Original article

UDC: 618.11-006.6:616-097
doi:10.5633/amm.2020.0404

CLINICAL SIGNIFICANCE OF CD44 EXPRESSION IN SEROUS OVARIAN CANCER

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Ovarian cancer is a devastating disease causing more than 180.000 deaths a year, with often insidious course, delayed clinical diagnosis, and limited response to therapy. The CD44 cell surface glycoprotein is involved in metastatic spread and progression in various types of cancer, including ovarian serous cancer. This study aimed to investigate the profile of CD44 immunohistochemical expression in ovarian serous cancer, and to determine its potential significance in prognosis of the disease. A total of 124 primary serous ovarian cancers were analyzed for the expression of CD44 by immunohistochemical method and assessed for possible relation with clinical and pathological parameters, as well as with patients' survival. High CD44 expression was observed in 67.7% of the investigated tumors. A positive family history of malignancies was associated with low expression CD44 in cancer cells ($p = 0.004$). Low expression of CD44 was more frequent in FIGO stage IV tumors than in other stages, as well as in high grade cancer compared to low grade, however these differences were not statistically significant. Mean survival was significantly longer in patients with high CD44 expression compared to those with absent or low expression ($p = 0.009$). The fatal outcome during the follow-up period occurred in 65% of patients with low CD44 expression, and in 42.86% of patients with high CD44 expression, with statistically significant difference between the groups ($p = 0.035$). In conclusion, the adverse clinical course of serous ovarian cancer was associated with the absence or low expression of CD44.

Acta Medica Medianae 2020;59(4):26-33.

Key words: *ovarian cancer, serous cancer , CD44*

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Introduction

Ovarian cancer is a devastating disease causing more than 180.000 deaths a year (1), with often insidious course, delayed clinical diagnosis, and limited response to therapy. Most ovarian cancers start in the cells covering the ovaries and are called epithelial ovarian cancer. High-grade serous ovarian carcinoma (HGSOC) is the most frequent type of ovarian cancer and has a poor outcome (2).

There are different types of cells in the tumor environment, such as vascular cells, fibroblasts, cells of the immune system, extracellular matrix (ECM) components, as well as growth factors and cytokines. The tumor cells receive paracrine signals from the local microenvironment. In this way they often alter the cellular and molecular composition and lead to tumor progression. The tumor environment is important for the occurrence of the metastatic phenotype of cancer cells and it has been the subject of extensive research (3, 4). The disruption of the ECM results in abnormal intercellular and/or intracellular signaling, so that dysregulation of cell proliferation, growth, and cytoskeletal reorganization can occur (5, 6).

The CD44 cell surface glycoprotein is involved in the interaction between cells, cell adhesion and migration. It is considered to be a cell surface marker of metastasis and progression in various types of cancer, including ovarian cancer. CD44 is a receptor for hyaluronic acid (7). Hyaluronic acid is a major component of the ECM in most mammalian tissues and it accumulates at the site of cell division and rapid matrix remodeling, which occurs during

embryonic morphogenesis, inflammation, and tumorigenesis. Hyaluronic acid is the basis of glycosaminoglycans and it is found in the extracellular matrix. It is the main component of the peritoneum where ovarian cancer metastases mostly occur. Hyaluronic acid (HA) induces signals upon binding to CD44, and in turn, CD44 can react with other molecules, including collagen, fibronectin, osteopontin, growth factors and matrix metalloproteinase (MMPs) (8-9).

CD44 interacts with hyaluronic acid and activates Nanog-Stat3 and signaling pathways into which ankyrin is included. The activation of these signaling pathways is thought to be responsible for the specific behavior of tumor stem cells because it has an effect on transcriptional activation, on the growth of tumor cells and drug resistance in ovarian and breast cancers. The interaction of CD44 with the tumor stroma and the tumor environment is closely related to the metastatic growth of cancer (10-11).

Based on the previous findings, the question arises whether the suppression of the CD44 protein can improve chemotherapy efficacy and prevent the occurrence of metastases. Such suppression can potentially be achieved by using siRNAs generated by targeting CD44 with mRNA (7). This study aimed to investigate the profile of CD44 immunohistochemical expression in ovarian serous epithelial cancer, and to determine its potential clinical significance in this devastating disease.

Material and methodology

This study included female patients with serous epithelial ovarian cancer diagnosed between 2005 and 2011 in the region of Southern Serbia. Their survival was monitored until October 2013, with median follow-up of 60 months. A total of 124 primary ovarian cancers were analyzed including the following: ovarian cancer limited to the ovaries (FIGO stage I), ovarian cancer extended to the pelvic organs (FIGO stage II), ovarian cancer with peritoneal metastases (FIGO stage III) and ovarian cancers with distant metastases (FIGO stage IV).

The clinical parameters of the patients with ovarian cancer were monitored, as well as their pathological characteristics. The clinical parameters analyzed were: age, FIGO stage, the presence and size of residual tumor, the type of therapy, and the response to the therapy. The pathological characteristics analyzed were: histologic tumor type, histologic grade, and nuclear grade.

Case histories of the female patients with ovarian cancer who were treated at the Oncology Clinic of the Clinical Center Niš were used as the source of the relevant clinical data.

Pathohistological analysis and immunohistochemical reaction scoring

The pathological and immunohistochemical analysis of the ovarian cancer samples was performed at the Institute of Pathology of the Faculty of Medicine in Niš.

The pathohistological analysis was performed on the biopsy specimens of ovarian cancers that were fixed in 10% buffered formalin, processed in an automatic tissue processing machine, embedded in paraffin and cut in the microtome at 5 μm thickness. The monoclonal antibody to CD44 (ab157107, Abcam, 1:100 dilution) was used for the immunohistochemical analysis. Briefly, the sections were deparaffinized, rehydrated and heat mediated antigen retrieval procedure was performed. After incubation with primary antibody at 4 °C overnight, the slides were further treated with standard immunoperoxidase detection system, and diaminobenzidine (DAB) was used as a chromogen for the visualization of reaction. Slides were counterstained with Mayer's hematoxylin, dehydrated, and mounted with DPX.

The analysis of the immunohistochemically stained microscopic ovarian cancer preparations was performed using a Leica DM 1000 light microscope. The positive finding was a brownish cytoplasmic or membranous staining. The immunohistochemical reaction of the expression of CD44 was based on the evaluation of the positive response in the tumor cells, and was characterized as low expression if less than 25% of the cells showed immunoreactivity, or high expression, if ≥ 25% of cancer cells showed staining with moderate to strong intensity, i.e. marked or intense brown precipitate within the tumor cells (7).

The results obtained were systematized and grouped, and the statistical significance was tested by appropriate statistical tests according to the examined parameters and the size of the samples.

Statistical methods

Microsoft Office 2007 Excel was used to write, rank, group, tabulate and graph the data, while SPSS 26.0 Software was used for quantitative statistical analysis. Comparison of mean values of numerical features between two groups of subjects was performed by Student's t test. The comparison of the frequency of individual categories of attribute characteristics between some groups of the subjects was performed by Chi square test or Fisher exact test in cases where some of the expected frequencies were less than 5. As a threshold for statistical significance, a permissible error rate of less than 5% ($p < 0.05$) was used in the inference.

Results

High CD44 expression was observed in 67.7% of the investigated tumors (Figure 1). The mean age of the patients with high CD44 expression was 58.75 ± 13.69 years, and they were not significantly older than the subjects with low expression (Figure 2) whose mean age was 55.13 ± 12.1 years ($p > 0,05$) (Table 1).

A statistically significant difference was observed in term of a positive family history for malignancies between the two groups; more often family history was positive for cancer in the group of patients with low CD44 expression compared to

those with high CD44 (30% vs. 9.52%; p = 0.004) (Table 1).

The highest ratio of the tumors with low expression of CD44 was recorded in FIGO stage IC (low CD44 found in 66.6% of the tumors), and in FIGO stage IV, where half of the tumors (50%) had low CD44 expression, in contrast to other FIGO stages, where tumors with high CD44 expression predominated. However, these differences were not statistically significant ($p \geq 0.05$) (Table 2).

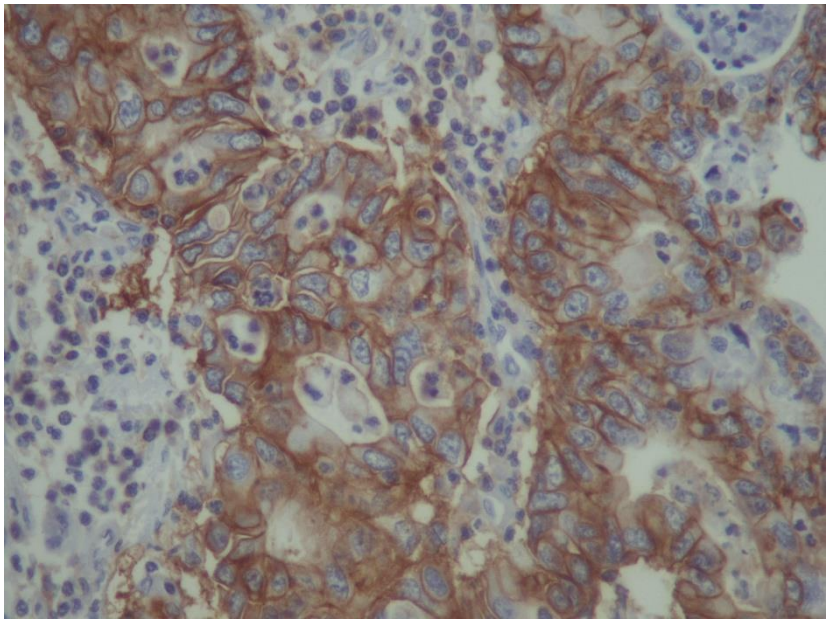

Figure 1. Strong diffuse membranous expression of CD44 in poorly differentiated high grade serous ovarian carcinoma (x400)

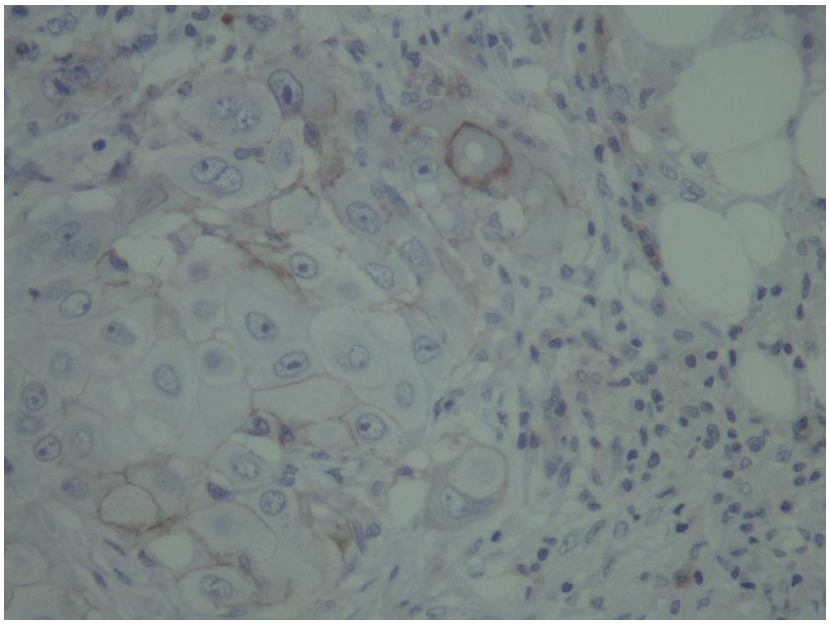

Figure 2. Loss of immunoreactivity of CD44 in metastatic serous ovarian carcinoma (x400)

Table 1. The characteristics of the subjects and tumor type in relation to CD44 expression

Characteristics	Expression of CD44		Comparison
	Low expression (n = 40)	High expression (n = 84)	
Age (years)	58.75 ± 13.69	55.13 ± 12.1	p = 0.069
Menarhe (years)	13.55 ± 1.55	13.53 ± 1.59	p = 0.481
Menopause (years)	39.2 ± 19.93	34.1 ± 22.07	p = 0.108
First birth (years)	19.57 ± 6.12	20.75 ± 6.57	p = 0.172
Number of children	1.82 ± 0.64	1.8 ± 0.79	p = 0.424
Number of abortions	1.6 ± 3.04	1.37 ± 2.01	p = 0.312
Positive family history	12 (30%)	8 (9.52%)	p = 0.004
Time to diagnosis(months)	3.55 ± 3.21	4.5 ± 4.03	p = 0.096

Chi square test was performed. A p-value of ≤ 0.05 was considered significant.

Table2. CD44 immunohistochemical expression in relation to FIGO stage

FIGO stage	Expression CD44		Comparison
	Low expression (n = 40)	High expression (n = 84)	
borderline	4 (10%)	8 (9.5%)	p = 0.933
IA	1 (2.5%)	3 (3.6%)	p = 1.000
IB	0 (0%)	0 (0%)	/
IC	4 (10%)	2 (2.4%)	p = 0.085
IIA	0 (0%)	2 (2.4%)	p = 1.000
IIB	0 (0%)	5 (5.9%)	p = 0.174
IIC	1 (2.5%)	3 (3.6%)	p = 1.000
IIIA	5 (12.5%)	11 (13.1%)	p = 0.926
IIIB	9 (22.5%)	18 (21.4%)	p = 0.977
IIIC	8 (20%)	24 (28.6%)	p = 0.308
IV	8 (20%)	8 (9.5%)	p = 0.103

Chi square test was performed. A p-value of ≤ 0.05 was considered significant

According to the FIGO grading system, each patient group was divided into two categories: high grade and low grade. In both patient groups, the majority of tumors belonged to a more aggressive histologic grade (high grade). In the group of patients with low CD44 expression high grade tumors comprised 80%, while in the group of patients with high CD44 expression 75% of the tumors, with no significant difference in the distribution between the groups (p = 0.318) (Table 3).

Mean survival was significantly longer in patients with high CD44 expression compared to those with absent or low expression (43.81 ± 21.9: 32.81 ± 28 months; p = 0.009) (Table 4).

The fatal outcome (death) during the follow-up period occurred in 65% of patients with low CD44 expression, and in 42.86% of patients with high CD44 expression, with statistically significant difference between the groups (p = 0.035).

Table 3. CD44 immunohistochemical expression in relation to FIGO grade

FIGO grade	Expression CD44		Comparison
	Low expression (n = 40)	High expression (n = 84)	
High grade	32 (80%)	73 (75%)	p = 0.318
Low grade	8 (20%)	11 (15%)	

Table 4. Disease outcome in relation to CD44 expression

Disease outcome	Expression CD44		Comparison
	Low expression (n = 40)	High expression (n = 84)	
Survival (months)	32.81 ± 28	43.81 ± 21.9	p = 0.009
Fatal outcome	26 (65%)	36 (42.86%)	p = 0.035

Discussion

The results of our study indicated that the patients with high CD44 expression in cancer cells had significantly longer mean survival compared to those with decreased or absent CD44 (43.81 ± 21.9 vs. 32.81 ± 28 months; p = 0.009). According to Sillanpaa et al. (12), the decreased expression of CD44 is associated with the advanced stage of ovarian epithelial cancer and it is an independent prediction factor of shorter survival time, which is in agreement with our results. On the other hand, we failed to recognize the significant association between CD44 expression and FIGO stage. Although tumors of advanced stage demonstrated more frequent loss of immunohistochemical expression of CD44, this difference was not significant (p > 0.05).

The general prognostic role of CD44 in human cancers is controversial. The reduced expression of CD44 and its variants (CD44v and CD44s) is associated with poor disease outcome in other malignant tumors as well, such as melanoma (13), prostate cancer (14), and colorectal cancer (15). Conversely, the increased expression of CD44 is a predictor of poor prognosis and survival in kidney cancer, non-small cell lung cancer breast cancer in stage II and III and cervical cancer in FIGO stage IB (16-19).

The studies regarding the prognostic role of CD44 in ovarian cancer have yielded inconsistent results so far. Several previous studies were congruent that high CD44 expression was associated with a relatively good prognosis for ovarian cancer, but these studies included relatively small number of patients. No association between CD44 expression and disease prognosis has been found in three studies, while one study has shown that the poor prognosis of a disease is associated with high CD44 expression, which contradicts our results. Regardless of the sufficient number of samples, the reasons for the discrepancy in the results may lay in the type of the used antibodies. In addition, this study revealed an interesting finding about the possible association of hereditary background and CD44 expression in ovarian tumors. Namely, patients with positive family anamnesis for malignant disease had significantly lower expression of CD44 in cancer tissue. The significance of this association is yet to be elucidated (20-24).

Epithelial ovarian cancer is spread by the implantation of tumor cells into the peritoneal cavity. *In vitro* studies have shown that CD44 on the surface of ovarian cancer cells binds the hyaluronic sheath of mesothelial cells and may contribute to the formation of peritoneal metastases (25, 26). The monoclonal antibodies whose target is CD44 significantly inhibit the adhesion of ovarian cancer cells to mesothelial cells and their peritoneal implantation in mice (27, 28). This indicates that CD44 in tumor cells may contribute to the spread of ovarian cancer in humans. However, our results do not support the idea that high expression of CD44 is associated with high grade histology of serous epithelial carcinoma or aggressive clinical behavior. On the contrary, a high percentage of CD44 positive ovarian cancer cells occur in well-differentiated tumors and less aggressive histological subtypes in the presented material. In addition, high CD44 expression in tumor tissue is associated with a favorable disease prognosis, and longer overall survival. The other molecular mechanisms, such as integrins (28) and proteoglycans (29), may play a role in the implantation of ovarian cancer cells.

Previous studies additionally suggested that the expression of CD44 in cancer tissue did not alter during the metastatic process (29, 30), while some authors observed a downregulation of CD44 during

tumor progression in mice (31) and tumor cells from ascitic fluid in humans. It must be taken into account that changes in CD44 other than total expression levels may also contribute to malignant growth (32-33). The regulation of receptor's ability to bind hyaluronan may modify the roles and significance of CD44 in various cancer types (34). In epithelial ovarian cancer (34), a positive correlation present in primary tumors between cells bound by hyaluronan and CD44 was lost in metastases, possibly reflecting the changes in the function of the hyaluronan receptor for CD44. However, there is no straightforward direct relationship between the hyaluronan accumulation in tumor stroma and CD44 expression in tumor cells. CD44 expression does not necessarily mean tumor cell adherence to hyaluronan and, on the other hand, the levels of CD44 do not always correlate with affinity for hyaluronan. A previous study suggests that hyaluronan accumulation in the stroma represents independent prognostic factor in ovarian cancer, as well as the loss of CD44 positivity in primary tumors, indicating that both molecules have independent, separate influence to the prognosis of ovarian cancer (10). The results of our study are in accordance with these conclusions, and suggest that the decrease of CD44 expression is linked with poor clinical outcome. The fatal outcome after follow-up period occurred in 65% of patients with low CD44 expression, and in 42.86% of patients with high CD44 expression, with statistically significant difference between the groups ($p = 0.035$).

Conclusion

1. A positive family history of ovarian cancer malignancies is associated with low expression of CD44 in cancer cells.
2. No significant association was found between the immunohistochemical expression of CD44 and FIGO stage and grade of serous epithelial ovarian carcinoma.
3. The adverse clinical course of ovarian cancer was associated with the absence or low expression of CD44.

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Originalni rad

UDC: 618.11-006.6:616-097
doi:10.5633/amm.2020.0404

KLINIČKI ZNAČAJ EKSPRESIJE CD44 KOD SEROZNOG KARCINOMA JAJNIKA

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Karcinom jajnika je bolest koja uzrokuje više od 180.000 smrtnih slučajeva godišnje, sa često podmuklim tokom, kasnim simptomima i kliničkom dijagnozom i ograničenim odgovorom na terapiju. Površinski glikoprotein CD44 uključen je u širenje i pojavu metastaza kod različitih vrsta karcinoma, uključujući i serozni karcinom jajnika. Ovo istraživanje imalo je za cilj da analizira profil imunohistohemijske ekspresije CD44 kod seroznog karcinoma jajnika i da utvrdi njegov potencijalni značaj u prognozi bolesti. Na ekspresiju CD44 analizirano je ukupno 124 primarnih seroznih karcinoma jajnika imunohistohemijskim metodama i procenjena je moguća povezanost sa kliničkim i patološkim parametrima, kao i sa preživljavanjem bolesnika. Primećena je visoka ekspresija CD44 kod 67,7% ispitivanih tumora. Pozitivna porodična anamneza maligniteta bila je povezana sa niskom ekspresijom CD44 u ćelijama karcinoma ($p = 0,004$). Niska ekspresija CD44 bila je češća kod tumora u FIGO stadijumu IV, nego u ostalim stadijumima, kao i kod karcinoma visokog gradusa, u poređenju sa karcinomima niskog gradusa. Međutim, ove razlike nisu bile statistički značajne. Prosečno preživljavanje bilo je značajno duže kod bolesnika sa visokom ekspresijom CD44, u poređenju sa onima kod kojih je bila odsutna ili slaba ekspresija CD 44 ($p = 0,009$). Smrtni ishod tokom perioda praćenja dogodio se kod 65% bolesnika sa niskom ekspresijom CD44 i kod 42,86% bolesnika sa visokom ekspresijom CD44, sa statistički značajnom razlikom između grupa ($p = 0,035$). Istraživanje je pokazalo to da je nepovoljni klinički tok seroznog karcinoma jajnika bio povezan sa odsutvom ekspresije ili slabom ekspresijom CD44.

Acta Medica Medianae 2020;59(4):26-33.

Ključne reči: *karcinom jajnika, serozni karcinom jajnika, CD44*