EPİTELYAL OVER KANSERLERİNDE CD24 VE CD44'ÜN İMMUNOHİSTOKİMYASAL OLARAK KARŞILAŞTIRILMASI VE PROGNOSTİK DEĞERİ

Immunohistochemical Comparison of Cd-24 And Cd-44 in Epithelial Ovarian Cancer And Prognostic Values

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ÖZET

Giriş: Bu çalışmada epitelyal over kanserlerinden rezeke edilen tümör spesmenlerinde, CD 44 ve CD 24'ün ekpresyonları analiz edilerek, bu ekspresyon ve klinikopatolojik parametreler arasındaki ilişkiyi analiz edilmiştir.
Gereç Ve Yöntemler: Bu çalışma, Kliniğimizin Jinekolojik Onkoloji Anabilim Dalı'nda tedavi edilen primer over kanseri olan 31 hastayı içermektedir.
Bulgular: Anti-CD24 için incelenen 14 seröz karsinomlu spesmende; 6 örnekte şiddetli (+++) immünoreaktivite, 4 örnekte orta / şiddetli (++ / +++) immünoreaktivite, 2 numunede orta / şiddetli (++ / +++) immünoreaktivite, 2 örnekte hafif / orta (+ / + +) immünoreaktivite gözlendi. Bu 14 hasta CD 44 için incelendiğinde; 3 örnekte (++) modereta immünoreaktivitesi, 2 örnekte + / ++ (hafif / orta) immünoreaktivite, 9 örnekte + (hafif) immünoreaktivite gözlendi.
Sonuç: CD44 immünoreaktivitesinin boyanma yoğunluğunun over epitelyal kanserlerinde sağkalım oranı ile ilişkili olduğu, ancak istatistiksel olarak anlamlı olmadığı tespit edildi. Her ne kadar CD 24 sağkalımı ile ilişkinin istatistiksel olarak anlamlı bulunmamasına rağmen, Over tümörlerde tanısal bir belirteç olarak kullanılabileceği düşünüldü.

Anahtar Kelimeler: *Cd-24; Cd-44; Immünohistokimya; Over Kanseri.*

ABSTRACT

Objective: The present study evaluated the CD24 and the CD44 expression in resected tumor specimens of ovarian carcinom and analyzed the correlation between this expression and the clinicopathological parameters.
Material Methods: The present study included 31 patients with primary ovarian cancer who were treated in the Department of Gynecologic Oncology of our Clinic
Results: 14 serous carcinomas examined for anti-CD24; severe (+++) immunoreactivity was observed in 6 samples, moderate / severe (++ / +++) immunoreactivity was observed in 4 samples, moderate (++) immunoreactivity was observed in 2 samples and mild / moderate (+ / ++) immunoreactivity was observed in 2 samples. When these 14 patients were examined for CD 44; (++) modereta immunoreactivity was observed in 3 samples, + / ++ (mild / moderate) immunoreactivity was observed in 2 samples and + (mild) immunoreactivity was observed in 9 samples.
Conclusion: It was determined that the staining intensity of CD44 immunoreactivity was related to the survival rate in ovarian epithelial cancers, but it was not statistically significant. Although the association with survival of CD 24 was not found to be statistically significant, it was thought that it could be used as a diagnostic marker in over-tumors.

Key words: *CD24; CD44; Immunohistochemistry; Ovarian tumor*

INTRODUCTION

Ovarian carcinom is about 3% of all cancers seen in women and it is the fifth most common cancer-related death in women after lung, breast, colorectal, and pancreatic cancer. Early diagnosis of this disease, the most lethal disease among gynecologic cancers, is difficult [1]. Molecular Markers are the most frequently searched topic in over the past decade in ovarian carcinom [2-5]. Nowadays, molecular markers which can show poor prognosis with high sensitivity and specificity are being investigated, but there are no markers that can stand out yet.

Cluster of differentiation (CD)24 is a small, heavily glyco-sylated, mucin-like cell surface protein (27 amino acids long) that binds to the membrane via a glycosyl-phosphatidylinositol anchor [6]. CD24 molecules are expressed in hematopoietic cells, such as B lymphocytes and neutrophils, and in certain epithelial cells, including ovarian epithelial cells [6,7]. It has been reported that CD24 is important in cell selection and maturation for specific cellular functions [8]. CD24 has also been reported to be a ligand for P-selectin, an adhesion receptor on activated endothelial cells and platelets [9,10], suggesting that the molecule functionally enhances the metastatic potential of cancer cells. CD24 has recently received attention in tumor biology research, as several studies have reported that the protein is broadly overexpressed in numerous types of cancer cell from the lung, breast, prostate, liver, kidney, pancreas and ovary, as well as in lymphomas [7,8].

CD44 is a homing cell adhesion molecule, a cell surface glycoprotein for hyaluronic acid. This marker is expressed on the surface of red blood cells and platelets and they have been known as lymphocytic homing receptors. CD44 plays an important role in adhesion to the extracellular matrix and matrix functions, such as degeneration, proliferation and cell survival [11-14]. The expression of CD44 in cancer cells has also been implicated in cell migration, invasion and metastasis [15,16]. Furthermore, CD44 has recently been recognized as a major marker for cancer stem cells (CSCs) in several types of cancer [16,17].

The present study evaluated the CD24 and the CD44 expression in resected tumor specimens of ovarian carcinom and analyzed the correlation between this expression and the clinicopathological parameters.

MATERIAL METHODS

The present study included 31 patients with primary ovarian cancer who were treated in the Department of Gynecologic Oncology of Izmir Ege Maternity and Women's Disease Training and Research Hospital between 2005 and 2008. The patients were diagnosed as serous carcinoma (14), endometrioid carcinoma (10), endometrioid + clear cell carcinoma (1), clear cell carcinoma (2), mucinous carcinoma (2), transitional epithelial carcinoma (1) and borderline serous tumor (1). Ovarian cancer tissue specimens were fixed in 10% neutral buffered formalin and subsequently embedded in paraffin. The specimens were sectioned to a thickness of 5 µm, then de-paraffinized with xylene and rehydrated for further staining with hematoksilen-eosin (HE) (Surgipath, 01562E, 01602E, Peterborough, UK) or immunohistochemistry. Additional sections made from the same tissues were prepared for indirect immunohistochemical staining by avidin-biotin peroxidase method. Preparations to be coated by immunohistochemical method were inkubated at 60 ° C for 1 night, after incubated 1 hour with xylene, the deparaphinization process was completed. The sections were passed through gradually decreasing alcohol series to bring the distillate into the water phase. The endogenous peroxidase activity in the rehydrated sections was blocked with 3% H2O2 and the antigen was retrieved by heat treatment for 30 min in 10 mmol/l citrate buffer. The sections were incubated for 10 min in 10% normal goat serum, then incubated overnight at 4˚C with a primary rabbit polyclonal antibody against the CD24 and the CD44 antigens (1:100 dilutions). The avidin-biotin-peroxidase system was used as the second kit (Zymed). Sections were washed with PBS (Phosphate Buffer Solution) and streptavidin was applied for 30 minutes. The sections to which DAB (diaminobenzidine) was applied were stained with Mayer's hematoxylin and closed with the closing medium in order to immunoreactivity to become visible. One section test left for the cross control to test whether the immunoreactivity is specific

or not. Histochemical and immunohistochemical stained sections were evaluated semi-quantitatively for staining intensity under the Olympus BX40 light microscope. Staining intensity was determined as + (mild), ++ (moderate), +++ (severe), or ++++ (very severe). The obtained data were statistically evaluated with SPSS 15.0. A value of P <0.05 was considered statistically significant. Photographs of the sections were taken using Fuji 100 ASA photo film.

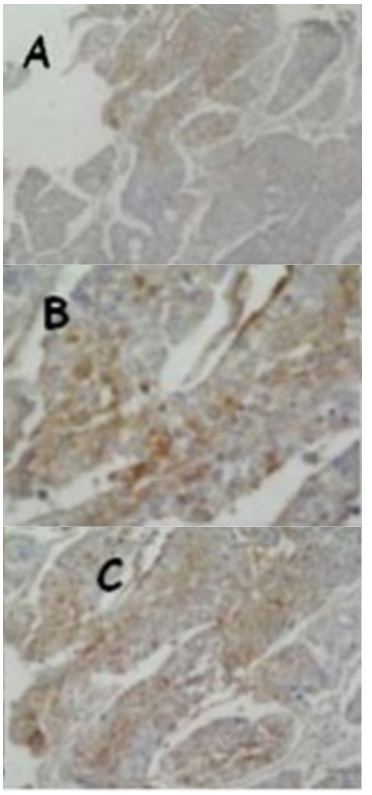
RESULTS

Demographic and Morphological Features are summarized in Table 1.

Table 1 : Demographic and Morphological Features

Age	
< 60	22
>60	9
Parity	
< 3	18
> 3	13
Histopathology	
Borderline	
Serous	1
Invaziv	
Serous	14
Endometrial	10
Müsinöz	2
Clear Cell	2
Variant type	1
Endometrioid + Clear cell.	1
FIGO	
I	11
II	5
III	15
IV	-
Grade	
I	4
II	7
III	20

In this study, 14 serous carcinomas examined for anti-CD24; severe (+++) immunoreactivity was observed in 6 samples, moderate / severe (++ / +++) immunoreactivity was observed in 4 samples, moderate (++)immunoreactivity was observed in 2 samples and mild / moderate (+ / ++) immunoreactivity was observed in 2 samples (Picture 1).



Picture 1 : (+++) CD 24 immunoreactivity with serous adenocarcinoma. X100 (A), X200 (B), and X400 (C).

When these 14 patients were examined for CD 44; (++) modereta immunoreactivity was observed in 3 samples, + / ++ (mild / moderate) immunoreactivity was observed in 2 samples and + (mild) immunoreactivity was observed in 9 samples.

Anti CD24 immunoreactivity was observed (+++) severe in 3 cases, moderate / severe (++ / +++) in 3 cases, mild/moderate (++) in 2 cases, and mild (+) in 2 cases with endometrioid carcinoma. When these 10 patients were examined for CD 44; (++) modereta

immunoreactivity was observed in 2 samples, mild / moderate (+ / ++) immunoreactivity was observed in 1 samples and mild (+) immunoreactivity was observed in 3 samples.

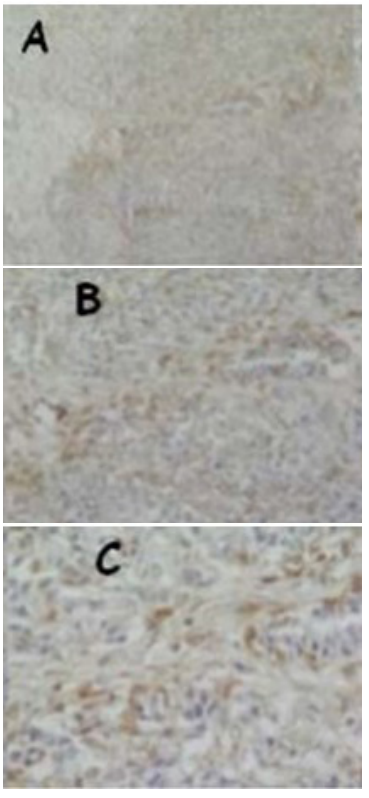
CD24 immunoreactivity of the endometrioid and clear cell carcinoma preparate was observed as moderate / severe (++ / +++), whereas CD44 immunoreactivity was observed as mild / moderate (+ / ++).

CD24 immunoreactivity was found as severe (+++) in both patients with clear cell carcinoma, whereas CD44 immunoreactivity was observed in moderate (++) in one sample and mild (+) in other sample.

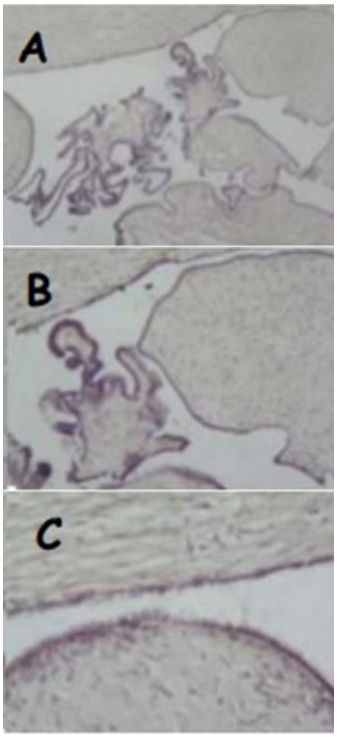
CD24 immunoreactivity in patients with mucinous carcinoma was observed as severe (+++) in one sample and moderate (++) in one sample, whereas CD44 immunoreactivity was observed as mild (+) in both samples.

CD24 immunoreactivity was seen as moderate (++) in a patient with transitional epithelial carcinoma, CD44 immunoreactivity was'nt observed in the epithelium, but severe (+++) immunoreactivity was observed in stroma with transitional epithelial carcinoma.

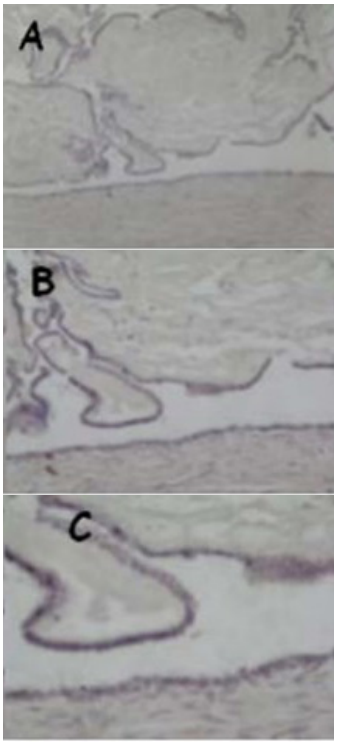
Both CD24 and CD44 immunoreactivity were mild (+) in patients with borderline serous tumors (Picture3-4).



Picture 2: (++) CD 44 immunoreactivity with serous adenocarcinoma. X100 (A), X200 (B), and X400 (C).



Picture 3: (+) CD 24 immunoreactivity with serous borderline. X100 (A), X200 (B), and X400 (C).



Picture 4: (+) CD 44 immunoreactivity with serous borderline. X100 (A), X200 (B), and X400 (C).

Anti CD 24 and anti CD 44 positivity in all samples are summarized in Table 2.

Table 2: Anti CD 24 and anti CD 44 positivity in all samples

Group	CD 24	CD 44
Serous adenocarcinoma		
1	+++	+/++
2	++	+
3	+++	++
4	+++	+
5	++/+++	+/++
6	+/++	++
7	+++	++
8	++/+++	+
9	++/+++	+
10	+++	+
11	+++	+
12	+/++	+
13	++/+++	+
14	++	+
Endometrioid Carcinoma		
1	++/+++	+++
2	+/++	+/++
3	++/+++	++
4	+	++
5	+	+++
6	+++	+
7	+++	+
8	++	++
9	+++	+
10	++/+++	++
Endometrioid clear cell		
1	++/+++	+/++
Clear cell carcinoma		
1	+++	++
2	+++	+
Mucinous carcinoma		
1	+++	+
2	++	+
Variable epithelium		
1	++	+++
Serous borderline		
1	+	+

DICUSSION

Expression level of CD44 and its variants varies during development of various malignant tumors[18]. These variations can lead to the following changes; adhesion between the tumor cells and the extracellular matrix, increased invasion and induction of growth[18,19]. The overall prognostic role of CD44 is controversial in human cancers. Reduced expression of CD44 and its variants is associated with poor prognosis in melanoma, prostate and colorectal carcinom[20-22]. In the current study, Overall Survival (OS) was found as 89 ± 9 months in patients with mild (+) CD44 immunoreactivity, 78 ± 6 months in patients with moderate (++) CD44 immunoreactivity, and 66 months in patients with severe (+++) CD44 immunoreactivity. Only one of our cases was serous borderline type and she had mild (+) CD44 immunoreactivity. Although statistical significance was not observed with Long Rank statistical analysis due to the low number of cases, it was determined that the intensity of staining with CD44 was inversely proportional to the survival and it was found that there was a relationship between severe CD44 immunoreactivity and poor prognosis. It is thought that integrins, proteoglycans and other molecular mechanisms play a role in the implantation step of over cancer cells [23,24]. Epithelial ovarian cancers are spread by implantation of tumor cells in the peritoneal cavity along the mesothelium line. In vitro studies have suggested that CD44 on the surface of over cancer cells binds to hyaluran cover on mesothelial cells and contributes to peritoneal metastasis [25,26]. Monoclonal antibodies against CD44 inhibit the adhesion of over-cancer cells to mesothelial cells and peritoneal implants in mice[23-25]. In our study, severe (+++) CD44 immunoreactivity was observed during the metastatic process, but in other studies it was observed that CD44 decreased during tumor progression in mouse , and in human acidic tumor cells [27,28]. CD44 expression changes may have a role in malignant growth [29]. In our study, severe (+++) CD44 immunoreactivity was found in patients with tumor metastasis, and it was observed a correlation between CD44 immunoreactivity and stages of the patients. Although the biological function of CD 24 is not fully understood, In a study by Kristiansen G et al. it was observed that cancerous cells showed

immunoreactivity varying from membrane staining to dense cytoplasmic staining. In this study by Kristiansen G. et al. It was observed that 84% of patients with epithelial invasive carcinoma had cytoplasmic and 59% had membrane staining [30]. In our study, CD 24 immunoreactivity was observed on both cytoplasmic and cell membranes in all of the 30 invasive epithelial ovarian cancer samples. Cell membrane staining assessed as mild (+) immunoreactivity was observed in only one the serous borderline type pathology patient but cytoplasmic staining was not observed. The study by Kristiansen G. et al, it was reported that CD24 immunoreactivity was observed in 6 of the 8 cases on the cell membrane of borderline over-cancer cells and only one in the cytoplasmic pattern. They reported that cytoplasmic CD24 expression is associated with strong and independent short survival. [30]. In the current study, overall Survival (OS) was found as 78 ± 4 months in patients with mild (+) CD24 immunoreactivity, 82 ± 12 months in patients with moderate (++) CD24 immunoreactivity, and 78 ± 2 months in patients with severe (+++) CD24 immunoreactivity. There was no correlation between the severity of immunoreactivity and survival, and there was no statistically significant relationship between CD 24 positivity and survival in the evaluation of surveys performed by Long Rank statistical analysis. Kristiansen G. et al. reported that shorter survival rates in patients with cytoplasmic CD 24 expression. In our study, OS was 78 ± 4 months in patients with mild cell membrane immunoreactivity and 85 ± 7 months in patients with cytoplasmic immunoreactivity. It is thought that the cytoplasmic staining may have good prognostic value in the surveillance direction.

CD 24 immunoreactivity positivity could be evaluated as a tumor marker and could be used as a diagnostic marker for tumors [30]. CD 24 uses P-selectin, an adhesion receptor for the endothelial cells and platelets, and an adhesion receptor capable of contributing to the metastatic capacity of CD 24 expressing tumor cells, as ligand[31,32]. There is evidence that CD 24 may be pro-metastatic in tumor cells containing CD 24 using P-selectin as ligand[31,33]. P-selectin is produced in activated endothelial cells and platelets and plays an important role in the adhesion and migration of cells in the bloodstream. Hematogenous metastasis is uncommon and is seen in late stages in epithelial ovarian cancers. Peritoneal mesothelial cells do not expreses P-selectin, so metastatic spread in the peritoneal cavity is not due to CD 24-P-selectin interaction. Interaction between the tumor and the mesothelium may be mediated by another unknown ligand of CD 24. Post-transplant B-cell proliferation syndrome may be treated with antibodies specific to intravenous CD 21 and CD 24, and similarly it may be used as a future treatment option in ovarian-cancer with cytoplasmic CD 24 immunoreactivity [34,35].

CONCLUSION

The staining intensity of CD44 immunoreactivity was related to the survival rate in ovarian epithelial cancers, but it was not statistically significant. Although the association with survival of CD 24 was not found to be statistically significant, it was thought that it could be used as a diagnostic marker in over-tumors.

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