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Expression of CD44 Alternative Splicing Variants in Primary and Lymph Node Metastatic Lesions of Gynecological Cancer

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ABSTRACT

CD44 is known as an adhesion molecule which is involved in lymphocyte activation and lymphocyte homing. In recent years, its role in the invasion and metastasis of malignant tumors has attracted the attention of investigators.

In this study, the expression of CD44 variants was investigated in primary lesions and metastasis into the lymph node in 53 patients with gynecological cancer.

The following patients with various types of gynecological carcinoma, established by operation and pre-treatment biopsy, were included in this study: 19 patients with cancer of the uterine cervix, 23 with cancer of the uterine endometrium, and 11 with ovarian cancer. Tissue samples were obtained from a primary lesion and a nodal metastasis of each patient, and immunohistochemical staining was performed by the ABC method through the use of monoclonal antibodies against CD44v1–10. Specimens proving CD44v1–10 positive were then submitted to immunohistochemical staining through the use of monoclonal antibodies against CD44v6 and CD44v9. Expression of CD44v was judged positive when DAB revealed color development, irrespective of the degree of staining intensity.

CD44v were all expressed in the cancer cell membrane. In normal endometrium, expression of CD44v1–10 and v9 was observed in the endometrial gland cell membrane. In normal ovarian tissues, CD44v6 and v9 were not detected.

The expression of CD44v6 in patients with endometrial cancer was noted in 13 (72.2%) of 18 patients with vascular invasion and in one (20.0%) of 5 patients without it, indicating a significant relation to vascular invasion. It was also remarkably higher in those for whom the invasion exceeded 1/2 of the myometrium than in those for whom the invasion did not exceed 1/2 of the myometrium, and was higher too in advanced stages and in node-positive patients. In one patient, CD44v6 was detected not in the primary lesion but in the nodal metastasis. The expression of CD44v6 in patients with ovarian cancer occurred more frequently in node-positive patients.

Our study results suggest that the expression of CD44v6 in endometrial adenocarcinoma cells is involved in the progression of the carcinoma, nodal metastasis, myometrial invasion, and vascular invasion, and that in ovarian cancer, the expression of CD44v6 is involved in nodal metastasis.

Key words: *CD44 variant 6, Endometrial adenocarcinoma cells, Ovarian carcinoma*

With regard to the onset mechanism of cancer metastasis, cancer cells released from a primary lesion infiltrate into the surrounding connective tissue and invade into the blood vessels, from where they adhere and implant in the capillary blood vessels of a target organ. After leaking back out of the capillary blood vessels, the cancer cells then establish a microcirculatory environment, through blood vessel formation or other actions, to grow and form a metastatic lesion. Thus, factors regulating the capacity of a cancer cell to cause metastasis are complicated, and a variety of regulatory factors expressed by cancer cells may be involved in the metastasis.

CD44 is known as an adhesion molecule which is involved, among other functions, in T-cell activation and information transmission[5,14,31], lymphocyte homing[15,28], myelopoiesis[24], and the dissemination of cancer[2,11,33]. In recent years, its role in invasion and metastasis of malignant tumors has attracted the attention of investigators[23,35], and it has been suggested that the adhesion molecule is useful for the diagnosis of early stage carcinoma in breast cancer or colorectal cancer.

CD44 is a glycoprotein which penetrates into the membrane[6,10,16,32]. The gene of standard form was first cloned from human by Seed[32] and

Butcher et al[10]. With regard to variant forms of CD44, 20 exons are identified at present. It is known that Exons 1–5, 16, and 17 undergo splicing in the constant region, whereas Exons 6–15 (variant 1–10) located in the extracellular region undergo splicing irregularly[36,37]. In variant regions, into which the molecule can go in a variety of combinations, it exists in various forms on cells[13,29]. Previous studies have pointed out variation in the intracellular region, and it has been proved that this variation is caused by the irregular splicing of Exons 19 and 20[30]. More recently, Matsumura et al have proved in urinary bladder carcinoma that not only addition of exons but also introns, which continue to follow the exons, are incorporated in transcription products[22].

CD44 possesses a variety of functions. Its biochemical and cytobiologic features may communicate between extracellular matrix which are collagen[4] or hyaluronic acid[1,25] and cytoskeleton[4,19], and may be involved in homo-[36] or hetero-type[15,31] cell adhesion. In addition, it has been pointed out that CD44 accelerates an interaction between surface molecules on other cells and their ligands[12]. However, which function of CD44 is involved in the process of forming the metastasis has not yet been understood. The sole finding obtained so far in this respect is that in melanoma cells, CD44 is involved in a process of adhesion to vascular endothelial cells[27].

In this study, expression of the CD44 variant 1–10 (v1–10) was investigated in primary lesions and metastasis into the lymph nodes in 53 patients with gynecological cancer. In those in whom the expression of CD44v1–10 was noted, expression of CD44 variant 6 (v6) and variant 9 (v9), both of which have been shown to be related to the metastasis of cancer in other organs, were also investigated, and the relation of CD44v6 and v9 to lymph node metastatic lesions was evaluated.

MATERIALS AND METHODS

Of women who underwent an operation or radiotherapy at the Department of Obstetrics and Gynecology at Hiroshima University School of Medicine between 1984 and 1995, the following patients with various types of gynecological carcinoma established by operation and pre-treatment biopsy were included in this study: 19 patients with cancer of the uterine cervix (17 with squamous cell carcinoma and 2 with adenocarcinoma), 23 with cancer of the uterine endometrium (14 with adenocarcinoma, 5 with adenosquamous carcinoma, and 4 with adenoacanthoma), and 11 with ovarian cancer (6 with serous adenocarcinoma, one with endometrioid adenocarcinoma, 2 with clear cell adenocarcinoma, one with yolk sac tumor, and one with dysgerminoma). Evaluation of the clinical progress of each cancer type revealed the following: in patients with cancer of the uterine cervix, 2 patients were classified as Stage 0, 6 as Stage I, 7 as Stage II, 2 as Stage III, and 2 as Stage IV; in those with cancer of the uterine endometrium, 10 as Stage I, 4 as Stage II, 6 as Stage III, and 3 as Stage IV; and in those with ovarian cancer, 2 as Stage I, 2 as Stage II, 4 as Stage III, and 3 as Stage IV. Nodal metastasis was noted in 11 patients with cancer of the uterine cervix, 13 with cancer of the uterine endometrium, and 5 with ovarian cancer. We also performed the same investigation on normal uterine cervical epithelium, endometrium, and ovaries. The expression of the CD44v1–10 was not investigated in normal ovaries.

Tissue samples were obtained from a primary lesion and a nodal metastasis from each patient, fixed in 10% formalin, and embedded in paraffin. The deparaffinized tissue specimens were then pretreated with microwaves and subjected to immunohistochemical staining by the ABC method through the use of monoclonal antibodies against CD44v1–10 (20 μg/ml, Novocastra Company). Specimens proving CD44v1–10 positive were then submitted to immunohistochemical staining through the use of monoclonal antibodies against CD44v6 (1 μg/ml, R&D system Europe Company) and monoclonal antibodies against CD44v9 (1 μg/ml, Biochemistry Industries Company).

Expression of CD44v was judged negative when cancer cell membrane showed negative, and positive when it showed a positive color irrespective of the degree of staining. In the case of adenosquamous carcinoma and adenoacanthoma in the group with cancer of the uterine endometrium, expression was judged positive when an intense positive color showed in the cell membrane of the adenocarcinoma.

The expression of CD44v was analyzed separately for primary lesions and for nodal metastasis. With regard to the primary lesions, analysis was performed by individual clinical progress stage, by the presence or absence of nodal metastasis, by individual histological types, and by presence or absence of vascular invasion. For statistical analysis, Fisher's exact test and the Chi-square test were used.

RESULTS

Immunohistochemical findings of CD44v expression-positive primary lesions and nodal metastasis are shown in Figs. 1–3 and Figs. 4–6, respectively. In these specimens, CD44v1–10, v6, and v9 were all expressed in the cancer cell membrane. In normal cervical squamous epithelium, expression of CD44v1–10, v6, and v9 was noted in the basal cell layer through to the middle cell layer of the stratified squamous epithelium, whereas in normal cervical glandular epithelium, none of the CD44v types was detected. The dif-

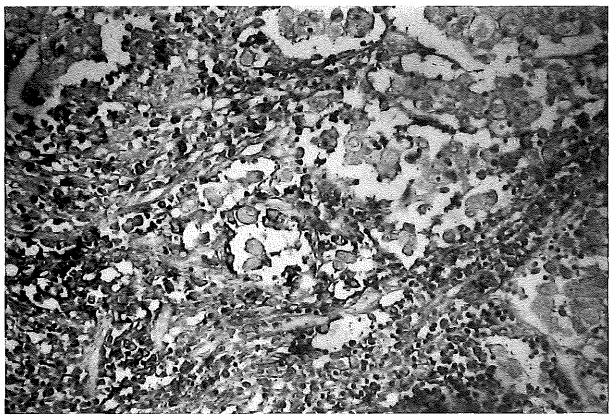

Fig. 1. Histological micrographs of CD44v expression-positive primary lesions: CD44v1–10 was expressed in the cancer cell membrane.

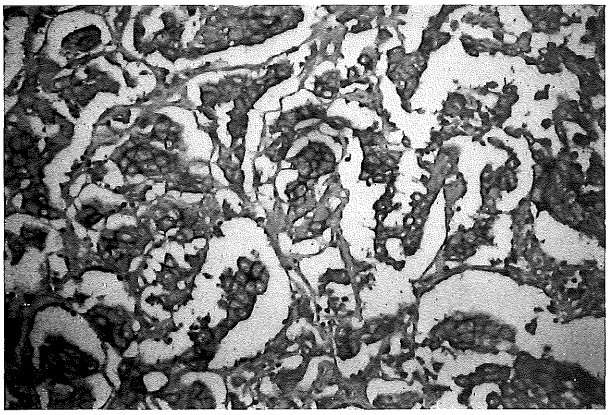

Fig. 2. Histological micrographs of CD44v expression-positive primary lesions: CD44v6 was expressed in the cancer cell membrane.

Fig. 3. Histological micrographs of CD44v expression-positive primary lesions: CD44v9 was expressed in the cancer cell membrane.

Fig. 4. Histological micrographs of CD44v expression-positive nodal metastatic lesions: CD44v1–10 was expressed in the cancer cell membrane.

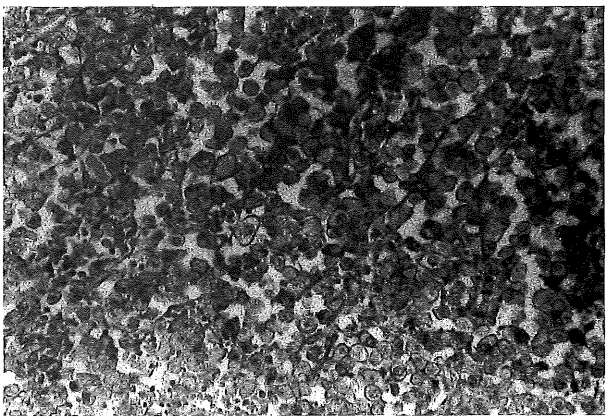

Fig. 5. Histological micrographs of CD44v expression-positive nodal metastatic lesions: CD44v6 was expressed in the cancer cell membrane.

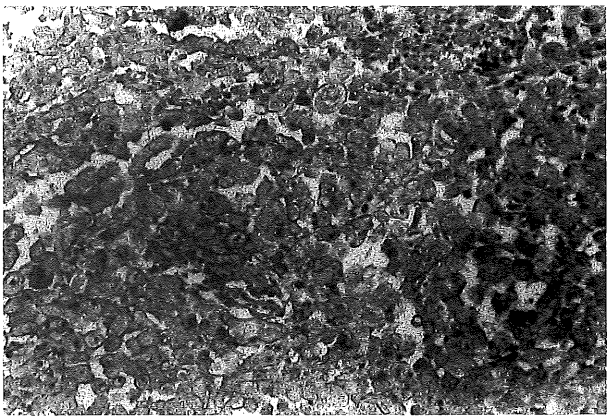

Fig. 6. Histological micrographs of CD44v expression-positive nodal metastatic lesions: CD44v9 was expressed in the cancer cell membrane.

fuse type in the staining of uterine cancer and ovarian cancer was various. In normal endometrium, expression of CD44v1–10 and v9 was observed in the endometrial gland cell membrane. In normal ovarian tissues, CD44v6 and v9 were not detected.

Table 1 shows the expression of CD44v in patients with squamous cell carcinoma of the uterine cervix. In almost all patients, expression of CD44v1–10, v6, and v9 was noted both in the primary lesions and nodal metastasis.

Table 2 shows patients with uterine cervical adenocarcinoma who presented a positive expression of CD44v. Patients No. 1 and 2 showed nodal metastasis and vascular invasion. In patient No. 1, the expression of CD44v9 was noted in both the primary lesion and the nodal metastasis. In Patient No. 2, the expression of CD44v6 was noted in the primary lesion, and CD44v6 and v9 in the nodal metastasis.

Table 3 shows the expression of CD44v in patients with endometrial cancer. CD44v1–10, v6, and v9 were detected in both the primary lesions and nodal metastasis. Evaluation of the expression in the primary lesions by individual clinical stages revealed that the rates of detection of CD44v1–10, v6, and v9 were all higher in advanced stages, and the same finding was observed by the new FIGO stage classification (1988). Analysis according to the presence or absence of nodal metastasis revealed that the rate of expression of CD44v1–10, v6, and v9 were all higher in node-positive patients. In particular, expression of CD44v6 was found in 10 (76.9%) node-positive patients but in only 4 (40.0%) node-negative patients. The expression of CD44v9 was detected in all node-positive patients and in 5 (50.0%) node-negative patients. Analysis by individual histological type revealed the expression of CD44v1–10 in 12 (85.7%) of 14 patients with adenocarcinoma, in all patients with adenosquamous carcinoma, and in all patients with adenoacanthoma. The expression of CD44v6 was noted in 6 (42.9%) patients with adenocarcinoma, in all

Table 1. Expression of CD44 splicing variants in squamous cell carcinoma of the uterine cervix

		CD44v1–10 expression		CD44v6 expression		CD44v9 expression	
		positive cases	p.	positive cases	p.	positive cases	p.
Primary lesions	(n=17)	17(100.0%)		16 (94.1%)		17 (100.0%)	
Stage							
0	(n=2)	2 (100.0%)	NS*	2 (100.0%)	NS*	2 (100.0%)	NS*
I	(n=5)	5 (100.0%)		4 (80.0%)		5 (100.0%)	
II	(n=6)	6 (100.0%)		6 (100.0%)		6 (100.0%)	
III	(n=2)	2 (100.0%)		2 (100.0%)		2 (100.0%)	
IV	(n=2)	2 (100.0%)		2 (100.0%)		2 (100.0%)	
L.N. metastasis							
present	(n=9)	9 (100.0%)	NS**	9 (90.9%)	NS**	9 (100.0%)	NS**
absent	(n=8)	8 (100.0%)		7 (87.5%)		8 (100.0%)	
Vascular invasion							
present	(n=13)	13 (100.0%)	NS**	12 (92.3%)	NS**	13 (100.0%)	NS**
absent	(n=4)	4 (100.0%)		4 (100.0%)		4 (100.0%)	
L.N. metastatic lesions	(n=5)	5 (100.0%)		5 (100.0%)		4 (80.0%)	

L.N. lymph node
* Chi-square test
** Fisher's exact test
significant results with $p \leqq 0.05$

Table 2. Characteristics of cervical adenocarcinoma patients and CD44 splicing variants expression

Sample No.	Stage	L.N. metastasis	V.I.	primary lesions			lymph node metastatic lesions		
				v1–10	v6	v9	v1–10	v6	v9
1	Ib	+	+	+	−	+	+	−	+
2	IIa	+	+	+	+	−	+	+	+

L.N. lymph node
V.I. vascular invasion

Table 3. Expression of CD44 splicing variants in endometrial carcinoma

		CD44v1–10 expression		CD44v6 expression		CD44v9 expression	
		positive cases	p.	positive cases	p.	positive cases	p.
Primary lesions	(n=23)	21 (91.3%)		14 (60.9%)		18 (78.3%)	
Stage							
I	(n=10)	8 (80.0%)	NS*	5 (50.0%)	NS*	7 (70.0%)	NS*
II	(n=4)	4 (100.0%)		2 (50.0%)		3 (75.0%)	
III	(n=6)	6 (100.0%)		4 (66.7%)		5 (83.3%)	
IV	(n=3)	3 (100.0%)		3 (100.0%)		3 (100.0%)	
FIGO stage, 1988							
I	(n=3)	1 (33.3%)	NS*	0 (0%)	NS*	0 (0%)	NS*
II	(n=2)	2 (100.0%)		1 (50.0%)		1 (50.0%)	
III	(n=14)	14 (100.0%)		10 (71.4%)		13 (92.9%)	
IV	(n=4)	4 (100.0%)		3 (75.0%)		4 (100.0%)	
L.N. metastasis							
present	(n=13)	13 (100.0%)	NS**	10 (76.9%)	NS**	13 (100.0%)	0.0075**
absent	(n=10)	8 (80.0%)		4 (40.0%)		5 (50.0%)	
Histology							
adenocarcinoma (G1)	(n=10)	8 (80.0%)	NS**	3 (30.0%)		5 (50.0%)	NS**
adenocarcinoma (G2)	(n=3)	3 (100.0%)		2 (66.7%)	0.026**	3 (100.0%)	
adenocarcinoma (G3)	(n=1)	1 (100.0%)		1 (100.0%)	0.045**	1 (100.0%)	
adenosquamous cell carinoma	(n=5)	5 (100.0%)		5 (100.0%)		5 (100.0%)	
adenoacanthoma	(n=4)	4 (100.0%)		3 (75.0%)		4 (100.0%)	
Myometrial invasion							
limited to endometrium	(n=3)	2 (66.7%)	NS*	1 (33.3%)	NS*	1 (33.3%)	NS*
≦1/2	(n=9)	8 (88.9%)		5 (55.6%)		8 (88.9%)	
>1/2	(n=11)	11 (100.0%)		10 (90.9%)		9 (81.8%)	
Vascular invasion							
present	(n=18)	17 (94.4%)	NS**	13 (72.2%)	NS** (0.034*)	15 (83.3%)	NS**
absent	(n=5)	4 (80.0%)		1 (20.0%)		3 (60.0%)	
L.N. metastatic lesions	(n=13)	8 (61.5%)		7 (53.8%)		8 (61.5%)	

L.N. lymph node
*Chi-square test
**Fisher's exact test
significant results with p≦0.05

patients with adenosquamous carcinoma, and in 3 (75.0%) patients with adenoacanthoma, and the expression of CD44v6 in patients with adenocarcinoma was significantly lower than in patients with adenosquamous cell carcinoma. The expression of CD44v9 was noted in 9 (64.3%) patients with adenocarcinoma, in all patients with adenosquamous carcinoma, and in all patients with adenoacanthoma. In adenocarcinoma, the CD44-v6- and v9-positive rates tended to be higher as the cancer was poorly differentiated.

Analysis by the presence or absence of myometrial invasion revealed that the rates of expression of CD44v1–10, v6, and v9 were all higher in patients with myometrial invasion. In particular, The expression of CD44v6 was remarkably higher in those for whom the invasion exceeded 1/2 of the myometrium than in those for whom it did not exceed 1/2 of the myometrium. Analysis by the presence or absence of vascular invasion revealed that the rates of expression of CD44v1–10, v6, and v9 were all higher in patients with vascular invasion than in those without it. Specifically, the expression of CD44v6 was noted in 13 (72.2%) of 18 patients with vascular invasion and in one (20.0%) of 5 patients without it, indicating a significant relation to vascular invasion. The rates of expression of CD44v1–10, v6, and v9 were all lower in nodal metastasis than in primary lesions. In one patient, CD44v6 was detected not in the primary lesion but in the nodal metastasis.

Table 4 shows the expression of CD44v in patients with ovarian cancer. Evaluation of the expression in primary lesions revealed no relation to clinical stage. Analysis by the presence or absence of nodal metastasis revealed that expression of CD44v6 was noted in all node-positive patients but in only 3 (50.0%) node-negative patients. Thus, expression of CD44v6 occurred more

Table 4. Expression of CD44 splicing variants in ovarian carcinoma

		CD44v1–10 expression		CD44v6 expression		CD44v9 expression	
		positive cases	p.	positive cases	p.	positive cases	p.
Primary lesions	(n=11)	10 (90.9%)		8 (72.7%)		7 (63.6%)	
Stage							
I	(n=2)	2 (100.0%)	NS*	2 (100.0%)	NS*	2 (100.0%)	NS*
II	(n=2)	2 (100.0%)		0 (0%)		1 (50.0%)	
III	(n=4)	3 (75.0%)		3 (75.0%)		3 (75.0%)	
IV	(n=3)	3 (100.0%)		3 (100.0%)		1 (33.3%)	
L.N. metastasis							
present	(n=5)	5 (100.0%)	NS**	5 (100.0%)	NS**	3 (60.0%)	NS**
absent	(n=6)	5 (83.3%)		3 (50.0%)		4 (66.7%)	
Histology							
serous cystadenocarcinoma	(n=6)	6 (100.0%)	NS**	5 (83.3%)	NS**	5 (83.3%)	NS**
endometrioid adenocarcinoma	(n=1)	1 (100.0%)		1 (100.0%)		1 (100.0%)	
clear cell adenocrcinoma	(n=2)	1 (50.0%)		1 (50.0%)		1 (50.0%)	
yolk sac tumor	(n=1)	1 (100.0%)		0 (0%)		0 (0%)	
dysgerminoma	(n=1)	1 (100.0%)		1 (100.0%)		0 (0%)	
L.N. metastatic lesions	(n=4)	4 (100.0%)		3 (75.0%)		1 (25.0%)	

L.N. lymph node significant results with $p \leqq 0.05$
* Chi-square test
** Fisher's exact test

frequently in node-positive patients. No significant differences were obtained in the expression of CD44v1–10 or v9 between node-negative and node-positive patients. Analysis by individual histological type revealed that the rate of expression of CD44v1–10 was 50% for clear cell adenocarcinoma, although in the other types, no great differences were noted. Among ovarian adenocarcinoma, the rates of expression of both CD44v6 and v9 were as high as over 80% in serous adenocarcinoma. The expression of CD44v9 was not noted in yolk sac tumor or dysgerminoma. The expression of CD44v1–10 and v6 occurred more frequently in nodal metastasis than in primary lesions, although all patients who showed expression in the nodal metastasis also showed expression in the primary lesions. The expression of CD44v9 occurred more frequently in primary lesions than in nodal metastasis.

DISCUSSION

With regard to the relation of the expression of CD44 variants to the infiltration and metastasis of cancer[23,35], the involvement of v6 and v8–10 has been especially pointed out. It has been shown that CD44v6 is involved in metastasis forming in pancreatic carcinoma, breast cancer, and colorectal cancer. In pancreatic carcinoma, Günthert et al[11] and Koopman et al[21] conducted experiments using cell strains, and their results support the involvement of v6 in metastasis formation. In breast cancer, irregular splicing of CD44 occurs in the early stage of tumor development and overexpression in the v6 region is pointed out[23]. In colorectal cancer, immunological staining through the use of monoclonal or polyclonal antibodies reveals the relation of the adhesion molecule to the progression and metastasis of tumors and a possibility that the adhesion molecule may be employed as a factor in predicting the prognosis[26,37].

An immunohistochemical study of CD44v8–10 in gastric cancer has indicated a possibility that v8–10 may not correlate with histological type, depth of invasion, or nodal metastasis, although it may accelerate hematogenous metastasis but inhibit peritoneal dissemination[9]. A study using the RT-PCR method has demonstrated the overexpression of CD44v8–10 in lymph nodes and hepatic metastasis when compared to primary lesions in some patients with gastric cancer[7]. Immunohistochemical studies of colorectal cancer also reveal that CD44v8–10 is related to metastasis and that the expression of CD44v8–10 occurs more frequently in lymph node-positive patients than in lymph node-negative patients. The expression is also correlated with hematogenous metastasis and recurrence rates, and the 5-year survival rate is significantly lower[38]. A study using Northern blot hybridization has revealed that the level of CD44v8–10 expression is significantly higher in carcinomas with hepatic metastasis

than in those without[34].

A study of renal cell carcinoma using the RT-PCR method has revealed that intensified expression of CD44 variants, including v10, of approximately 700 bp was noted very frequently in advanced carcinoma and in carcinoma of high malignancy, which indicates a possibility that CD44 may be involved in malignancy[20].

In this study, we used antibodies which are able to detect all of the CD44v1–10 to determine if its expression occurred in primary and lymph node metastatic lesions in 53 patients with gynecological cancer. We found the expression of CD44v1–10 in our study subjects. Since it is pointed out that CD44v6 and v9 are related to metastasis in other cancers, we then focused on the expression of CD44v6 and v9.

The expression of CD44v1–10 in squamous cell carcinoma of the uterine cervix was not related to clinical stage, nodal metastasis, or vascular invasion, and was also noted in normal cervical squamous epithelium. In this study, we therefore failed to identify the relation of the detection of CD44v1–10 in squamous cell carcinoma to nodal metastasis. When particular types of variants are focused on, the expression of CD44v6 is noted frequently in patients with advanced cancer, as reported by Furugen et al, and the rate of expression of CD44v6 is high in patients with nodal metastasis whose disease state is classified as Stage Ib or II, as reported by Kainz et al[18]. In addition, it has been reported that the expression is noted more frequently in patients with metastasis into the pelvic lymph nodes than in patients without, which indicates a possibility that expression is related to vascular invasion and poor prognosis. Henceforth, further studies using new antibodies are necessary.

Furugen et al did not observe the expression of CD44v6 in 8 patients with infiltrating adenocarcinoma of the uterine cervix. However, in this study, we noted its expression in one of 2 patients with adenocarcinoma of the uterine cervix. Further studies using a larger number of patients are necessary.

In endometrial adenocarcinoma, the expression of CD44v1–10, v6, and v9 was noted quite frequently in patients with advanced cancer, nodal metastasis, and myometrial invasion. In particular, the expression of CD44v9 was considered to indicate some significant relation to nodal metastasis. However, since the expression of CD44v1–10 and v9 was also noted in normal endometrium, the possibility was considered that the expression of CD44v6 may be involved in the progression of endometrial adenocarcinoma , nodal metastasis, and myometrial invasion. With regard to vascular invasion, Fujita et al[8] used the RT-PCR method using a probe to detect CD44v3–10, and reported that the rate of occurrence of splicing variants was significantly lower in endometrial carcinoma than in normal endometrium. They also reported that the rate of expression of CD44v3–10 was significantly lower in patients with vascular invasion than in those without indicating a possibility that a lower rate of expression of CD44v3–10 is involved in invasion of carcinoma cells into vessels. In this study, the expression of CD44v6 was not noted in normal endometrium, and the expression of CD44v6 was detected more frequently in patients with vascular invasion than in those without. It is therefore considered that the rate of expression of CD44v6 increased in patients with endometrial adenocarcinoma who showed vascular invasion, which indicates that CD44v6 is involved in vascular invasion in endometrial adenocarcinoma. Analysis by individual histological type revealed that the CD44v6- and v9-positive rates in adenocarcinoma tended to be higher as the cancer was poorly differentiated. However, the expression of CD44 glycoprotein with variant exons 8–10 in gastric cancer was significantly higher in well differentiated adenocarcinomas than in poorly differentiated adenocarcinomas[39]. In this study, one patient exhibited an expression of CD44v6 not in the primary lesion but in the nodal metastasis. This finding indicates a possibility that the adhesion molecule may undergo splicing in nodal metastasis, although less frequently.

In ovarian cancer, the expression of CD44v6 and v9 did not significantly relate to clinical stage or histological type. This finding in this study agreed well with the results reported by Stephen et al[3] who studied 21 patients with serous adenocarcinoma, 5 with endometrioid adenocarcinoma, and 1 with clear cell adenocarcinoma. Yuki et al studied 11 patients with clear cell adenocarcinoma and reported that the expression of CD44v6 tended to reduce in patients with advanced carcinoma. In this study, the expression was noted in one patient at Stage I but not detected in one patient at Stage III. There have been no reports regarding the relation between the presence or absence of nodal metastasis and the expression of CD44v. In this study, we found that in patients with nodal metastasis, the rate of expression of CD44v6 was higher than that of CD44v9. On the other hand, considering that the expression of CD44v6 was not noted in normal ovarian tissues, there may be a possibility that in ovarian cancer, the expression of CD44v6 is involved in nodal metastasis.

In conclusion, our study results suggest that the expression of CD44v6 in endometrial adenocarcinoma cells is involved in the progression of the carcinoma, nodal metastasis, myometrial invasion, and vascular invasion, and that in ovarian cancer, the expression of CD44v6 is involved in nodal metastasis. It is therefore expected that

further studies of the expression of CD44v will allow the adhesion molecule to become a useful tool for assessing the malignant potential of a carcinoma and to function as a factor for predicting prognosis.

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