The Association of an Elevated Thrombocyte Count with Clinicopathological Prognostic Factors and Survival in Patients with Uterine Carcinosarcoma

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ABSTRACT: **Background:** Uterine carcinosarcoma (UCS) is a rare tumor with a poor prognosis. An elevated thrombocyte count and thrombocytosis were found to be associated with poor prognosis in several gynecological tumors. Data regarding an elevated thrombocyte count and thrombocytosis, particularly in UCS, are scarce.

Objectives: To assess the frequency of a preoperative elevated thrombocyte count and of thrombocytosis in UCS patients and their association with clinicopathological prognostic factors and survival.

Methods: The preoperative thrombocyte count of 29 consecutive verified USC patients diagnosed in our medical center from January 2000 to July 2015 was recorded, and clinicopathological data of these patients were abstracted from hospital files.

Results: Thrombocytosis was found in two patients (6.8 %) and both died of the disease. An elevated thrombocyte count was found in nine patients (31.0%). The percentage of patients with the poor prognostic factors who had a preoperative elevated thrombocyte count was not statistically different from those without these risk factors. The cumulative survival of patients with an elevated count was 22.1 months and that of those without an elevated count was 31.1 months. This difference was statistically not significant (P = 0.85). There was also no difference between the groups regarding the progression free survival.

Conclusions: No association between an elevated thrombocyte count and prognosis was found. Larger studies are needed to clarify this issue.

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KEY WORDS: uterine carcinosarcoma, thrombocytosis, survival

Uterine carcinosarcoma (UCS) is a rare neoplasm that comprises only 2–3% of uterine cancers [1] in which both the epithelial and stromal component of the endometrium are malignant. It is an aggressive tumor with a poor prognosis due to unsatisfactory treatment. The risk factors for USC are similar to those of endometrial carcinoma, namely nulliparity, advanced age, obesity, and unopposed estrogen use. Previous pelvic irradiation and prolonged use of tamoxifen are also associated with UCS. The tumor is most often diagnosed in postmenopausal women and the most common presenting symptom is postmenopausal bleeding. Surgery is the primary treatment for uterine carcinosarcoma (UCS) usually followed by adjuvant therapy (chemotherapy, radiotherapy, or both). Poor prognostic factors of UCS are also similar to those of endometrial carcinoma and include higher age, lymph-vascular space involvement (LVSI), depth of myometrial invasion, and extrauterine spread. Disease stage is the most important prognostic factor. At present, UCSs are considered to be metaplastic endometrial carcinomas [2,3].

Preoperative elevated platelet count (platelets > 300,000/ mcL) and thrombocytosis (platelets ≥ 400,000/mcL) have been previously assessed in many studies of endometrial carcinoma [4-13]. However, only one small study assessed preoperative thrombocytosis specifically in UCS [14].

The aim of the present study was to assess the frequency of a preoperative elevated thrombocyte count and of thrombocytosis in UCS patients and their association with selected clinicopathological prognostic factors and survival.

PATIENTS AND METHODS

This study was approved by the institutional review board at our medical center.

The preoperative thrombocyte count was evaluated in 29 consecutive verified USC patients diagnosed in our institution from January 2000 to December 2015. Clinicopathological data of these patients were abstracted from hospital files. A comparison of selected clinicopathological characteristics between those with and without an elevated thrombocyte count was made. Differences between the groups were evaluated by Fisher's exact test. Survival was calculated by the Kaplan–Meier analysis and differences in survival by the log-rank test.

*The authors dedicate this article to the memory of Prof. Joseph Menczer, who passed away on 31 December 2017.

RESULTS

The mean age of the patients was 68.13 ± 10.75 years. Selected characteristics of the study group patents are presented in Table 1. The majority of the patients (72.4%) presented with postmenopausal bleeding, underwent surgical staging (79.3%), and received some mode of adjuvant treatment (72.4 %). Almost half of them (44.8%) were diagnosed at stages II–IV. The majority of the patients had homologous tumors (69.0%) and had deep myometrial invasion (58.6%). In approximately one-third of the tumors, LVSI was present and in about one-quarter of those with known data the lymph nodes were involved.

Thrombocytosis was found in two patients (6.8 %) and both died of the disease. An elevated thrombocyte count was found in nine patients (31.0%). The distribution of selected risk factors according to platelet count is shown in Table 2. With the exception of LVSI, the percentage of patients with the other poor prognostic factors (i.e., older age, stage II–IV, > 50% myometrial invasion, and lymph node involvement), who had a preoperative elevated thrombocyte count, was higher than the percentage of those without these risk factors, but the difference did not reach statistical significance.

The cumulative survival of the study group patients according to the thrombocyte count is shown in Figure 1. The median survival of patients with an elevated count was 22.1 months and that of those without an elevated count was 31.1 months. This difference was statistically not significant ($P = 0.85$). There was also no difference between the groups regarding the progression free survival (not shown).

Table 1. Selected characteristics of patients with uterine carcinosarcoma

Characteristic	No.	%
Mean age, years (range)	68.13 (36–84)	-
Total	29	100.0
Main complaint		
Postmenopausal bleeding	21	72.4
Other	8	27.6
Surgery		
TAH, BSO + staging	23	79.3
TAH, BSO + omentectomy	5	17.2
Refused surgery	1	3.5
Adjuvant treatment		
Chemotherapy + irradiation	13	44.8
Chemotherapy only	6	20.7
Irradiation only	2	6.9
Refused adjuvant treatment	4	13.8
Not recorded	4	13.8
Stage*		
I	16	55.2
II-IV	13	44.8
Histological type		
Homologous	20	69.0
Heterologous	9	31.0
Myometrial invasion depth		
≤ 50%	17	58.6
> 50%	11	38.0
Unknown	1	0.4
Lymph-vascular space involvement		
Present	10	34.5
Absent	18	62.1
Unknown	1	0.4
Lymph node involvement		
Present	7	24.1
Absent	16	55.2
Unknown	6	20.7

*In six patients the stage was assessed clinically

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy

Figure 1. Cumulative survival of the study group patients according to the thrombocyte count

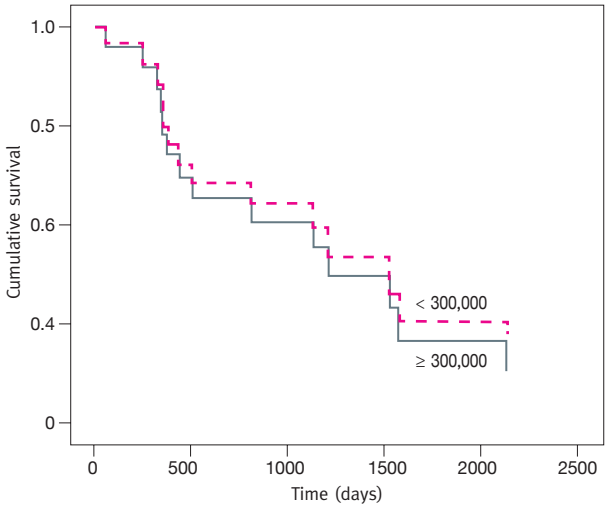

Table 2. Distribution of selected risk factors according to platelet count in UCS patients

	Age		Stage		Myometrial invasion		LVSI		Lymph node involvement	
	≤ 65 No. (%)	> 65 No. (%)	I	II–IV	≤ 50%	> 50%	Absent	Present	Absent	Present
Total*	11 (100.0)	18 (100.0)	17 (100.0)	12 (100.0)	17 (100.0)	11 (100.0)	18 (100.0)	10 (100.0)	16 (100.0)	7 (100.0)
< 300,000	8 (72.7)	12 (66.7)	12 (70.6)	8 (66.7)	13 (76.5)	6 (54.5)	12 (66.7)	7 (70.0)	12 (75.0)	4 (57.1)
≥ 300,000	3 (27.3)	6 (33.3)	5 (29.4)	4 (33.3)	4 (23.5)	5 (45.5)	6 (33.3)	3 (30.0)	4 (25.0)	3 (42.9)
P	0.53		0.64		0.21		0.60		0.35	
Unknown					1		1		6	

*Total with available data, LVSI = lymph-vascular space invasion

DISCUSSION

We found that thrombocytosis occurs infrequently in patients with UCS. Only 2/29 of UCS patients (6.8 %) had preoperative thrombocytosis. Although both of these patients died of the disease, the number of patients is too small for a meaningful analysis to determine an association between thrombocytosis and clinicopathological prognostic factors and survival. An elevated thrombocyte count was found in close to one-third (31%) of the study group patients.

Although the percentage of patients with most of the poor prognostic factors who had a preoperative elevated thrombocyte count was somewhat higher than the percentage of those without such prognostic factors, the difference did not reach significance, possibly due to the small number of patients. There was no statistical difference between survival and progression-free intervals between patients with and without thrombocytosis.

We encountered only one previous study that assessed various hormone receptors and growth factors by immunohistochemistry as well as preoperative thrombocyte count in 15 UCS patients [14]. In this smaller study eight of the patients (53.3%) had thrombocytosis, which was found to be a significant prognostic factor. The authors did not indicate how survival and the difference in survival were calculated. The discrepant results with regard to frequency and prognostic significance between our study and the previous one are obscure.

Thrombocytosis at the time of diagnosis in patients with solid tumors is associated with poor survival [15].

In endometrial carcinoma the frequency of preoperative thrombocytosis varies widely and ranges between 1.5% and 33.9% [4,5,7,8,10,12]. As in other solid tumors, preoperative thrombocytosis was found to be a poor prognostic factor in this malignancy [5,6,7,9-12]. In only one study of endometrial carcinoma, preoperative platelet count was not correlated with two factors known to be of prognostic significance namely stage and grade of the tumor [13].

An elevated thrombocyte count may also be associated with some poor prognostic factors. Endometrial carcinoma grades 2 and 3 were found to be significantly more common in patients with a platelet count higher than 300,000 [4]. In this study, patients with an elevated count also had a poorer survival rate and a higher prevalence of older age, high stage, and deep myometrial invasion, but this trend did not reach statistical significance. Another study of endometrial carcinoma [8] found that a higher preoperative platelet count, even in the normal range (150,000–400,000/μl), was associated with poor prognostic factors such as cervical involvement and high grade.

Malignant cells produce cytokines, such as interleukin (IL)-6 and other growth factors capable of inducing platelet production. Platelets in turn may contribute to tumor growth and metastases [16,17]. In this context, the study by Stone et al. [18] analyzed 619 human ovarian carcinoma samples and mouse models of epithelial ovarian cancer to explore the underlying mechanisms of thrombocytosis. Their findings indicated that increased production of thrombopoietic cytokines in tumor and host tissue leads to thrombocytosis in ovarian carcinoma and that the use of an antiplatelet antibody in tumor-bearing mice significantly reduced tumor growth and angiogenesis. They therefore suggested that targeting these cytokines may have therapeutic potential. Assessment of elevated platelet count and thrombocytosis may therefore be of clinical significance.

The limitations of our study are inherent in its retrospective nature and the relatively small number of USC patients. However, in view of the rarity of UCS we think that this study adds some information with regard to the association between elevated platelet count, thrombocytosis, and USC. Larger studies are needed to clarify the significance of an elevated platelet count and thrombocytosis in UCS.

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Capsule

An alternate route for metastatic cells

Metastatic tumor cells are thought to reach distant organs by traveling through the blood circulation or the lymphatic system. Two studies of mouse models now suggest a hybrid route for tumor cell dissemination. **Pereira** and colleagues and **Brown** and co-authors used distinct methodologies to monitor the fate of tumor cells in lymph nodes. They found that tumor cells could invade local blood vessels within a node, exit the node by entering the blood circulation, and then go on to colonize the lung. Whether this dissemination route occurs in cancer patients is unknown. The answer could potentially change the way that affected lymph nodes are treated in cancer.

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Eitan Israeli

Capsule

Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection

Obesity, diabetes, and related manifestations are associated with an enhanced, but poorly understood, risk for mucosal infection and systemic inflammation. **Thaiss** and co-authors showed in mouse models of obesity and diabetes that hyperglycemia drives intestinal barrier permeability through glucose transporter 2 (GLUT2)-dependent transcriptional reprogramming of intestinal epithelial cells and alteration of tight and adherence junction integrity. Consequently, hyperglycemia-mediated barrier disruption leads to systemic influx of microbial products and enhanced dissemination of enteric infection. Treatment of hyperglycemia, intestinal epithelial-specific GLUT2 deletion, or inhibition of glucose metabolism restores barrier function and bacterial containment. In humans, systemic influx of intestinal microbiome products correlates with individualized glycemic control, indicated by glycated hemoglobin levels. Together, these results mechanistically link hyperglycemia and intestinal barrier function with systemic infectious and inflammatory consequences of obesity and diabetes.

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Eitan Israeli

Capsule

Bacterial involvement in autoimmunity

The composition of the commensal microbiota is known to influence autoimmune disease development and persistence. **Manfredo Vieira** and colleagues identified a gut microbe, *Enterococcus gallinarum*, which translocates from the gut into the organs of mice with a genetic predisposition to lupus-like autoimmunity. Molecular signatures of gut barrier disintegration and pathogenic T helper cells were evident in the gut, liver, and lymphoid organs during colonization with the pathobiont. The ensuing pathology could be reversed by vancomycin treatment and by vaccination against *E. gallinarum*. The same bug was also found in liver biopsies of autoimmune patients, but not in healthy controls. Pathobiont translocation in monocolonized and autoimmune-prone mice induced autoantibodies and caused mortality, which could be prevented by an intramuscular vaccine targeting the pathobiont. *E. gallinarum*-specific DNA was recovered from liver biopsies of autoimmune patients, and co-cultures with human hepatocytes replicated the murine findings; hence, similar processes apparently occur in susceptible humans. These discoveries show that a gut pathobiont can translocate and promote autoimmunity in genetically predisposed hosts.

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Eitan Israeli