

RESEARCH ARTICLE

Editorial Process: Submission:04/21/2017 Acceptance:11/27/2017

Preoperative Monocyte Count as a Mirror of Tumor Characteristics and Likelihood of Recurrence in Endometrial Carcinoma Cases

Mitra Modares Gilani¹, Zohreh Kazemi^{2*}, Narges Zamani¹, Hadis Shahrami², Akram Ghahghaei-Nezamabadi¹, Soureh Sheikham¹

Abstract

Background: Recently preoperative hematologic parameters have attracted attention for their capacity to predict tumor characteristics and recurrence. Considering the established role of tumor-associated macrophages (TAM) in the tumor microenvironment, we evaluated the role of the preoperative monocyte count as a surrogate for TAM. **Methods:** We retrospectively reviewed 166 patients with histopathologically proven endometrial cancers from January 2011 to March 2015 and assessed any association of preoperative monocyte count with tumor characteristics and recurrence. **Results:** The majority of patients had tumors with the following characteristics: endometrioid histology (83.1%), low grade (grade I-II, 71.7%) and stage I disease (68.1%). The mean \pm SD monocyte, neutrophil and platelet counts were $8.23 \times 10^9/L \pm 3.56 \times 10^9/L$, $64.0 \times 10^9/L \pm 11.3 \times 10^9/L$ and $261.6 \times 10^9/L \pm 74.6 \times 10^9$. Statistically significant associations were noted with between preoperative monocyte count and tumor stage (p value=0.044), recurrence (p value<0.001) and omentum involvement (p value< 0.001) but not with tumor grade (p value=0.897), depth of myometrium involvement (p value=0.479), lymphovascular space invasion (p value=0.269) and lymph node involvement (p value=0.377). **Conclusion:** An elevated preoperative monocyte count is related to more aggressive tumors and a higher recurrence rate in patients with endometrial cancer.

Keywords: Endometrial cancer- preoperative monocyte count- recurrence- tumor-associated macrophage

Asian Pac J Cancer Prev, **19** (4), 897-899

Introduction

Endometrial cancer is the most common gynecologic cancer in the western countries (Siegel et al., 2015). The fact that the most cases of endometrial cancer are diagnosed in early stages provide an opportunity to reach the cure in the majority of patients (Fotopoulou et al., 2015). The current treatment approach is mainly based on surgical procedures. Systemic chemotherapy and/or radiotherapy in a group of non-responder patients are complementary treatment options. Despite this favorable prognosis, the cluster of patients with endometrial cancer manifests disease recurrence which makes the treatment difficult (Braun et al., 2016; Salinas et al., 2016). Thus, there is a need to detect these tumors using simple available approaches to optimize treatment leading to subsequent improvement of survival.

Tumor suppression or progression is mainly dependent on the interaction between immune cells and cancer cells. In this regard, tumor-associated macrophages have been identified to be the main mediator (Tong et al., 2016). Recent studies have shown that as the accumulation

of tumor-associated macrophages increase, the tumor shows more aggressive behavior (Kübler et al., 2014). Tumor-associated macrophages are differentiated form of monocytes which are known to play a significant role in tumor microenvironment through immune response to cancer cells (Noy and Pollard, 2014; Mantovani and Allavena, 2015). Given that circulating monocytes are the potential source of tumor-associated macrophages, we aimed to investigate the relation between circulating monocyte count and tumor characteristics in patients with different endometrial cancers.

Materials and Methods

After obtaining the institutional review board and the ethic committee of Tehran University of Medical Sciences, Tehran, Iran approval, we retrospectively reviewed medical profiles of all consecutive patients who underwent surgical treatment for endometrial carcinoma between January 2011 and March 2015 at Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran. A single surgical team performed

¹Department of Gynecology and Obstetrics, Tehran University of Medical Sciences, ²Department of Gynecology and Obstetrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran. *For Correspondence: zohrekazemi1122@yahoo.com

all procedures, and the extent of surgical staging and tumor removal was based on surgical team discretion, but the primary surgical staging procedure consisted peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic-para aortic lymphadenectomy, and infra-colic omentectomy. Following the histopathological evaluation, all patients were staged according to the 2009 classification of the International Federation of Gynecology and Obstetrics (FIGO)(Pecorelli, 2009).

All subsequent therapies were chosen at a multidisciplinary meeting based on pathologic findings, oncologist and radiotherapist discretion and patients' will.

Preoperative blood sampling was performed in all patients at one day before the surgical staging. We registered Age, histologic subtype, stage, grade, the presence of lymphovascular space invasion (LVSI), the extent of myometrial invasion, lymph node involvement (LNI), the presence of recurrence, omentum involvement, complete blood count, different leukocyte type count and the platelet count for each patient. Patients were excluded if one of the following features were positive: coexistence of hematologic or other malignancies at the time the endometrial carcinoma was diagnosed, neoadjuvant chemotherapy, previous history of taking corticosteroid or recombinant G-CSF, and any acute or chronic infection or HIV/AIDS infection.

Categorical variables are shown as frequency (%), and continuous variables are presented as mean (standard deviation). A non-parametrical Mann-Whitney U-test was used to compare continuous data of hematological values. The relationships between monocyte count and tumor characteristics and recurrence were assessed using the chi-squared student t-test. The SPSS, Statistical Package for the Social Sciences, version 20.0 (Chicago, IL, USA) was utilized for all statistical analyses, and the results were considered statistically significant as if the p value was <0.05.

Results

Medical profiles of 166 patients with mean age \pm SD of 55.36 ± 11.08 years were reviewed. The majority of tumors had endometrioid histology (83.1%), low grade (grade I-II, 71.7%) and stage I disease (68.1%). Histopathological evaluation revealed that 18 (10.8%) had a papillary serous carcinoma, 7 (4.2%) had a clear cell and 3 (1.8%) individuals suffered from other types of endometrial cancer. Tumor characteristics are demonstrated in Table 1.

The mean \pm SD of monocyte, neutrophil and platelet count was $8.23 \times 10^9/L \pm 3.56 \times 10^9/L$, $64.03 \times 10^9/L \pm 11.27 \times 10^9/L$ and $261.56 \times 10^9/L \pm 74.64 \times 10^9/L$.

It was shown that despite statistically significant association between monocyte count and tumor stage (p value=0.044), recurrence (p value<0.001) and omentum involvement (p value<0.001) is observed but its association with tumor grade (p value=0.897), depth of myometrium involvement (p value=0.479), LVSI (p value= 0.269) and LN (p value=0.377) is not significant. We categorized age distribution into three groups: <50, 50-60 and >60 years and 42, 73 and 51 patients were in each group respectively.

Table 1. Patients' Characteristics of Endometrial Cancer

Characteristic		n (%)
Grade	1	71 (42.8)
	2	48 (28.9)
	3	47 (28.3)
Stage	1	113 (68.1)
	2	21 (12.7)
	3	22 (13.3)
	4	10 (6)
Myometrial invasion	<50%	114 (68.7)
	>50%	52 (31.3)
LVSI	Absence	94 (56.6)
	Presence	59 (35.5)
LNI	Absence	151 (91)
	Presence	13 (7.8)
Omentum Involvement	Absence	157 (94.6%)
	Presence	9 (5.4%)
Recurrence	Negative	163 (98.2)
	Positive	2 (1.2)

LVSI, lymphovascular space invasion; LNI, lymph node involvement

Using Kruskal-Wallis test, revealed that mean monocyte count is different in age groups (p value=0.031). After adjusting for age, previous relations between monocyte count and tumor characteristics remained statistically significant (all p value< 0.05).

Discussion

We found that preoperative circulating monocytes count is associated with stage and omentum involvement which leads to higher recurrence rate. These findings are in line with previous reports indicating that there is an association between circulating monocyte count and tumor characteristics. Although we have not assessed monocyte count in a histological specimen of uterine tissue indirectly, it might be indicative that there is a role for monocyte-macrophage lineage in the microenvironment of endometrial cancer.

Kim et al., (2012), proposed that preoperative neutrophil and monocyte counts in patients with endometrial cancer may be useful to predict with a sensitivity of 62.9% and specificity of 69.1%. Later in 2012, Brooks et al., (2012), revealed that peripheral blood monocytes of patients with endometrial cancer have functional deficiencies mainly reflected in phenotypic changes. Considering the vascular endothelial growth factor (VEGF) production of the tumor and increased VEGF receptor one expression on monocyte surface (Dobrzycka et al., 2013), it can be understood why elevated levels of monocytes are observed in endometrial cancer. Previous studies were indicative of the prognostic value of monocyte counts in other gynecological cancer (Armaiz-Pena et al., 2015; Akhavan et al., 2017) and Matsu et al.(Matsuo et al., 2015), claimed to be the first one to recognize its significant in endometrial cancer. We found that preoperative monocyte count is associated with recurrence.

Leukocytosis is a paraneoplastic syndrome have been identified in different gynecological cancers (Pelosof and Gerber, 2010). It is believed that granulocyte colony-stimulating factor (GCSF) produced by the tumor or in the case of endometrial cancer pro-inflammatory cytokine expression by monocytes explains the pathogenesis of increased leukocyte count (Takahashi et al., 2015). Worley et al., (2012), investigated 1144 endometrial cancer patients and reported that patients with preoperative leukocytosis had higher FIGO stages, greater cervical stromal involvement, adnexal involvement and lymphovascular space invasion. Also, they indicated that there was no association between leukocytosis and time to recurrence. Njolstad et al., (2013), followed 557 patients with endometrial cancer prospectively for the association of preoperative hematological parameters and clinicopathological characteristics and reported that those patients with high FIGO stage and lymph node metastasis had significantly higher leukocyte count. On the other hand, not only leukocytosis has been proved to be a prognostic factor for poor survival in endometrial cancer patients (Njolstad et al., 2013; Takahashi et al., 2015), but also Matsuo et al., (2015), showed that both neutrophil and monocyte counts were associated with decreased disease-free survival and overall survival.

The elevated levels of monocyte count may also be indicative for treatment application in patients with endometrial cancer. Ribas et al., (2012), have discussed the role of increased tumor-associated macrophages in the suppression of programmed cell death 1 (PD-1) in tumor cells. Thus an immunosuppression therapy targeting interaction of PD-1 and its ligand may be an alternative anti-tumor treatment.

In conclusion, we found that preoperative monocyte count is associated with tumor stage, omentum involvement, and recurrence. These findings are of great value to first better understanding of tumor pathogenesis and other clinical management of patients with endometrial cancer. We emphasize that future studies should be dedicated to investigating the role of preoperative monocyte count in response to different treatments.

Funding

No special grant or funding was used.

Conflict of interest

All authors declare no conflict of interest.

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