13.3	3	3.9	
	Carcinosarcoma	0.0	0.0	1.0	1.3	
	Mixt Mesodermal	1	0.9	0.0	0.0	

*Plt: platelet count

the researchers confirmed preoperative thrombocytosis to be an independent prognostic factor in patients with advanced endometrial carcinoma [22]. In another study by Gorelic et al., they also confirmed these results and they concluded that overall survival rate was only affected by the stage, presence of thrombocytosis, and cervical involvement, but not the age, histological subtype, grade, myometrial invasion, or lymphovascular space invasion (LVSI). They also reported that the platelet count in stage II patients with cervical involvement was slightly higher than in stage I, however it did not reach the statistical significance [3]. Limitation of this study was about the study of which 37.7% of the patients were with advanced stages [3]. Ayhan et al. [23] was reported that poorly differentiated tumor grade, the presence of cervical and adnexal involvements were associated with elevated preoperative platelet counts in patients with endometrial cancer. In the study conducted by Metindir et al, [7] the higher median preoperative platelet value was correlated with the presence of cervical involvements and lymphatic metastasis in univariate analysis, however it was not statistically significant when comparing with the multivariate analysis. In our study, we detected no statistical significance between thrombocytosis and advanced stages of endometrial carcinoma. We may explain our results with lower number of patients with advanced stages of endometrial cancer to achieve statistical significance when compared to the studies conducted by Gorelic et al. [3] and Ayhan et al. [23]. The authors also mentioned that there could be a correlation between race and incidence of endometrial cancer presentations [3]. According to this theory, our results may be informative for the relation between race and incidence of endometrial cancer in our national population.

The threshold value of thrombocytosis varies in the literature. In a study conducted by Menczer et al. [24], they concluded that when 300× 10^9/L platelet count was taken as a threshold value, advanced grades were significantly higher in patients with higher platelet counts. On the other hand, Gucer et al. [22] reported that thrombocytosis was a poor prognostic factor when a cut-off value of 400×10^9/L was taken into account. In our study, we accepted 300×10^9/L platelet count as a threshold value to detect patients with advanced endometrial cancer.

In conclusion, a study with larger number of the patients with advanced endometrial cancer can reflect our national population results. New prognostic factors may also be important in predicting risk groups, and identifying patients that may respond to treatment modalities.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey (24.06.2009. 244).

Informed Consent: Informed consent was obtained from the participants who participated in this study.

Peer-review: Externally peer-reviewed.

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