Cd44

by Indah Puspasari

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ORIGINAL ARTICLE

Association of high expression of CD44 in clinicopathological factors of endometrial cancer

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ABSTRACT

BACKGROUND: Clinical stages, histologic type, degree of cell differentiation, myometrial invasion, and lymph-vascular space invasion (LVSI) have been identified as clinicopathological factors that are predictive for endometrial cancer, however, further prognostic indicators are still required to account for the heterogeneity of this cancer. Adhesion molecule CD44, affects the invasion, metastasis, and prognosis of many forms of cancer. The purpose of this study is to examine the expression of CD44 in endometrial cancer and its correlation with established prognostic variables.

METHODS: A cross-sectional study was conducted on 64 samples of endometrial cancer from Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital. Immunohistochemical analysis was used to detect CD44 expression using mouse anti-human CD44 monoclonal antibody. Differences in Histoscore were studied to determine the association between CD44 expression and clinicopathological factors of endometrial cancer.

RESULTS: Of the overall sample, 46 samples were in the early stage, whereas 18 samples were in the advanced stage. High expression of CD44 was associated with advanced stage compare than early stage (P=0.010), poor differentiation compare than well-moderate differentiation (P=0.001), myometrial invasion >50% compare than myometrial invasion <50% (P=0.004), and positive LVSI compare than negative LVSI (P=0.043) in endometrial cancer, but not associated with histological type of endometrial cancer (P=0.178).

CONCLUSIONS: High expression of CD44 may be considered as a poor prognostic marker and predictive marker for targeted therapy in endometrial cancer.

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KEY WORDS: Endometrial neoplasms; Human CD44 protein; Histological techniques; Immunohistochemistry.

With an incidence of 61,880 cases in 2019, endometrial cancer is the most prevalent gynecologic cancer among women in the USA.[1] In Southeast Asia, it ranks third after cervical and ovarian cancer, with an incidence of 26,091 cases in 2018.[2]

Clinical stages, histologic type, degree of differentiation, myometrial invasion, and lymph-vascular space invasion (LVSI) are clinicopathological variables that have been established as prognostic indicators for endometrial cancer, however more predictive variables are still required to account for the heterogeneity of this cancer. Many molecular biology researches have been conducted recently to investigate the relationship with endometrial cancer, and CD44 is one of the molecules connected to the occurrence and prognosis of endometrial cancer.[3]

One of the surface indicators of CSCs is CD44, which is a member of a family of adhesion mol-

ecules involved in the invasion, migration, and metastasis of many cancers. The CD44 isoform is thought to promote tumor growth in some malignancies, but CD44 is thought to decrease tumor growth in other cancers. Since CD44 is expressed in normal cells at various levels and not just in cancer cells, it is clear that CD44 is crucial for maintaining normal cell function.[4]

Increased expression of CD44 and its variations has been linked to disease progression, metastasis, and a worse prognosis in a variety of cancers, including colorectal cancer, lung cancer, breast cancer, leukemia, lymphoma, melanoma, pancreatic cancer, and head and neck cancer.[5-9] Ovarian cancer has been extensively researched in relation to gynecological cancer, and it has been established that CD44 also contributes to the development, prognosis, and resistance of ovarian cancer chemotherapy.[10-12] The decrease of CD44 expression, on the other hand, is associated with a worse prognosis in cancers such as atypical carcinoid, non-planoepithelial lung cancer, neuroblastoma, bladder, and prostate.[13-16] This demonstrates the tissue-specificity and intricacy of CD44 regulation in cancer.

Materials and methods

This study is an observational study with a cross-sectional design, using a population of all endometrial cancer cases at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital from January 2016 to December 2020 which has complete medical record data and intact paraffin blocks. Cases of double primary tumors were excluded from this study.

Paraffin blocks containing endometrial cancer specimens were cut with a 3 m thick microtome and placed on a custom slide (covered with poly L lysine), which was then dried at 37 °C and heated on a slide heater at 60 °C for 30 minutes. After that, the paraffin was removed using graded xylol (xylol I, II, and III, for 5 minutes each), and the paraffin was rehydrated with serial alcohol (96% 2 80%, respectively, for 4 minutes). Utilizing 1.5% hydrogen peroxide in methanol for 10 minutes at room temperature, then blocking. Tris EDTA (ethylene diamine tetraacetic acid pH 9.0) was used as a pretreatment for the preparation, which was then chilled for 45 minutes and rinsed in PBS (phosphate buffered saline). After that, it was continued with non-specific protein blocking using Background Sniper Universal for 15 minutes.

To detect CD44, specific antibodies against CD44 (Monoclonal anti-human CD44) were taken from mice. The preparations were incubated with CD44 primary antibody (dilution 1:200), for 1 hour at room temperature and then washed with S (pH 7.4) for 5 minutes. The preparations were then incubated with secondary antibody against biotin-labeled mouse immunoglobulin (Tr kie Universal Link) for 20 minutes, and the preparations were washed again in PBS (pH 7.4) for 5 minutes. The next step was incubatio ith trackAvidin-HRP labeled for 15 minutes, then washed in PBS (pH 7.4) for 5 minutes. Then, diaminobenzene (DAB) was mixed with 1mL of substrate and then vortexed for 15 seconds. The substrate containing DAB was dripped o the preparation and incubated for 2 minutes, then washed with running water for 10 minutes.

Counterstained was performed with CAT (Counterstain Kit) hematoxylin, then the preparation was immersed in saturated lithium car ate (5% in distilled water) for 5 seconds, then washed with running water for 5 minutes. Then dehydrated with graded alcohol (80%, 96%, absolute, absolute) for 5 minutes each and cleared with graded xylol (xylol I, II, and III) for 5 minutes each. The preparation was covered using a mounting solution and a cov glass.

For each smear included an internal positive control on the stromal tissue and a negative control without providing primary antibodies. Then the CPI was examined by giving Mouse anti-Human CD44 Monoclonal Antibody. The CPI preparations were observed using a Leica ICC 50 HD microscope by two independent observers.

This research has obtained ethical approval from the Health Research Ethics Committee of Hasanuddin University Hospital and Dr. Wahidin Sudirohusodo Hospital (n. 603/ 4.6.4.5.31/ PP36/2020).

Statistical analysis

The data obtained were processed using IBM SPSS v. 26 program. CD44 expression was calculated semiquantitatively using a Histoscore by multiplying the staining intensity (unstained:

0, seen at 400× magnification: +1, seen at 100× magnification: +2, seen at 40× magnification: +3) by percentage of area stained. The median Histoscore of all samples was used as a cut-off point to determine high and low expression. The Chi-square test was used to examine the correlation between CD44 expression and clinical stages, histological type, degree of differentiation, myometrial invasion, and LVSI. If the P value <0.05, the findings are deemed to be significant.

Results

Sixty-four samples were obtained over the study period. The majority of samples were over 50 years old (64.1%), premenopausal (56.3%), nulliparous (48.5%), had a normal BMI (40.6%), and had no history of either hypertension (78.1%) or diabetes (87.5%). Most samples for endometrial cancer's pathological characteristics were stage I-II (71.9%), endometrioid type (82.5%), grade 1-2 (65.6%), had <50% myometrial invasion (51.6%), and had negative LVSI (67.2%) (Table I).

All samples had a median Histoscore of 100, after which the samples were divided into two categories: high expression (Histoscore ≥100) and low expression (Histoscore <100) (Table II).

The proportion of high CD44 expression was higher in stage III-IV endometrial cancer (88.9%) than in stage I-II endometrial cancer (50.0%). There was a correlation between CD44 expression and endometrial cancer stage (chi square, P=0.010). High CD44 expression has an 8 times chance of developing stage III-IV endometrial cancer compared to low CD44 expression.

TABLE I.—*Sample characteristics.*

Characteristics	Frequency	Percentage (%)
Parity		
Nullipara	31	48.5%
1-2	18	28.1%
≥3	15	23.4%
Hypertension		
Yes	14	21.9%
No	50	78.1%
Diabetes mellitus		
Yes	8	12.5%
No	56	87.5%
Body Mass Index		
Underweight	7	10.9%
Normal	26	40.6%
Overweight	21	32.8%
Obese	10	15.6%
Clinical stages		
I-II	46	71.9%
III-IV	18	28.1%
Histologic types		
Endometrioid	53	82.8%
Non endometrioid	11	17.2%
Grade		
1-2	42	65.6%
3	22	34.4%
Myometrial invasion		
<50%	33	51.6%
≥50%	31	48.4%
Lymph-vascular space invasion		
Positive	21	32.8%
Negative	43	67.2%

TABLE II.—*Correlation between CD44 expression and clinicopathological factors of endometrial cancer.*

Clinicopathological Factors	CD44				Odds ratio	95% CI	P value
	High expression		Low expression				
	N.	%	N.	%			
Clinical stages					8	1.649-38.821	0.01
I-II	23	50%	23	50%			
III-IV	16	88.9%	2	11.1%			
Histologic types					3.45	0.679-17.531	0.178
Endometrioid	30	56.6%	23	43.3%			
Non endometrioid	9	81.8%	2	18.2%			
Grade					12.105	2.205-58,503	0.001
1-2	19	45.2%	23	54.8%			
3	20	90.9%	2	9.1%			
Myometrial invasion					5.655	1.832-17.455	0.004
<50%	14	42.2%	19	57.6%			
>50%	25	80.6%	6	19.4%			
Lymph-vascular space invasion					4.057	1.171-14.054	0.043
Positive	17	81%	4	19%			
Negative	22	51.2%	21	48.8%			

The proportion of high CD44 expression was higher in non-endometrioid type endometrial cancer (81.8%) than in endometrioid type endometrial cancer (56.6%). There was no significant correlation between CD44 expression and histological type of endometrial cancer (chi square, P=0.178).

The proportion of high CD44 expression was higher in endometrial cancer with a degree of differentiation 3 (90.9%) than in endometrial cancer with a degree of differentiation 1-2 (45.2%). There was a correlation between CD44 expression and the degree of differentiation of endometrial cancer cells (chi square, P=0.001). High CD44 expression has a 12.105 times chance of developing with poorly differentiated endometrial cancer compared to low CD44 expression.

The proportion of high CD44 expression was higher in endometrial cancer with positive LVSI (81%) than in endometrial cancer with negative LVSI (51.2%). There was a correlation between CD44 expression and LVSI in endometrial cancer (chi square, P=0.043). High CD44 expression has 4,057 times chance of developing endometrial cancer with positive LVSI compared to low CD44 expression (Figure 1, 2).

Discussion

Cancer is most likely curable when diagnosed at an early stage through conventional treatments such as surgery, chemotherapy, and radiotherapy. However, even though cancer is diagnosed and treated at an early stage, some residual cells remain and over time these cells can cause recurrence and often become more aggressive. Growing evidence has implied that these residual cells have the properties/functions of stem cells known as cancer stem cells (CSC).[17] In recent decades, the CSC theory has generated a great deal of attention, where scientists believe it will revolutionize our understanding of cellular and molecular events during cancer development that contribute to therapy resistance, recurrence and metastasis.

CSCs have similar properties to normal stem cells, including the ability to self-renewal and differentiate. Because of this similarity, CSCs are usually characterized by the expression of stem cell-associated surface markers, one of which is CD44, from which this surface marker can be isolated *in vitro* and *in vivo*.[18] Although research studies on CSCs have been numerous, there is still controversy about the origin of

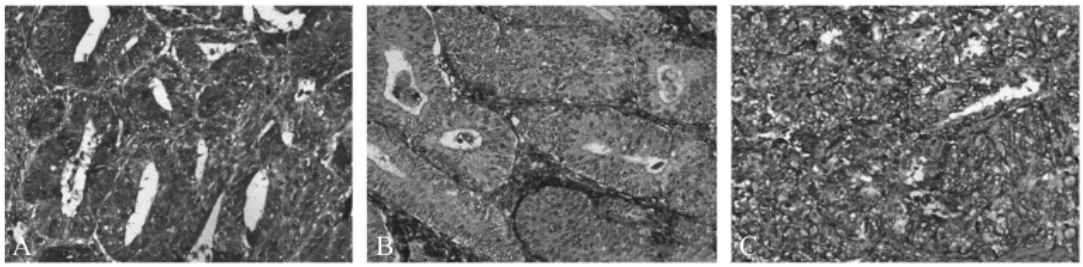

Figure 1.—Expression of CD44 in endometrial cancer based on color intensity: A) expression of CD44 +1; B) expression of CD44 +2; C) expression of CD44 +3.

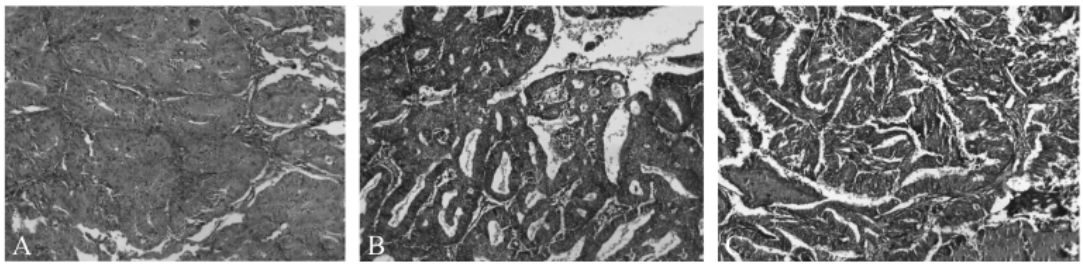

Figure 2.—Expression of CD44 in endometrial cancer by percentage of stained area: A) expression of CD44 5%; B) expression of CD44 40%; C) expression of CD44 90%.

CSCs, whether they arise from normal stem cells or non-stem cells. In addition, the actual phenotype and function are still controversial.

CD44 is one of the surface markers of CSCs, belonging to a family of adhesion molecules that play a role in the invasion, migration, and metastasis of various types of cancer. In certain cancers, the CD44 isoform is considered a promoter of tumor development, whereas in other cancers, CD44 is considered a tumor suppressor. Not only in cancer cells, CD44 is also expressed in normal cells at different levels, which indicates that CD44 is also an essential component of normal cell function.[4]

Increased expression of CD44 and its variants has been associated with disease progression, metastasis and poorer prognosis in colorectal cancer, lung cancer, breast cancer, leukemia, lymphoma, melanoma, pancreatic cancer, and head and neck cancer.[5-9] In gynecological cancer, ovarian cancer has been extensively studied, and it is proven that CD44 also plays a role in the progression, prognosis, and resistance of ovarian cancer chemotherapy.[10-12] On the other hand, loss of CD44 expression correlates with poorer prognosis in atypical carcinoid, non-planoepithelial lung cancer, neuroblastoma, bladder and prostate cancer.[13-16] This reflects the complexity of CD44 regulation in cancer, and its tissue specificity.

Several studies have shown that CD44 may play a role in carcinogenesis and prognosis of endometrial cancer, but the results are inconsistent. Most studies reported a change in CD44 expression, but these changes varied, some reported an increase in CD44 expression, some reported the opposite.

In this study, positive CD44 expression was found in all samples and high CD44 expression was associated with advanced endometrial cancer, poorer differentiation, myometrial invasion 50%, and positive LVSI. These results are consistent with several studies that have shown that endometrial cancer cells express CD44 more intensively than normal endometrium, and that CD44 expression is significantly higher in endometrial cancers with positive LVSI, >50% myometrial invasion, and advanced stages.[19-23] Hoshimoto *et al.* in their study concluded that CD44 expression is associated with the development, invasion, and metastasis of endometrial cancer, and the detection of CD44 variants, namely CD44v3 and CD44v6, can be useful diagnosing endometrial cancer and predicting its invasiveness. CD44v3 affects prognosis through lymph node metastasis, whereas CD44v6 affects prognosis independently.[24]

This study showed that both endometrioid and non-endometrioid endometrial cancers both had high CD44 expression. Research by El-Shorbagy *et al.* found that endometrioid endometrial cancer expressed significantly higher CD44 than serous type, which means that CD44 was associated with a better prognosis endometrial cancer.[25] Fujita *et al.* found that expression of CD44 and its variants was found in most normal endometrial tissue from both immunohistochemistry and reverse transcription polymerase chain reaction (RT-PCR), whereas >70% of endometrial cancer tissue did not express CD44 and this negative expression of CD44 was associated with LVSI is positive.[21] A study by Wojciechowski concluded that increased expression of CD44 may play a role in endometrial cancer carcinogenesis, but its role is not crucial, and it is not statistically proven that CD44 expression is associated with clinicopathological parameters of endometrial cancer.[26]

There are several factors that may cause the results of existing studies to vary. For example, different assay methods detect CD44, such as immunohistochemistry or RT-PCR, with different antibodies, which makes it difficult to compare results because some CD44 epitopes may not be targeted by some antibodies. In addition, tumor heterogeneity may also play a role.

This study used the Histoscore to assess CD44 expression in endometrial cancer tissue. The Histoscore was chosen because it is a semi-quantitative examination, so as to minimize the subjectivity of histopathological examination results. However, studies similar to this study have not yet used the Histoscore as an assessment criterion, making it difficult to compare the results of this study with the existing literature.

Limitations of the study

This study has several limitations, including: the small sample size, the heterogeneity of the samples, and the investigated marker's apparent lack of specificity given that it is elevated in many other malignant conditions.

Conclusions

High expression of CD44 may be considered as a marker of poor prognosis in endometrial cancer. With a greater understanding of the fundamental principles underlying how CD44 is regulated and identified, effective therapeutic approaches that attempt to eradicate cancer stem cells by targeting CD44 may be developed, providing new hope for endometrial cancer patients.

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