



Expression of CA125 in tissue and serum of uterine serous carcinoma patients

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Received: June 20, 2015

Accepted: July 13, 2015

Published: July 17, 2015

ABSTRACT

Objective: To compare tissue immunohistochemical expression of CA125 with its level in the serum of corresponding uterine serous carcinoma (USC) patients.

Materials and Methods: Paraffin-embedded tissue blocks of consecutive USC uterine specimens of 25 patients with known serum CA125 levels prior to treatment were examined. The clinicopathological records of these patients were retrospectively abstracted. Immunohistochemistry was performed in each case on deparaffinized 4 μ sections of paraffin-embedded tissue blocks for detection of CA125. Staining of more than 10% of cells was considered positive. A scoring index was calculated by multiplying the intensity grade by the percentage of stained cells and considered low when it was equal to 1 or less and high when it was more than 1.

Results: Positive immunohistochemical staining and a high staining score were found in 72.0% and 61.1% of the patients respectively. Elevated serum CA125 levels prior to treatment were observed in 36.0% of the patients. The difference between the percentage of USC patients with positive CA125 tissue staining and the percentage of those with elevated CA125 serum levels were significant. Elevated serum levels correlated significantly with advanced stage disease. No correlation was found between positive immunohistochemical tissue staining parameters and stage of the disease.

Conclusion: The higher proportion of USC patients with positive CA125 immunohistochemical tissue staining than with elevated serum CA125 levels indicates the presence of some mechanism that prevents the access of CA125 into the circulation.

KEY WORDS: CA125 immunohistochemical tissue staining, CA125 serum levels, uterine serous carcinoma

INTRODUCTION

Uterine serous carcinoma (USC) represents only about 10% of endometrial cancer cases. It is an aggressive tumor with a poor prognosis that is diagnosed in advanced stages in about 40% of the cases and it accounts for a disproportionate number of uterine cancer-related deaths. Even in apparent clinical early stage disease, USC is found to have unfavorable pathological prognostic factors such as lymphovascular space invasion, lymph node involvement, and microscopic intraperitoneal spread [1,2].

Serum CA125 levels in USC have been assessed in many previous studies [3-10] and their surveillance may be a useful indicator of disease response or progression [9,10]. However, data regarding immunohistochemical expression of CA125 in USC tissue are very scarce [11].

The purpose of the present investigation was to compare tissue immunohistochemical expression of CA125 with the level of this marker in the serum of corresponding USC patients.

MATERIALS AND METHODS

Paraffin-embedded tissue blocks of consecutive USC uterine specimens of patients diagnosed from 2000 to 2014 with known CA125 levels prior to treatment were examined after Institutional Review Board Approval.

Formalin-fixed hematoxylin-eosin stained 6 μ m slides from the tissue of the same cases were newly performed and reviewed by an expert pathologist (LS) in order to verify the diagnosis.

The records of the study group patients were retrospectively abstracted and their clinicopathological data were recorded.

Immunostaining

Immunohistochemistry was performed in each case on additional deparaffinized 4 μ m sections of paraffin-embedded tissue blocks, on a Ventana BenchMark Ultra staining system (Roche Diagnostics, Ventana product, Tucson AZ, USA).

The detection of CA125 was done using mouse monoclonal antibody (Invitrogen Corporation CA. USA) diluted to 1:100, and a biotin free, multimer technology based on Ultra View Universal DAB Detection system.

The immunohistochemical cell membrane staining in all specimens was evaluated with microscopy by counting 10 high power fields ($\times 400$) with a minimum of 1000 cells counted per slide. Staining of more than 10% of cells was considered positive.

The pathologist assessed two parameters in each section:

- The proportion of the positively stained cells of the total number of tumor cells counted in the fields examined, ranging from 0% to 100%.
- The intensity of immunohistochemical staining that was graded subjectively on a 0-3 scale, in which 0 reflected no detectable staining and 3 represented very intense staining.

The scoring index was then calculated by multiplying the intensity grade of the stained cells by the percentage of the positively stained cells.

The score was considered low when the index was equal to 1 or less and high when it was more than 1.

Sections of ovarian cancer tissue known to contain CA125 served as positive controls. The pathologist was blinded to the clinical data.

RESULTS

The study group comprised 25 consecutive USC patients with known CA125 levels prior to treatment diagnosed during the study period. The mean age of the study group patients was 72.5 (standard deviation = 9.6). Additional selected characteristics of the patient are presented in Table 1. The presenting symptom in 88.0% of the patients was postmenopausal bleeding. Only 28.0% patients were diagnosed in Stage I. Treatment consisted of surgery followed by platinum-based combination chemotherapy $\pm$ radiotherapy in the great majority (84.0%) of the patients. Positive immunohistochemical staining was found in 72.0% of the USC patients and elevated (>35 U/mL) serum CA125 levels prior to treatment were observed in only 36.0% of them. This difference was statistically significant (Fisher's exact test - $P = 0.02$). Of the 18 patients with positive staining, 6 (33.3%) had elevated serum CA125 levels. Elevated serum CA125 levels were also found in 3 (42.8%) of the 7 patients with negative staining. All 3 had advanced stage disease.

The median serum CA125 level in those with elevated levels was 345 U/mL (range 54-3172 U/mL). All 9 (100.0%) patients with elevated serum CA125 levels were diagnosed in Stages II-IV, while only 56.2% of the patients with CA125 serum levels in the normal range (≤ 35 U/mL) were diagnosed in these stages. This difference was also statistically significant (Fisher's exact test - $P = 0.02$).

No correlation was found between immunohistochemical tissue staining parameters and stage of the disease. There was also

Table 1: Selected characteristics of the USC patients

Characteristics	No.	%
Total	25	100.0
Presenting symptom		
Post-menopausal bleeding/irregular bleeding	22	88.0
Other	3	12.0
Stage		
I	7	28.0
II-IV	18	72.0
Treatment		
Surgery + chemotherapy $\pm$ radiotherapy	21	84.0
Surgery only	4	6.0
CA125 prior to treatment		
Elevated (>35 U/mL)	9	36.0
Stage I	0	0.0**
Stages II-IV	9	100.0**
Within normal range (≤ 35 U/mL)	16	64.0
Stage I	7	43.7 ^a
Stages II-IV	9	56.2 ^a
Immunohistochemical staining		
Positive	18	72.0
Negative	7	28.0
Immunohistochemical score* n=18 (100%)		
High	11	61.1
Low	7	38.9

*Only in those with positive staining, **Of those with elevated CA125,

^aOf those with normal range CA125, USC: Uterine serous carcinoma

no correlation between positive tissue staining parameters and elevated serum CA125 levels and other pathological prognostic factors such as, depth of myometrial invasion, presence of LVSI, and presence of lymph node involvement (not shown).

DISCUSSION

Our data indicate that although immunohistochemical staining for CA125 was positive in 72.0% of 25 USC specimens examined by us, elevated serum CA125 levels were present in only 36.0% of them. Among the patients with positive tissue immunohistochemical staining only a third had elevated serum CA125 levels. On the other hand, elevated serum CA125 levels were also observed in patients with negative tissue staining.

We could locate only one previous report regarding CA125 immunohistochemical expression specifically in USC tissue [11]. This study of 90 endometrial cancers included 15 USC patients. The authors state that the majority of USCs showed strong CA125 staining, but the exact percentage of tissues stained is not given. Serum CA125 levels in these USC patients were not assessed in this study.

As also reported by others [3-8], elevated serum levels in our study correlated significantly with advanced stage disease. The lack of correlation between elevated serum levels and staining parameters and pathological prognostic factors may be due to our limited number of cases.

The reason for the discrepancy between the percentage of tissue positive CA125 immunohistochemical staining and the percentage of elevated serum CA125 levels is obscure.

Discordance between tissue and serum CA125 was previously reported in endometrial endometrioid carcinoma (EEC) [12,13] and in carcinosarcoma [12]. Yamazawa *et al.* [12] assessed tissue and serum levels of CA125 in 52 EEC patients. Positive CA125 tissue staining was found in 35 (67%), while elevated serum CA125 (>20 U/ml) levels were found in only 15 (29%) of the patients. Ginath *et al.* [13] also assessed tissue and serum CA125 in 28 EEC as well as in 11 with carcinosarcoma patients. They found that the percentage of EEC patients with positive tissue staining was significantly higher than the percentage with elevated (>35 U/mL) serum levels (89.3% vs. 21.4%, $P < 0.0001$). In carcinosarcoma patients the percentage of positive tissue staining was also higher than that with elevated serum CA125 levels (72.7% vs. 54.4%), but the difference was statistically not significant.

The higher proportion of USC, EEC, and carcinosarcoma patients with positive CA125 immunohistochemical tissue staining than with elevated serum CA125 levels indicates the presence of some unknown mechanism that prevents the access of CA125 into the circulation. All USC patients with elevated serum CA125 levels had advanced stage disease. This may possibly be taken to indicate that CA125 may have easier access to the circulation from metastatic tumor than from the original tumor or that the source of the elevated serum level is from some irritation of the peritoneum by the metastases.

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Source of Support: Nil, Conflict of Interest: None declared.