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Prognostic Significance of Preoperative Thrombocytosis in Patients with Endometrial Carcinoma: Our Experience and Review of the Literature

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Abstract

Objective: In this study, we aimed to determine the prevalence and prognostic significance of preoperative thrombocytosis (defined as platelet count ≥ 400 × 103/μl) in patients with endometrial carcinoma.

Methods: This was a retrospective analysis of 389 consecutive patients diagnosed and treated at our Institution with endometrial carcinoma between 2004 and 2014. The clinicopathological characteristics of the patients (age, race, tumor type, AJCC stage, and preoperative hematological parameters) were recorded. Survival data were provided by the tumor registry.

Results: The mean age of the study population was 63.7 years at diagnosis (range=33 to 97 years), and the majority (n=350, 90%) of patients were Caucasian. Most patients (n=292, 75.1%) were diagnosed with Stage I endometrial carcinoma. In addition, seventeen patients (4.4%) had Stage II, 49 patients (12.6%) had Stage III, and 9 patients (2.3%) had Stage IV disease. The most common type of cancer (n=269, 69.2%) was endometrioid adenocarcinoma, followed by mixed cell (n=16, 4.1%) and serous (n=11, 2.8%) carcinoma, respectively. A small subset (n=24, 6.2%) of the patients had thrombocytosis at diagnosis. The prevalence of thrombocytosis increased with the stage, for example from 4.5% in Stage I to 17.6% Stage II carcinoma. Interestingly, thrombocytosis appeared to be more common in African American patients (30.8%) than in Caucasians (5.4%). Statistical analysis of the survival data revealed an adverse prognostic significance for thrombocytosis: patients with thrombocytosis died at a younger age (64.3 years) than did those with normal platelet count (74.5 years).

Conclusion: Thrombocytosis at diagnosis portends adverse prognostic significance in patients with endometrial carcinoma. Elevated platelet count seems to associate with higher stage disease and shorter survival. Thrombocytosis may serve as an independent prognostic factor in endometrial carcinoma or a surrogate marker for high stage disease.

Keywords: Paraneoplastic thrombocytosis; Endometrial adenocarcinoma; Prognostic significance

Introduction

Over the last decade, there has been a marked increase in the incidence of endometrial carcinoma, attributed to an aging and increasingly obese population [1]. Indeed, by 2014 endometrial carcinoma had become the most frequent gynecological cancer in the Western world. For example, according to the National Cancer Institute in the US 2.7% of women will develop endometrial carcinoma during their lifetime, accounting for an estimated 50,000 new cancer cases and 8,200 deaths annually (http://www.seer.cancer.gov/statfacts/html).

The prognosis of endometrial cancer is mostly favorable: with current treatment modalities, the 5-year survival was reported to exceed 80%. The standard treatment option with a curative intent is total hysterectomy with bilateral salpingo-oophorectomy [2]. The clinical value of adjuvant radiotherapy is still debated (http://cochrane.org/CD003916/GYNAECA), as is the role of pelvic and periaortic lymph node dissection [3]. There is a consensus in the literature that patients with large and/or deeply invasive cancers, as well as those with positive peritoneal cytology, need lymph node dissection [4]. Intraoperative frozen section analysis of the cancer may, however, underestimate the depth of myometrial invasion, and the result of cytology (peritoneal washing) is not available until after the surgery. Consequently, much effort has been invested in identifying subgroups of patients with high risk of poor outcome that could benefit from a more aggressive therapeutic approach [4].

Recently, elevated preoperative platelet count, a readily available, standard hematological parameter, has emerged as an adverse prognostic marker in various types of cancer, including ovarian, colorectal, lung, pancreatic, and renal cell carcinoma [5-11]. The prognostic value of elevated platelet count in endometrial carcinoma is, however, controversial, with some studies reporting a more aggressive behavior of the cancer in patients with thrombocytosis [12-15], whereas other studies finding no correlation at all between clinical outcome and platelet count [16].

Against this background, we performed a retrospective analysis of 389 consecutive patients diagnosed and treated with endometrial cancer at Monmouth Medical Center between 2004 and 2014.

Demographic factors (age and race), hematological values (platelet count, erythrocyte count, hemoglobin concentration, leukocyte count), clinicopathological variables (type of cancer and American Joint Committee on Cancer [AJCC] stage information), and survival data were collected. A multivariate statistical analysis was performed to identify possible correlation between preoperative platelet count, clinical stage, and post-surgery survival.

Materials and Methods

After approval by the Monmouth Medical Center Institutional Research Review Board (IRB Study #15-013), the medical records of 389 consecutive patients who underwent diagnostic workup and surgical resection at our institution between 2004 and 2014 were retrospectively reviewed. The data gathered included preoperative hematological parameters (hemoglobin, erythrocyte count, leukocyte count, and platelet count), histological type of the tumor, and AJCC stage information [17]. The database did not include BMI (body mass index) values and/or co-morbidities.

Preoperative hematological parameters were collected from our Laboratory Information System (LIS). Thrombocytosis was defined as platelet count ≥ 400.0 × 103/μl. Thrombocytopenia was defined as platelet count < 150.0 × 103/μl. Anemia was defined as erythrocyte count < 4.2 × 109/dl or hemoglobin < 12.0 g/dl. Polycythemia was defined as erythrocyte count ≥ 5.4 × 109/dl or haemoglobin ≥ 16.0 g/dl. Leukocytosis was defined as leukocyte count ≥ 11.0 × 109/l. Leukopenia was defined as leukocyte count < 4.0 × 109/l.

Histological type of the tumor, AJCC stage information, and survival data were provided by the Cancer Registry at the Leon Hess Cancer Center. Endometrial carcinoma was staged according to the AJCC Cancer Staging Manual, 7th Edition [17].

Statistical analyses were performed using the softwares TexaSoft Winks SDA Software (TexaSoft, Cedar Hill, TX); Statistic Calculator 4.0 (StatPac Inc., Bloomington, IN); and Graphpad Prism 6 (GraphPad Software, Inc., La Jolla, CA). P values less than 0.0500 in Fisher's exact test, Chi-square test, and independent group's t-test were considered statistically significant.

Results

The characteristics (including age and race of the patients, AJCC stage and histological subtype of tumor, and preoperative hematological parameters) of the patients in our study cohort are summarized in Table 1A and 1B.

	Number (%)
Total Patients	389
Age at Diagnosis/Surgery (Years)	63.7±11.6*
Ethnicity	
Caucasian	350 (90.0%)
African American	13 (3.3%)
Hispanic	7 (1.8%)
Asian or Pacific Islander	6 (1.5%)
Unknown or Other Races	13 (3.3%)
Thrombocytosis (Plate Count ≥ 400.0×103/μl)	24 (6.2%)
Thrombocytopenia (Plate Count < 150.0×103/μl)	12 (3.1%)
Anemia (Erythrocyte Count < 4.2×109/dl or Hemoglobin < 12.0 g/dl)	161 (41.4%)
Polycythemia (Erythrocyte Count ≥ 5.4×109/dl or Hemoglobin ≥ 16.0 g/dl)	4 (1.0%)
Leukocytosis (Leukocyte Count ≥ 11.0×109/l)	60 (15.4%)
Leukopenia (Leukocyte Count < 4.0×109/l)	13 (3.3%)

Table 1A: Characteristics of the study cohort. *Mean±Standard Deviation (SD).

AJCC Stage	
Stage 0	18 (4.7%)
0	18 (4.7%)
Stage 1	292 (75.8%)
1	25 (6.5%)
1A	135 (35.1%)
1B	109 (28.3%)
1C	23 (6.0%)
Stage 2	17 (4.4%)
2	9 (2.3%)
2A	1 (0.3%)
2B	7 (1.8%)
Stage 3	49 (12.7%)
3	1 (0.3%)
3A	17 (4.4%)
3B	5 (1.3%)
3C	11 (2.9%)
3C1	6 (1.6%)
3C2	9 (2.3%)
Stage 4	9 (2.3%)
4B	9 (2.3%)
Histotype	
Yolk Sac Tumor	1 (0.3%)
Carcinosarcoma	4 (1.0%)
Mullerian Mixed Tumor	2 (0.5%)
Endometrial Stromal Sarcoma	4 (1.0%)
Adenosquamous Carcinoma	4 (1.0%)

Mucinous Carcinoma	4 (1.0%)
Serous Surface Papillary Carcinoma	3 (0.8%)
Papillary Serous Adenocarcinoma	11 (2.8%)
Serous Carcinoma	9 (2.3%)
Endometrioid Adenocarcinoma	269 (69.2%)
Mixed Cell Adenocarcinoma	16 (4.1%)
Clear Cell Carcinoma	1 (0.3%)
Villous Adenocarcinoma	1 (0.3%)
Adenocarcinoma with Mixed Subtypes	6 (1.5%)
Adenocarcinoma in a Polyp	1 (0.3%)
Adenocarcinoma In Situ in a Polyp	3 (0.8%)
Adenocarcinoma	37 (9.5%)
Adenocarcinoma In Situ	10 (2.6%)
Squamous Cell Carcinoma	1 (0.3%)
Anaplastic Carcinoma	1 (0.3%)
Intraepithelial Carcinoma	1 (0.3%)

Table 1B: Characteristics of the study cohort (continued).

The mean age of the study population was 63.7 ± 11.6 years, with the youngest and oldest patient being 33 and 97 year-old, respectively. Most patients (n=350, 90%) identified themselves as Caucasian, 13 patients (3.3%) were African American, and the rest was Hispanic (n=7, 1.8%), Asian/Pacific Islander (n=6, 1.5%), or unknown/other race (n=13, 3.3%). The majority of our patients (n=292, 75.1%) had Stage I carcinoma. In addition, 17 patients (4.4%) had Stage II, 49 patients (12.6%) had Stage III, and 9 patients (2.3%) had Stage IV disease. The most common histological type of cancer was endometrioid carcinoma (n=269, 69.2%), followed by mixed cell (n=16, 4.1%) and serous (n=11, 2.8%) carcinoma, respectively. Almost half of the patients (n=161, 41.4%) were anemic at the time of diagnosis; by contrast, only 4 patients had polycythemia. Sixty patients (15.4%) had elevated white blood cell count, whereas 13 patients (3.3%) showed leukopenia. Finally, the overall prevalence of thrombocytosis was 6.2% (n=24).

Next, we analyzed the association between race and thrombocytosis. As shown in Table 2, African American patients (n=4, 30.8%) had higher prevalence of thrombocytosis than did Caucasians (n=19, 5.4%), with the difference being statistically significant (P=0.0060) when using the two-tailed Fisher's exact test. The small number of patients in the Hispanic and Asian/Pacific Islander groups has precluded analysis for statistical significance. Most patients in our study cohort (n=292, 75.1%) were diagnosed with Stage I endometrial carcinoma. Eighteen patients (4.6%) had Stage 0, seventeen patients (4.4%) had Stage II, 49 patients (12.7%) had Stage III, and 9 patients (2.3%) had Stage IV disease, respectively. Increased platelet count was associated with the stage of the disease (Table 3): the prevalence of thrombocytosis increased from 5.6% (Stage 0) and 4.5% (Stage I) to 17.6% (Stage II), 10.2% (Stage III), and 22.2% (Stage IV). Statistical significance (P=0.0497) was noted between Stage I and Stage II disease using two-tailed Fisher's exact test.

	Number (%) per Race	Number (%) with Thrombocytosis	% of Thrombocytosis per Race
Caucasian	350 (90.0%)	19 (79.2%)	5.40%
African American	13 (3.3%)	4 (16.7%)	30.8%*
Hispanic	7 (1.8%)	1 (4.2%)	14.30%
Asian/Pacific Islander	6 (1.5%)	0 (0.0%)	0.00%
Unknown/Other Race	13 (3.3%)	0 (0.0%)	0.00%
Summation	389 (100.0%)	24 (100.0%)	

*P=0.0060 in two-tailed Fisher's exact test comparing African American to Caucasian.

Table 2: Thrombocytosis and ethnicity.

	Number (%) per Cancer Stage	Number (%) with Thrombocytosis	% of Thrombocytosis per Cancer Stage
Stage 0	18 (4.6%)	1 (4.2%)	5.60%
Stage 1	292 (75.1%)	13 (54.2%)	4.50%
Stage 2	17 (4.4%)	3 (12.5%)	17.6%*
Stage 3	49 (12.6%)	5 (20.8%)	10.20%
Stage 4	9 (2.3%)	2 (8.3%)	22.2%**
Summation	389 (100.0%)	24 (100.0%)	

Table 3: Thrombocytosis and endometrial carcinoma AJCC Stages. *P=0.0497, **P=0.0682 when compared to Stage 1 using two-tailed Fisher's exact test.

Finally, we analyzed the prognostic significance of thrombocytosis by comparing the postoperative survival of patients with or without thrombocytosis. Patients with thrombocytosis died at a significantly younger age (64.3 ± 15.8, P=0.0433) compared to those with normal platelet count (74.5 ± 10.6) using the independent groups t-test (Table 4).

Discussion

It is a time-proven observation that thrombocytosis is often seen in patients with malignant diseases [18]. Recently, it was postulated that thrombocytosis is part of the spectrum of paraneoplastic syndrome [19]: that is, a symptom that cannot be directly attributed to tumor invasion. The molecular mechanisms underlying paraneoplastic thrombocytosis are only beginning to be understood [19]. One theory holds that the elevation in circulating platelets results from a direct promotion of megakaryocytopoiesis by tumor-derived humoral factors. Indeed, there is good evidence that in ovarian carcinoma the platelet count rises in response to increased levels of thrombopoietin (TPO) [20]. In turn, TPO synthesis is stimulated by interleukin-6 (IL-6) secreted by the tumor cells [20]. It is not unlikely that other malignant tumors also boost platelet production via IL-6 synthesis. If this hypothesis holds true, IL-6 production emerges as a potential therapeutic target for antitumor agents [21].

	Patients with Thrombocytosis	Patients without Thrombocytosis
Total Number	24	365
Death as of 12/31/2014 (Percentage)	6 (25.0%)*	43 (11.8%)
Age at Death (Years)	64.3 ± 15.8¥, **	74.5 ± 10.6¥
Post-surgery Survival (Months)	25.7 ± 30.2¥	28.8 ± 23.9¥

Table 4: Thrombocytosis and post-surgery survival. ¥Mean ± SD, *P=0.0587 when compared to patients without thrombocytosis using Chi-square test without Yate's correction, **P=0.0433 when compared to patients without thrombocytosis using independent groups t-test.

Indeed, this concept is already being tested in clinical trials with IL-6 blocking agents like siltuximab (http://www.cancer.gov/cancertopics/treatment/drugs/fda-siltuximab).Thrombocytosis was reported to herald poor prognosis in patients with various cancers, ranging from ovarian carcinoma [20] through glioblastoma [22] to breast [8], stomach [7], and colorectal cancer [6]. To explain the adverse prognostic significance of thrombocytosis, it was speculated that platelets may protect the circulating tumor cells from attacks by the patient's immune system, thereby promoting metastatic disease [23,24].

In this study, we wished to determine the prevalence and potential prognostic value of preoperative thrombocytosis in patients with endometrial cancers. The overall prevalence of thrombocytosis in our patient cohort with endometrial carcinoma was 6.2%. Patients with Stage II carcinoma had significantly higher prevalence of elevated platelet count (17.6%) than did those with Stage I carcinoma (4.5%). This is similar to the values reported by others [12-15]. For higher stage disease, the statistical analysis of thrombocytosis indicated trend (P=0.0682), but did not reach statistical significance. This may reflect the small number of patients (n=9) in the Stage IV group. Interestingly, African American patients seemed to have a higher prevalence of thrombocytosis (30.8%) compared to Caucasians. Of note, Gorelick et al. detected preoperative thrombocytosis in 14 of 77 inner-city black patients (18.2%): the majority (n=8, 57%) of these patients turned out to have advanced stage disease and died after a medium survival of 7 months [25].

In our study cohort, endometrial carcinoma patients with thrombocytosis had a higher mortality rate (25.0%) than did those with normal platelet counts (11.8%), although at present deemed statistically insignificant by the Chi-square test (P=0.0587) with the restricted sample size. The patients with thrombocytosis, however, died earlier (mean age at death, 64.3 years) than the patients with normal platelet count (74.5 years). This somewhat differs from the literature (5-year mortality, ~40%). The explanation for this discrepancy is not completely clear. For example, Trovik et al. studied 557 patients with endometrial carcinoma in a Norwegian university hospital [15]. Seventy-five percent of these patients had Stage I carcinoma, similar to our results (75.1%). Yet, 12% of their patients had thrombocytosis (compared to 6.2% in our study) at the time of diagnosis and only 61% of these patients were alive 5 years after the surgery. By contrast, another study found no correlation between thrombocytosis, tumor stage, and survival [14]. Clearly, it is difficult to compare these studies since they involve very different patient cohorts from different countries with dissimilar health care systems.

In conclusion, in our experience preoperative thrombocytosis in endometrial cancer patients is indicative of a more aggressive clinical course. Therefore, we propose that platelet count (a simple, readily available hematological parameter) should be taken into consideration when planning the surgical strategy: for example, patients with high platelet count may benefit from sentinel node sampling (or lymph node dissection) even if intraoperative frozen section analysis shows superficially invasive carcinoma. This may be especially true for African American patients. Furthermore, endometrial cancer patients with thrombocytosis may also benefit from postoperative pharmacotherapy, possible including anti-IL-6 agents.

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