Correlation Between Tumor CA-125 Content and Preoperative Serum CA-125 Antigen Levels in Patients With Endometrial Cancer

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Abstract

Objective: The aim of the present study was to evaluate the correlations between elevated preoperative CA-125 serum levels, the presence of immunohistochemically stainable tissue CA-125, and other pathological parameters in endometrial carcinoma.

Materials and Methods: Serum CA-125 levels were examined in 72 patients with endometrial cancer before definitive surgery and 20 U/ml was used as cutoff value. After diagnosis was reconfirmed, additional 4 μm unstained slides were prepared from each case for immunohistochemical staining. Immunohistochemical staining for CA-125 was assessed according to the ImmunoReactive Score (IRS).

Results: Statistical analyses were performed to identify independent factors contributing to high serum CA-125 levels, including CA-125 staining and conventional features. Thirty-two of patients (44.4%) had elevated CA-125 levels (mean 126.83; range, 2.95-6442 U/ml). The percentage of positive CA-125 tissue staining (62/72, 86.1%) was significantly higher than the percentage of elevated serum levels (86.1% vs 44.4%, p=0.01). Thirty-two patients with elevated serum CA-125 levels had positive tissue staining (p=0.018), positive washing cytology (p=0.031) and lymphovascular invasion (LVI) (p=0.013) compared with the patients with normal serum CA-125 levels. Multivariate analysis showed that elevated serum CA-125 significantly correlated with positive CA-125 tissue staining (p=0.045, OR:3.2, 95% CI: 1.02-10.167) and positive CA-125 staining significantly related with deep myometrial invasion (p=0.02, OR:6, 95% CI:1.3-27.2).

Discussion: We found that tissue CA-125 staining was an independent factor for high serum CA-125 levels in endometrial carcinoma.

Keywords: endometrial carcinoma, CA-125, immunohistochemistry

Özet

Endometriyum Kanserli Hastalarda Tümör CA-125 İçeriğinin Preoperatif Serum CA-125 Düzeyi ile İlişkisi

Amaç: Çalışmanın amacı endometriyum kanserinde yükselmiş preoperatif serum CA-125 düzeyleri ile tümör dokusunda immünhistokimyasal CA-125 boyanmasının ve diğer patolojik parametrelerin ilişkisinin araştırılmasıdır.

Materyal ve Metot: Cerrahi öncesi endometriyum kanserli 72 hastanın serum CA-125 düzeyleri "cutoff" değeri 20 U/ml kullanılarak araştırıldı. Tanı kesinleştikten sonra 4 mm boyanmamış slaytlar immünhistokimyasal çalışma için hazırlandı. CA-125 için immünhistokimyasal boyama İmmunoReaktif Skorlamaya göre değerlendirildi.

Sonuçlar: İstatistiki analiz yüksek serum CA-125 düzeyleri için, doku CA-125 boyaması ve konvansiyonel patolojik faktörleri içeren bağımsız faktörleri saptamak amacıyla yapıldı. Hastaların 22'sinde (%44.4) CA-125 seviyeleri yüksek bulundu (ortalama 126.83, 2.95-6442 U/ml). Pozitif CA-125 boyanması (62/72, %86.1), yüksek serum CA-125 düzeyine göre anlamlı derecede yüksekti (%86.1'e karşılık %44.4, p=0.01). Normal serum CA-125 düzeyli hastalara göre, yüksek serum düzeyli hastaların 32'sinde pozitif doku boyanması (p=0.018), pozitif batın sıvı sitolojisi (p=0.031) ve lenfovasküler invazyon (LVI)

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(*p*=0.013) saptandı. Çok değişkenli analiz, yüksek serum CA-125 düzeylerinin pozitif CA-125 doku boyanması ile anlamlı derecede ilişkili olduğunu gösterdi (*p*=0.045, OR:3.2, %95 CI: 1.02-10.167). Pozitif CA-125 boyaması derin myometriyal invazyonla da anlamlı derecede ilişkiliydi (*p*=0.02, OR:6, %95 CI:1.3-27.2).

Tartışma: Biz çalışmamızda, endometriyum kanserinde doku CA-125 boyamasının yüksek serum CA-125 düzeyleri için bağımsız bir faktör olduğunu saptadık.

Anahtar sözcükler: endometriyal karsinoma, CA-125, immünhistokimya

Introduction

The tumor antigen CA-125 is a coelomic epithelial antigen which has been used as a useful tumor marker for monitoring epithelial ovarian cancer (1). A cyclic pattern of serum CA-125 concentration is observed in healthy women, which may be a product of the endometrium (2). The frequency and tissue distribution of CA-125 expression in normal, hyperplastic, and neoplastic endometrium has been reported (3-5). Elevation of CA-125 was first described in patients with recurrent and advanced endometrial cancer by Niloff et al. in 1984 (6). Additional reports described elevations in CA-125 levels in both primary and recurrent endometrial cancer (7-9). Since Bast et al. (10) proposed initially that 35 U/ml was a normal value for serum CA-125 level, the value has been employed as a clinical cutoff level for most gynecologic disease such as endometriosis (11) and ovarian (12) and endometrial cancer (6,7). Duk et al. showed that serum CA-125 levels had a close correlation with the clinical staging of endometrial cancer, but little is known about whether preoperative CA-125 measurement can predict the depth of myometrial invasion (13). Recent studies have suggested that a CA-125 cutoff level of 20 U/ml may be more appropriate in endometrial carcinoma than the traditional level of 35 U/ml used in ovarian cancer (14-16). Some authors attempted to demonstrate a correlation between the presence of CA-125 in endometrial cancer tissue and preoperative serum CA-125 level (17,18). Our study was designed to assess the correlation between serum and tissue CA-125 expression and other pathological parameters in endometrial cancer.

Materials and Methods

Between January 2002 and December 2005, 72 patients with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) Stage I-IV endometrial carcinoma were treated by total abdominal hysterectomy, salpingo-oophorectomy and bilateral pelvic, para-aortic lymphadenectomy at Ankara Oncology Training and Research Hospital. Patients who underwent primary surgery, who had not a history of another malignancy and who had not pelvic infection and endometriosis were included. The study was approved by the Local Committee of Etthics of Ankara Oncology Training and Research Hospital.

The diagnosis of endometrial carcinoma was established by fractional dilatation and curretage. Serum levels of CA-125 were examined in patients with endometrial cancer prior to definitive surgery. An enzyme immunoradiometric assay with monoclonal antibody was used (Elecsys-CA-125 II; Roche Diagnostics, Indianapolis, USA). We used 20 U/ml as the cutoff CA-125 value in this study. The surgical procedures for endometrial cancers in our institution are defined as the extended surgical staging consisting of washing cytology, total abdominal hysterectomy and bilateral salpingo-oophorectomy, with full pelvic and para-aortic lymphadenectomy. The tumors were surgically staged according to the FIGO staging system (19). Endometrioid adenocarcinomas were graded according to FIGO classification. The histologic classification recommended by the World Health Organization Classification of Tumors was used (20). The histologic types of endometrial cancer in the present study included endometrioid carcinoma, undifferentiated carcinoma, clear cell carcinoma, and papillary serous carcinoma; they were categorized as endometrioid and non-endometrioid (clear cell carcinoma, papillary serous carcinoma, undifferentiated carcinoma) groups. Formalin-fixed hematoxylin and eosin-stained 5 µm slides of the tumor tissue from the same patients were prepared repeatedly and reviwed by two senior pathologists (GB, IP) to verify the diagnosis. Myometrial invasion was evaluated by assessing the percentage of myometrial thickness involved at the site of deepest tumor extension. Presence or absence of vascular invasion, cervical stromal invasion, lymph node metastasis, and ovarian metastasis from endometrial cancer was assessed. Tumor size was measured by its maximum diameter. Peritoneal washing was examined for the presence or absence of cancer cells.

For comparison, the serum CA-125 levels were stratified into two groups: ≤20 U/ml versus >20 U/ml. Vascular invasion, ovarian metastasis, positive washing cytology, and lymph node metastasis were dichotomized based on the presence or absence of each factor. Tumor size (<2 cm versus ≥2 cm), tumor grade (grade 1 versus grade 2 and 3), depth of myometrial invasion (myometrial invasion <1/2 versus ≥1/2), stage (stage I and II versus stage III, IV) and immunuhistochemical CA-125 staining (negative versus positive) were divided into two groups.

Immunohistochemistry of CA-125

Briefly, 4 µm, unstained sections from each of all 72 patients were prepared for immunohistochemical staining. After deparaffinization and rehydration, sections were placed in %3 hydrogen peroxide for 15 minutes to inactivate endogenous peroxidase, they were then autoclaved at 121°C in citrate buffer (10mM, pH 6.0) for 6 minutes for antigen activation. After cooling at room temperature for 30 minutes, the specimens were nonspecifically blocked by incubation with UltraV block for 5 minutes and endogenous avidin/biotin

blocking kit for 10 minutes for each at room temperature. Sections were then incubated with anti-CA-125 mouse monoclonal antibody (NeoMarkers, 1/20, Ab-1, Clone OV 185:1) for 2 hours at room temperature. Immunohistochemical staining was performed using a Standard avidin- biotin- peroxidase (Lab Vision). 3.3´- diaminobenzidine was used as chromogen. All sections were counterstained with Mayer's hematoxylin. Sections of ovarian serous carcinoma were used as positive controls.

The extent and location of immunohistochemical staining for CA-125 was assessed according to the ImmunoReactive Score (IRS) that evaluated the proportion of cells expressing CA-125 and the intensity of staining (21). The percentage of the cancer area stained in high-power fields was examined. Staining intensity was graded as 1, 2 and 3; percentage of positive cells examined was scored as 1 (<10%), 2 (11-50%), 3 (51-80%), and 4 (>80%). The two scores were multiplied to determine the IRS, which when equal to 0 was rated as negative, 1 to 3 as weak, 4-6 as positive, and 8,9,12 as strongly positive (Figure 1).

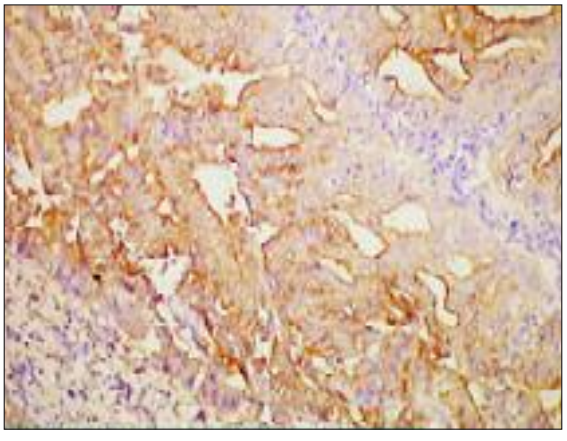

Figure 1. Positive staining for CA-125 is prominent at the apical cell surface (x200)

Statistical analyses

Statistical analyses was performed using "SPSS 10.05 for Windows" computer program. All variables were analyzed statistically as categorical covariates. The χ^2/Fisher's exact test (univariate analysis) and logistic regression model (multivariate analysis) were employed to examine the effect of clinicopathological factors on elevated serum CA-125 and immunohistochemical CA-125 staining. *P* values of less than 0.05 derived from two-tailed tests were considered significant.

Results

Seventy-two patients underwent surgery for endometrial adenocarcinoma during the 48-months period. Ages ranged from 35 to 87 years, with a mean age of 58.59±9.87 years.

Four patients (5.6%) with grade 1 or grade 2 tumors underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy with collection of peritoneal fluid for cytologic testing. Sixty-eight (94.4%) patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and bilateral pelvic and periaortic lymphadenectomy, biopsies, or debulking or different combination of these. The mean number of nodes sampled per patient was 21.95±13.43. All patients had peritoneal fluid collected for cytological testing.

Only eight patients were premenopausal. Seven patients had positive tissue staining and only two patients had elevated serum CA-125 levels. None of the patients had conditions such as pelvic inflamatory disease or endometriosis that might have influenced serum CA-125 levels.

Table 1. Clinicopathologic profile of patients with endometrial carcinoma

Factor	No. of cases (%) n=72
Age(yr)	58.59±9.87 (35-87)
FIGO Stage	
I	38 (52.7)
II	12 (16.7)
III	16 (22.2)
IV	6 (8.4)
Tumor grade	
Well differentiated	28 (38.9)
Moderately differentiated	25 (34.7)
Poorly differentiated	19 (26.4)
Myometrial ınvasion	
None	1 (1.4)
<1/2	23 (31.9)
≥1/2	48 (66.7)
Lymphovascular invasion	
No	43 (59.7)
Yes	29 (40.3)
Histologic subtype	
Endometrioid	66 (91.7)
Non-endometrioid	6 (8.3)
Ovarian metastasis	
No	60 (83.3)
Yes	12 (16.7)
Lymph node metastasis*	
No	58 (85.3)
Yes	10 (14.7)
Washing cytology	
Negative	63 (87.5)
Positive	9 (12.5)
Cervical involvement	
No	47 (65.3)
Yes	25 (34.7)
Tumor diameter(cm)	
≤2	13 (18.1)
>2	59 (81.9)

*No of cases=68

Table 1 shows the clinicopathologic profile of patients with endometrial carcinoma.

Out of 72 patients preoperative CA-125 levels ranged from 2.95 to 6442 U/ml, with a mean of 126.83 U/ml for the entire group.Thirty-two patient (44.4%) had CA-125 levels of >20 U/ml.

Table 2 shows the correlation between elevated serum level of CA-125 (>20 U/ml) and each factor. Under investigation univariate analyses showed that there was a significant correlation of elevated CA-125 levels with positive washing cytology, lymphovascular space involvement and positive CA-125 tissue staining (Table 2). Multivariate analyses showed that positive CA-125 staining had a significant effect on elevation of preoperative CA-125 level at cutoff value of 20 U/ml and that odds ratio was 3.2 (Table 3). Other factors containing positive washing cytology, and lymphovascular space involvement which had a significant affect on elevated serum CA-125 level in univariate analysis, were no longer significant.

The percentage with positive CA-125 tissue staining (62/72, 86.1%) was found to be significantly higher than the percentage with elevated serum levels (86.1% vs 44.4% p=0.01).

Table 2. Characteristics of the patients and univariate analysis of elevated (≥20 U/ml) serum CA-125 and positive tissue staining in patients with endometrial carcinoma

Factor	Serum CA-125>20 U/ml		Positive tissue staining	
	No (%)	*p* value	No (%)	*p* value
CA-125 staining				
Negative	1 (10)	0.018		
Positive	31 (50)			
Age				
≤50	6 (54.5)	0.464	10 (90.9)	0.617
>50	26 (42.6)		52 (85.2)	
Stage				
I-II	19 (38)	0.097	44 (88)	0.485
III-IV	13 (59.1)		18 (81.8)	
Tumor size				
≤2 cm	7 (53.8)	0.451	11 (84.6)	0.863
>2 cm	25 (42.4)		51 (86.4)	
Histology				
Endometrioid	30 (45.5)	0.449	56 (84.8)	0.534
Non-endometrioid	2 (33.3)		6 (100)	
Grade				
1	11 (39.3)	0.482	25 (89.3)	0.848
2,3	21 (47.7)		37 (84.1)	
Myometrial invasion				
<1/2	7 (29.2)	0.065	17 (70.8)	0.008
≥1/2	25 (52.1)		45 (93.8)	
Cervical involvement				
No	20 (42.6)	0.658	40 (85.1)	0.735
Yes	12 (48)		22 (88)	
Ovarian metastasis				
No	26 (43.3)	0.671	52 (86.7)	0.761
Yes	6(50)		10 (83.3)	
Washing cytology				
Positive	7 (39.7)	0.031	54 (85.7)	0.797
Negative	25 (77.8)		8 (88.9)	
LVI				
No	14 (32.6)	0.013	36 (83.7)	0.475
Yes	18 (62.1)		26 (89.7)	
Lymph node metastasis				
No	23 (39.7)	0.07	50 (86.2)	0.609
Yes	7 (70)		8 (80)	
Presence of leiomyoma				
No	21 (39.6)	0.239	43 (81.1)	0.04
Yes	10 (55.6)		18 (100)	

Negative staining was noted in 10 (13.9%) of tumors, weakly positive in 23 (31.9%), positive in 16 (22.3%) and strongly positive in 23 (31.9%). Positive staining correlated with deep myometrial invasion (p=0.008) and presence of leiomyoma (p=0.04) (Table 3). Multivariate analysis showed that positive CA-125 staining significantly correlated with deep myometrial involvement (p=0.02, OR:6) (Table 4).

In our study, 25 of 28 (89.2%) grade 1 tumors 20 of 25 (80%) grade 2 tumors, and 17 of 19 (89.5%) grade 3 tumors were CA-125 positive. Fifty-six of 66 (84.8%) endometrioid, and 6 of 6 (100%) non-endometrioid tumors were CA-125 positive.

Elevated pretreatment CA-125 levels and positive staining were found in 31 of 72 (43.1%) patients. An elevated serum CA-125 level coinciding with a negative tissue staining was found in only one patient. This patient had advanced disease (stage IV A).

Discussion

Several studies investigated whether serum CA-125 assay may provide additional information in the preoperative assessment of endometrial carcinoma, and in particular in the identification of those patients with high risk of microscopic extrauterine spread who need a lymphadenectomy (3-6,8,9,13,14,17). However, to our knowledge, only a few studies have assessed the presence of CA-125 within endometrial cancer tissue and evaluated the correlation between tissue expression of the antigen with the corresponding serum value (3-5,15,17).

Ginath et al. examined 28 endometrioid type endometrial cancers and reported a discrepancy between the tissue CA-125 content and serum CA-125 level (17). Duk et al. immunohistochemically tested 20 endometrial cancer for CA-125 and found a correlation between elevated serum CA-125 levels and vessel invasion (13). Yamazawa et al. examined 52 endometrioid adenocarcinoma and found a relation between elevated serum CA-125 levels and the presence of disseminated cancer cells in the peritoneal cavity (18). Their results indicate that the main source of elevated serum CA-125 levels is not intrauterine tumor cells, and elevated serum CA-125 level is closely related to the presence of disseminated cancer cells in the peritoneal cavity. Our results show that there is a relationship between the primary tumor load and serum antigen levels, rather than between elevated CA-125 levels and the presence of infiltrative growth and/or metastases.

The distribution and expression of CA-125 suggests that the antigen is the secretory product of the normal endometrium (4). CA-125 was expressed by the glandular tissue in endometrial carcinomas and accumulated on apical cell surface and in cytoplasm. Tumors with solid features had a less glandular component and had less CA-125 expression. Endometrioid grade 1 adenocarcinomas were more likely to express CA-125. Tumors of the clear cell and papillary serous histologic types contributed disproportionately to the positive staining seen in grade 2 and grade 3 tumors (4). In our study, 25 of 28 (89.2%) endometrioid grade 1 tumors and six of 6 (100%) non-endometrioid tumors were CA-125 positive.

Berchuck et al evaluated CA-125 expression in endometrial adenocarcinomas using a histologic score that evaluated the proportion of cells expressing CA-125 and the intensity of staining (22). A high CA-125 score correlated with the presence of lymph node metastases and increased metastatic potential. In our study, positive CA-125 staining significantly correlated with deep myometrial invasion (p=0.02, OR:6).

Our study indicates that the majority of endometrioid carcinoma tissues contain CA-125. The percentage of the tumors positive for CA-125 staining was significantly higher than

Table 3. Multivariate analysis of clinicopathological variables in relation to preoperative CA-125 levels greater than 20 U/ml

Variables	B	SE	Wald	*p* value	OR	95% CI	
						Lower	Upper
Positive tissue staining	1.174	0.584	4.035	0.045	3.234	1.029	10.167
Washing cytology	1.444	0.933	2.393	0.122	4.236	0.680	26.391
LVI	1.013	0.544	3.465	0.063	2.754	0.948	8.001

B: risk ratio; SE: standart error; Wald: Wald statistics

Table 4. Multivariate analysis of clinicopathological variables in relation to preoperative tissue staining

Variables	B	SE	Wald	*p* value	OR	95% CI	
						Lower	Upper
Presence of leiomyoma	8.647	36.924	0.055	0.815	5690.402	0.000	1.5E+35
Myometrial invasion	1.796	0.769	5.453	0.02	6.028	1.335	27.223

B: risk ratio; SE: standart error; Wald: Wald statistics

that of elevated CA-125 levels in the corresponding blood samples. This indicates the presence of some mechanism that prevents the access of CA-125 into circulation. The intact basement membrane surrounding the tumors may constitute a barrier between the CA-125 harboring tissue and the serum (23). The basement membranes can function as important barriers to the transfer of tumor antigens from the tumor cells to the plasma. Carcinomas of the endometrium arise from the mucosal surface and usually show a glandular growth pattern, and the tumor must erode the basement membrane before the tumor-associated antigens can gain access to the vascular compartment.It has been shown that infiltrative growth does cause erosion of the basement membrane and this is turn causes release of antigen into the circulation (4). After local invasion of the gland's wall, antigen escape into the lymphatics and microvasculature of the endometrium. This mechanism is important for explanation of the elevated levels observed in lymphovascular space and lymph node positive disease. Cells on the peritoneal surface are not surrounded by an intact basement membrane and can interact directly with the surrounding fluid. This view is compatible with the elevated serum CA-125 levels in positive washing cytology. In the present study, thirty-two patients with elevated serum CA-125 levels had positive tissue staining (p=0.018), positive washing cytology (p=0.031) and lymphovascular invasion (p=0.013) compared with patients with normal serum CA-125 levels. Elevated CA-125 levels were not associated with lymph node metastasis in our study, possibly because the mean number of nodes sampled per patient was less than 30 (21.95±13.43). Also, elevated CA-125 levels were not associated with tumor size. There were limited number of patients with less than 2 cm of tumor size.

The presence of peritoneal metastases and extrauterine infiltrative growth of the primary tumor in stages III and IV might explain the elevated serum levels without positive tissue staining. An elevated serum CA-125 level coinciding with a negative tissue staining was found in only one patient. This patient had advanced disease (stage IV A).

It has been well-documented that other common gynecological abnormalities, such as pelvic inflamatory disease, endometriosis, and uterine leiomyomas, may raise serum CA-125 levels. In the current study, there were 18 patients who had leiomyomas. In our study, elevated serum CA-125 level did not correlate with presence of leiomyoma, but positive staining did (p=0.04).

We found that the serum CA-125 level in the endometrial cancer patient is closely related to intrauterine tissue expression of the antigen. Our results show that there is a relationship between the primary tumor load and serum antigen levels, rather than between elevated CA-125 levels and the presence of infiltrative growth and/or metastases.

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