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The significance of preoperative leukocytosis in endometrial carcinoma

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ABSTRACT

Objective. To evaluate the impact of preoperative leukocytosis among patients with endometrial carcinoma.

Methods. The medical records of all patients that underwent surgical treatment for endometrial carcinoma between January 2005 and December 2010 were retrospectively reviewed. Patients were separated into two groups based on the presence or absence of preoperative leukocytosis (WBC ≥10,000 cells per μl). The groups were then compared with respect to pathologic findings, progression-free survival and overall survival.

Results. 1144 patients were identified, 156 (13.6%) with preoperative leukocytosis and 988 (86.4%) without leukocytosis. The leukocytosis group had a greater percentage of patients with stage 3 (15.4% vs. 9.8%, crude $p=0.02$) and 4 (7.1% vs. 3.0%, crude $p=0.007$) disease. Leukocytosis was associated with a greater mean tumor size (4.4 vs. 3.4 cm, $p=0.0002$) and a greater percentage of patients with cervical stromal involvement (14.8% vs. 8.7%, crude $p=0.02$), adnexal involvement (14.1% vs. 7.5%, crude $p=0.007$) and lymphvascular space invasion (24% vs. 16.3%, crude $p=0.02$). On multivariate analysis, mean tumor size (OR, 95% CI; 1.10, 1.02–1.18) remained significantly associated with preoperative leukocytosis. There was no difference between groups, with respect to time to recurrence. However, leukocytosis was independently associated with an increased risk of death (HR, 95% CI; 1.69, 1.07–2.68).

Conclusions. Preoperative leukocytosis, among endometrial cancer patients, was independently associated with increasing tumor size and independently imposed an increased risk of death.

Introduction

Paraneoplastic syndromes represent a collection of signs and symptoms that are not related to direct invasion of the primary or metastatic tumor and may confer negative prognostic significance [1,2]. Hematologic paraneoplastic manifestations represent a single category within this broad collection. Though often asymptomatic, hematologic paraneoplastic manifestations are typically observed in advanced disease [3]. Examples include: thrombocytosis, anemia and leukocytosis. While some of these examples have been described in the context of gynecologic malignancies, others have yet to be evaluated.

Endometrial cancer represents the most common gynecologic malignancy in the United States. In 2011, the American Cancer Society estimated that about 40,000 new cases would be diagnosed and that about 8,000 deaths would occur from endometrial cancer [4]. Among patients with endometrial cancer, thrombocytosis has been associated with advanced disease, unfavorable grade, deep myometrial invasion and lymphvascular space invasion (LVI). In addition, thrombocytosis is independently predictive of worse disease-free survival and overall survival [5–8]. Anemia is also associated with several unfavorable histopathologic features, but independently does not appear to impose a poor prognosis [5]. In contrast to thrombocytosis and anemia, leukocytosis has yet to be evaluated in the context of endometrial cancer. The objective of the current study was to evaluate the significance of preoperative leukocytosis among patients with endometrial cancer.

Materials and methods

After obtaining institutional review board (IRB) approval, we conducted a retrospective chart review of all patients that underwent surgical treatment for endometrial carcinoma between January 2005 and December 2010 at the Brigham and Women's Hospital. The extent of surgical staging (i.e. pelvic and/or para-aortic lymphadenectomy) was left at the discretion of the surgeon. All procedures consisted of at least a total hysterectomy and bilateral salpingo-oophoectomy (if the adnexa had not been previously removed).

All adjuvant therapies were discussed at a multidisciplinary tumor board. Adjuvant therapies were tailored to pathologic findings, patient preference and physician discretion. Therapies consisted of either radiation therapy (RT) or chemotherapy. Adjuvant RT consisted of external beam whole pelvic RT and/or vaginal brachytherapy. Adjuvant chemotherapy varied over the years but was predominantly cisplatin-

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based. Postoperative therapy was typically administered in women with documented extrauterine disease, high-risk early stage disease and/or in those with unfavorable histologies. Most of the patients treated with adjuvant RT or chemotherapy were treated at the Dana Farber Cancer Institute. The remainder received treatment at facilities closer to their homes. Advanced age alone was not a contraindication to adjuvant therapy. As with surgical staging, patients with multiple comorbidities were less likely to receive adjuvant therapy.

Patients were separated into two groups based on the presence or absence of preoperative leukocytosis. Leukocytosis was defined as a white blood cell count (WBC) of ≥10,000 cells per μl [9–12]. The two groups were then compared with respect to: age, WBC count, histologic type, stage, histologic grade, primary tumor diameter, myometrial invasion, cervical stromal involvement, adnexal involvement, positive peritoneal cytology, LVI and lymph node metastasis. Patients were staged according to the 2009 classification of the International Federation of Gynecology and Obstetrics (FIGO).

Patients were excluded from analysis if their medical charts were incomplete or if their preoperative WBC value was drawn prior to two weeks before the operation. Patients were also excluded based on the presence of any of the following: synchronous primary at the time of endometrial carcinoma diagnosis, neoadjuvant chemotherapy, pure sarcoma of the uterine body, coexisting hematologic malignancies, preoperative corticosteroid or recombinant G-CSF use, acute or chronic infection or HIV/AIDS infection.

We performed univariate and multivariate logistic regression analyses with leukocytosis as the outcome. Continuous variables were modeled categorically and continuously. We used Cox regression to examine the relationships between leukocytosis and other clinical variables and both recurrence and survival. A survival curve was generated by the Kaplan-Meier method. Associations are shown as odds ratios (OR) and 95% confidence intervals (CI) and as hazard ratios (HR) with 95% confidence intervals. The SAS version 9.2 statistical package (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

A total of 1,404 patients diagnosed with endometrial carcinoma were identified, with a total of 260 meeting exclusion criteria. This provided 1,144 evaluable patients and preoperative leukocytosis was observed in 156 patients (13.6%), leaving the remaining 988 patients within the non-leukocytosis group. Of the 1,144 evaluable patients, a total of 696 patients (60.8%) underwent comprehensive surgical staging. This included 99 patients (63.5%) within the leukocytosis group and 597 patients (60.4%) among the non-leukocytosis group. Table 1 displays a comparison between these two groups. The leukocytosis group and non-leukocytosis groups were similar with respect to the patient's age at cancer diagnosis. However, the leukocytosis group had a greater percentage of patients with stage 3 (15.4% vs. 9.8%, crude $p=0.02$) and 4 (7.1% vs. 3.0%, crude $p=0.007$) disease. Leukocytosis was also associated with a greater mean primary tumor diameter (4.4 vs. 3.4 cm, $p=0.0002$) and a greater percentage of patients with cervical stromal involvement (14.8% vs. 8.7%, crude $p=0.02$), adnexal involvement (14.1% vs. 7.5%, crude $p=0.007$) and lymphvascular space invasion (24% vs. 16.3%, crude $p=0.02$). There were no differences between the two groups with respect to histologic grade, histologic type (endometrioid vs. non-endometrioid), myometrial invasion, pelvic and/or paraaortic involvement or the presence of positive peritoneal cytology.

Multivariate analysis confirmed that pre-operative leukocytosis was independently associated with primary tumor size (OR, 95% CI; 1.10, 1.02–1.18; p = 0.009). However, when each variable was adjusted for all others, preoperative leukocytosis did not appear to be influenced independently by patient's age at cancer diagnosis, stage, histologic grade, histologic type, myometrial invasion, cervical stromal involvement, adnexal involvement, positive peritoneal cytology, lymphvascular space invasion or lymph node metastasis (Table 1).

Of the 156 patients in the leukocytosis group, there were 20 recurrences (12.8%) and of the 988 patients in the non-leukocytosis group, there were 92 recurrences (9.3%). The overall mean time to recurrence for the study population was 23.1 months (median 16.5, range 0–83.3). Kaplan–Meier curves for recurrence-free survival between patients with and without pretreatment leukocytosis are displayed in Fig. 1. There was no difference between the leukocytosis and non-leukocytosis group, with respect to time to recurrence. On univariate/multivariate Cox-proportional hazard regression analysis of prognostic factors for recurrence-free survival, pretreatment leukocytosis did not appear to be associated with an increased risk of recurrence (Table 2).

Table 1
Patient characteristics and pathologic findings among patients with and without preoperative leukocytosis.

	WBC<10 N=988	WBC≥10 N=156	Crude OR (95% CI)	p-value	Multivariate[a] OR (95% CI)	p-value
Mean WBC count (SD)	7.0 (1.5)	11.8 (1.8)				
Mean age (SD)	61.2 (10.6)	60.3 (11.7)	0.99 (0.98, 1.01)	0.34	0.99 (0.97, 1.01)	0.23
Stage, n (%)						
1	812 (82.2%)	111 (71.2%)	1.00		1.00	
2	49 (5.0%)	10 (6.4%)	1.49 (0.74, 3.03)	0.27	0.91 (0.30, 2.76)	0.87
3	97 (9.8%)	24 (15.4%)	1.81 (1.11, 2.95)	0.02	1.70 (0.60, 4.80)	0.31
4	30 (3.0%)	11 (7.1%)	2.68 (1.31, 5.50)	0.007	2.45 (0.64, 9.34)	0.19
Grade, n (%)						
1	559 (56.6%)	81 (51.9%)	1.00		1.00	
2	178 (18.0%)	35 (22.4%)	1.36 (0.88, 2.09)	0.16	1.18 (0.73, 1.90)	0.50
3	190 (19.2%)	27 (17.3%)	0.98 (0.62, 1.56)	0.93	0.58 (0.30, 1.15)	0.12
Ungraded	61 (6.2%)	13 (8.3%)	1.47 (0.77, 2.80)	0.24	0.98 (0.40, 2.36)	0.96
Histology, n (%)						
Non-endometrioid	189 (19.1%)	33 (21.2%)	1.00		1.00	
Endometrioid	799 (80.9%)	123 (78.8%)	0.88 (0.58, 1.34)	0.55	1.04 (0.52, 2.04)	0.92
Mean tumor size (SD)	3.4 (2.5)	4.4 (3.0)	1.12 (1.06, 1.20)	0.0002	1.10 (1.02, 1.18)	0.009
Myometrial Invasion, n (%)	636 (64.4%)	111 (71.2%)	1.36 (0.94, 1.98)	0.1	1.13 (0.73, 1.75)	0.59
Cervical stromal involvement, n (%)	86 (8.7%)	23 (14.8%)	1.83 (1.11, 3.00)	0.02	1.43 (0.62, 3.31)	0.40
Adnexal involvement, n (%)	74 (7.5%)	22 (14.1%)	2.02 (1.22, 3.36)	0.007	0.96 (0.38, 2.42)	0.93
Positive peritoneal cytology, n (%)	117 (12.2%)	18 (12.5%)	1.02 (0.60, 1.74)	0.93	0.80 (0.43, 1.48)	0.47
LVI, n (%)	151 (16.3%)	35 (24.0%)	1.62 (1.07, 2.47)	0.02	1.20 (0.70, 2.04)	0.50
Pelvic/para-aortic involvement, n (%)[b]	78 (13.1%)	20 (20.2%)	1.68 (0.98, 2.90)	0.06	0.84 (0.34, 2.10)	0.71

[a] Each variable adjusted for all others in the table.
[b] Percentage is with respect to the number of patients undergoing lymph node assessment.