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〔原著〕A FUNDAMENTAL INVESTIGATION ON CANCER ANTIGEN 54/61 (CA 54/61) IN RELATION TO MENSTRUAL CYCLES PREGNACY AND DELIVERY AND ITS CLINICAL SIGNIFICANCE AS A TUMOR MARKER

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SUMMARY

The supernatant extract from the culture of the human pulmonary adenocarcinoma cell line (C1509) was inoculated in mice for immunization and two different monoclonal antibodies (MA54 and MA61) were obtained. Using these monoclonal antibodies, we performed fundamental investigation into the antigens that are detected by MA54 and MA61 (cancer antigen 54/61; CA54/61) in various cases seen in the field of gynecology and obstetrics to assess the value of CA54/61 as a new tumor marker. Serum CA54/61 was assayed using the double determinants sandwich enzyme immunoassay (DDS-EIA), and an immunohistochemical investigation of tissue antigens was performed using the avidinbiotin immunoperoxidase (ABC) technique. The results obtained are as follows:

1) The mean serum CA54/61 level was 6.98u/ml (SD:4.56u/ml) in 104 nonpathologic individuals (NPI: 87 females 17 males). Based on mean+3SD, the normal upper limit (NUL) of serum CA54/61 was set at 20.0u/ml and then the serum CA54/61 level distributed in a range below this NUL in 98% of NPI in this series. The serum CA54/61 level decreased slightly in the luteal phase in nonpathologic ovulatory women, was slightly higher in menopausal women and was low in men.

2) The serum CA54/61 level showed no significant increase in pregnant women at any gestentional stage in comparison with the level in the nonpregnant population, and the level excessed NUL in only 5.5% of the pregnant population. The serum CA54/61 level at the time of delivery showed no significant difference from the level during pregnancy although a slight increase was noted in postpartum women. The CA54/61 level in umbilical artrerial and venous blood was low (≦7.5u/ml), while the level in amniotic fluid was extremely high with a mean of 220.9u/ml.

3) The serum CA54/61 assay in 91 pretherapeutic women with benign gynecologic disease

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千葉大学医学部産科婦人科学講座
慶應義塾大学医学部産婦人科講座
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yielded a positive rate in only 2.2% (for the level exceeding 20.0u/ml). The serum CA 54/61 level in women with gynecologic malignancies varied greatly among the type of disease, i. e. the positive rate was 5.3% in cervical cancer, 33.3% in ovarian cancer and notable 66.7% in mucinous ovarian cystadenocarcinoma (mucinous OCACa). The positive rate in ovarian cancer increased along the progression in stage (FIGO), although the positive rate in stage I was rather low (20.0%). The assay for the combination of CA54/61 and CA125 (which is cancer antigen yielding a high positive rate in serous OCACa) increased CA54/61-positive rate in cases overall of ovarian cancer by 33.3% (from 38.1 to 71.4%) and increased the positive rate in serous OCACa by 50.0% (from 16.7 to 66.7%). Since the corelation coefficient between CA54/61 level and CA125 level was low ($r=0.38$), a combination assay for CA54/61 and CA125 may be useful for detection of ovarian cancer.

4) An immunohistochemical investigation revealed the localization of MA54 and MA61 in gynecologic malignancies at higher than 50.0%. In paticular, in the cases of mucinous OCACa the tissue localization of CA54/61 was shown at a rate 83.3%. The positive rate before treatment reached 83.3%. There was no separation between the detection of CA54/61 tissue preparations and serum CA54/61 levels.

5) An immunohistochemical investigation with placental samples revealed the presence of MA54 in the intravenous fetal endothelium, MA61 in the intravenous fetal endothelium and histiocytes in the fetal membrane. It was therefore suggested that CA54/61 was an oncofetoplacental antigen. However, since this assumption appears to be inconsistent with the low CA54/61 level in umbilical arterial and venous blood was as well as the extremely high level in amniotic fluid, this remains to be further investigated.

Key words: CA54/61, Tumor marker, Mucinous ovarian cystadenocarcinoma, Oncofetoplacental antigen, Immunohistochemistry

I. Introduction

Tumor markers developed for gynecologic cancer include human chorionic gonadotropin (hCG)[1] for choriocarcinoma, tumor antigen-4 (TA-4)[2] for cervical cancer and, α-fetoprotein (AFP)[3] for yolk sac tumor. Since these tumor markers show high specificity they have been adopted clinically as useful tumor markers. For ovarian cancer, many tumor markers such as cancer antigen 125 (CA 125)[4] and carbohydrate antign 19-9 (CA19-9)[5] have been developed and brought into clinical use although they do not show such high specificity and sensitivity. Because a variety of cell types are involved in ovarian cancers, it is difficult to screen all cell types with one type of tumor marker. To cope with this, combination assay and a computer aided multivariate pattern analysis system (CAMPAS) have been introduced into clinical staging[6,7], although these techiniques must still be improved from the sensitivity and cost-benefit efficiency points of view.

A combination of tumor markers for combination assay is desirable if they show less correlation and are complementary in sensitivity and specificity. CA125 is most frequently used for diagnostic investigation of gynecologic malignancies. However, the specificity of CA125 is poor and its sensitivity in mucinous ovarian cystadenocarcinoma (mucinous OCACa) is low[4]. As a new tumor marker, cancer antigen 54/61 (CA 54/61) have recently been developed from human pulmonary adenocarcinoma cells in collaborative effort between the Gynecologic and Obstetric Department of Keio University and Mochida Central Laboratory[8]. We perfomed fundamental investigation into CA54/61 in women in various stages of menstrual cycle, pregnancy or delivery to assess its clinical significance as a

tumor marker for gynecologic malignancies especially for ovarian malignancies. We also performed an immunohistochemical investigation in human placenta and various benign or malignant tumors to assess the possibility of CA54/61 being an oncofetoplacental antigen like CA125 and tissue polypeptide antigen (TPA)[9] as well as a pregna ncy and placental tissue proteins[10,11].

II. Meterial and Methods

Materials

Blood was obtaind from 17 non-pathological men, 79 normal, non pregnant ovulatory women (27 in follicular, 34 in luteal and 18 in menstrual phases), and 8 menopausal women. Blood was also sampled from 47 pregnant women, ie, 10 in the first, 16 in the second and 21 in the third trimester. In the 13 deliveries maternal sera were sampled before delivery (10 cases) and immediately after delivery (11). Amniotic fluid was successfully obtaind from all those 13 deliveries, and umbilical sera were also sampled from artery (10) and vein (12).

Ninty one patients with uterine myoma (28 cases), ovarian cyst (41), and endometriosis (22), and 72 cases presenting with gynecologic malignancies, ie, cevical cancer (19), endometrial cancer (21), ovarian cancer (30), and mixed mesodermal tumor (2) were bled pretherapeutically and serially as well. Sera and amniotic fluid obtaind were stored at -80°C until use.

Tissue samples were obtaind from the patients with cervical cancer (9), endometrial cancer (19), and ovarian cancer (28) at operation. Placentae were also obtaind from 8 normal deliveries. These samples were immediately cut into small cubes and embedded in paraffin after fixation in a mixture of 90 % ethanol and acetic acid[12].

Methods

CA54/61 and CA125 were measured by a double determinants sandwich enzyme immunoassay (DDS-EIA, Mochida Central Laboratory, Tokyo, Japan) and a RIA employing the sandwich solid phase method (Centocor, Pennsylvania, USA).

Tissue antigens (CA54 and 61) were demonstrated by avidin-biotin immunoperoxidase techinique[13] with a VECTASTAIN™ ABC kit (PK-4002, Vector Laboratory, California, USA). To unmask tissue antigens, sections were briefly exposed to 0.1 % trypsin solution after deparaffinization[14]. The sufficient blocking of endogenous peroxidase activities was achieved by pretreatment of the sections with 1.0 % hydrogen peroxide in phosphate buffered saline (PBS, pH7.2) for 60 min at room temperature[15]. Monoclonal antibodies 54 (MA54) and 61 (MA61) were kindly donated by Mochida Central Laboratory and used at graded dilutions of 1:20–1:320. The reagents containd in ABC kit were diluted as indicated. The substrate solution containd 0.015 % 3,3'-diamino-benzidine tetrahydrochydrochloride (Riedel de-Haen AG, Hannover, Germany) in PBS.

The solution was prepared fresh each time and 5μl of 30 % hydrogen peroxide was added to 5ml of the solution immediately before use. The specimens were incubated with the substrate for 5–10 min at room temperature.

Control sections were incubated with PBS (pH 7.2) or normal nonimmune mouse IgM in place of the first specific monoclonal antibodies.

III. Results

1) Serum concentration of CA54/64 in non-pathological individuals

Difference between the stages of ovulation was observed (Table I). The mean serum level in healthy women was 7.63u/ml in the folicular phase. The level was 9.94u/ml in menopausal women. In healthy men the mean CA54/61 level was 5.84 u/ml and the mean level in 104 nonpathologic adults overall was 6.98u/ml.

The mean+3SD was given as 20.0u/ml and individual data distributed in a range below 20.0 u/ml in 98 % of nonpathologic woman studied. This level was therefore set as the normal upper limit of serum CA54/61 in this study.

2) Measurement of CA54/61 in pregnancy and at delivery

The mean CA54/61 level levels in nonpathologic pregnant women were 7.87u/ml in the firit trimester, 9.73u/ml in the second trimester and 8.21

Table I. Serum CA54/61 legels in non-pathological individuals

	n	range (u/ml)	mean (u/ml)	SD (u/ml)	Positive cases (%)*
Ovulatory women					
follicular phase	27	4.0— 7.6	7.63	4.08	
luteal phase	34	1.3— 6.0	0.99	3.75	
menstrual phase	18	1.6—23.2	7.96	5.04	
meopausal women	8	0.7—24.5	9.13	9.25	
Men	17	3.2—12.3	5.84	3.42	
Total	104	0.7—24.5	6.98	4.56	2 (1.9)

* : Cases with serum CA54/61 levels over normal upper limit (mean±3SD : 20 u/ml)

Table II. Serum CA54/61 levels in normal pregnanicies

	n	range (u/ml)	mean (u/ml)	SD (u/ml)	Positive cases (%)
1st trimetser	10	3.7 - 14.6	7.87	4.20	
2nd trimester	16	20. - 18.2	9.73	4.97	
3rd trimester	21	1.0 - 29.3	8.21	6.36	
Total	37	1.0 - 29.3	8.65	5.45	2 (5.4)

Table III. CA54/61 concentrations at delivery (n=13, 37—42weeks in gestation)

	n	range (u/ml)	mean (u/ml)	SD (u/ml)
Maternal sera				
before delivery	10	4.0 - 29.3	8.46	7.96
after derivery	11	4.0 - 23.9	10.85	7.13
Umbilical sera				
artery	10	4.0 - 9.9	5.39	1.91
vein	12	4.0 - 7.4	4.63	1.04
Amniosic fluid	13	16.9 - 816.0	220.90	256.12

u/ml in the third trimester. There were no pronounced changes between these gestational terms. The mean level during pregnancy was 8.65 u/ml (Table II).

CA54/61 was also assayed in pre-and postterm maternal blood, umbilical arterial and venous blood and amniotic fluid to assess the difference in CA54/61 concentrations. The mean CA54/61 level was 8.46u/ml in prepartum maternal blood, 5.39u/ml in umbilical arterial blood, 4.63u/ml in umbilical venous blood and 220.9u/ml in amniotic fluid (Table III).

3) Pretherapeutic serum levels of CA54/61 in gynecologic disease

The mean pretherapeutic serum level of high level of CA54/61 were determined for secific gynecologic disease (Table IV). The mean serum CA54/61 level was 3.22u/ml in uterine myoma, 4.21u/ml in overian cyst and 8.11u/ml in endometriosis. The frequency of a high CA54/61 level exceeding the normal upper limit (positive rate) was 0 % in uterine myoma and in ovarian cyst, and 9.0 % in endometriosis.

The mean pretherapeutic serum levels in malignant gynecologic disease were 6.98u/ml in cervical cancer, 12.84u/ml in the endometrial cancer and 31.44u/ml in ovarian cancer. The serum CA 54/61 level in ovarian cancer was significantly higher than that in nonpathologic adults ($p<0.05$). The positive rates were 5.3 % in cervical cancer,

Table IV. Pretherapeutic serum levels of CA54/61 in gynecologic diseases

	n	mean (u/ml)	SD (u/ml)	Positive cases (%)
Benign diseases				
uterine myoma	28	3.22	2.06	0 (0)
ovarian cyst	41	4.21	3.79	0 (0)
endometriosis	22	8.11	6.95	2 (9.0)
total	91			2 (2.2)
Malignant diseases				
cervical cancer	19	6.98	4.76	1 (5.3)
endometrial	21	12.84	10.73	4 (10.0)
ovarian cancer	30	31.44	51.22	10 (33.3)
total	70			15 (21.4)

Table V. Pretherapeutic positive rates of CA54/61 in relation to clinical stagings (FIGO)

Stage	n	Positive cases (%)
I	15	3 (20.0)
II	6	3 (50.0)
III	5	2 (40.0)
IV	1	1
Metastatic	3	1 (33.3)
Total	30	10 (33.3)

Table VI. Prethesapeutic serum positive rates of CA54/61 in relation to pathological classification

Ovarian malignancies	n	Positive cases (%)
Serous CACa*	12	2 (16.7)
Mucinous CACa	9	6 (66.7)
Endometrioid CACa	1	0
Epidermoid Ca	1	0
Non-epithelial Ca	3	0
Krukenderg tumor	3	1 (50.0)
Unknown	1	1
Total	30	10 (33.3)

* : cystadenocarcinoma

19.0% in endometrial cancer, 33.3% in ovarian cancer (Table IV). Thus, CA54/61-positive cases tend to be frequent in ovarian cancer. The positive rate in ovarian cancer was classified in relation to staging (Table V). The positive rates in ovarian cancer were 20.0% in stage I, 50.0% in stage II, 40.0% in stage III, and 100% in stage IV. The positive rate thus increased with advancement of clinical stages.

This positive rate was also determined in relation to histopathological types in ovarian cancer (Table VI). The positive rates were 16.7% in serous cystadenocarcinoma (CACa) and 66.7% in mucinous CACa. The positive rate for pretherapeutic serum CA54/61 was significantly higher in case of mucinous CACa.

4) Combination assay of CA54/61 and CA125 in ovarian malignancies

The correlation between serum levels of CA54/61 and CA125 was investigated in ovarian cancer

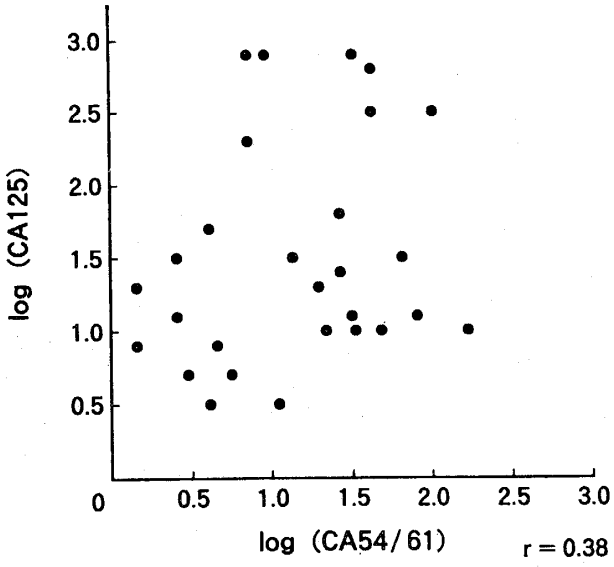


Fig. 1 Correlation between serum levels of CA54/61 and CA125

Table Ⅶ. Pretherapeutic combination asspy of CA54/61 and CA125 in serous and mucinous ovarian carcinomas

	Serous CACa	Mucinous CACa	Total
CA54/61	2/12 (17.7)	6/9 (66.7)	8/21 (38.1)
CA125	6/12 (50.0)	2/9 (22.2)	8/21 (38.1)
Both	8/21 (66.7)	7/9 (77.8)	15/21 (71.4)

*: No-positive (CA54/61> 20u/ml, CA125 >35u/ml)/No-tested

Table Ⅷ. MA54. 61-Immunohistochemical reaction in gynecologic malignacies

	n	MA54	MA61	Serum levels (%)
Cervical cancar	9	5(55.6)	5(55.6)	0/9
Endometrial cancer	9	5(55.6)	6(66.7)	1/9 (11.1)*
Ovarian cancer	28	19(69.9)	20(71.4)	
serous CACa	12	6(50.0)	7(58.3)	1/10 (10.0)
mucinous CACa	12	10(83.3)	10(83.3)	5/6 (83.3)
endometrioid CACa	4	3(75.0)	3(75.0)	
Total	46	29(63.0)	31(67.4)	

* No-positive/No-tested (%)

(Fig. 1). The logarithm (log) of the CA125 levels was the ordinate and the log of the CA54/61 was abscissa showing that plots are scattered over the chart and a low correlation coefficient (r=0.38) was observed.

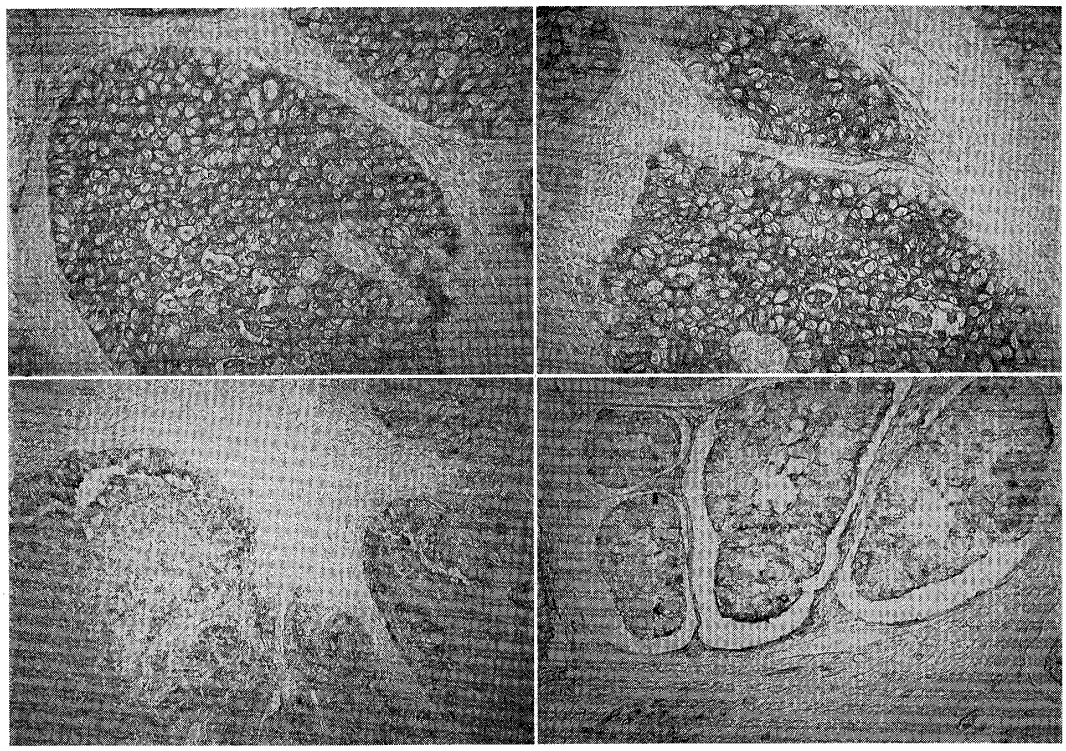
Since CA54/61 showed high specificity to mucinous OCACa and CA 125 has been established as a tumor marker of serous OCACa, the advantage of the combination assay of CA54/61 and CA125 was assessed (Table Ⅶ).

In all cases of ovarian cancer, the positive rate increased to 59.3 % in the assay for both CA54/61 and CA125 compared with the CA54/61-positive rate of 37 % In serous OCACa, the positive rate increased to 66.7 % in the combination assay compared with 16.7 % in the assay for CA54/61 alone. In mucinous OCACa, the positive rate for combinationassay was 77.8 % compared with 66.7 % for CA54/61 alone. Thus, the positive rate increased in the combination assay in both serous and mucinous OCACa.

5) Immunohistochemical detection of CA54/61 in gynecologic malignancies

The immunohistochemical reartion of MA54 and MA61 were investigated in a total of 46 cases of gynecologic malignancies including 28 cases of ovarian cancer (12 cases of serous OCACa, 12 cases of mucinous OCACa and 4 cases of endometrioid OCACa), 9 cases of uterine endometrial cancer and 9 cases of uterine cervical cancer (Table Ⅷ). The positive rate for pretherapeutic serum CA54/61 in these malignancies are also presented in Table Ⅷ for reference. An immunohistochemical reaction of MA 54 was observed in 29/46 cases (63.7 %) of gynecologic mailgnancies and that of MA61 was observed in 31/46 cases (67.4 %). Immunohistochemistry in mucinous OCACa showed a positive rate of 83.3 % for both MA 54 and MA 61 and this high immunohistichemical positive rate was consistent with the high positive rate for pretherapeutic serum CA54/61 in mucinous OCACa (66.7 %). The immunohistochemical reactions of CA54/61 were observed predominantly in the stroma of cancer cells. Nuclei or other tissue compornents were found to be negative (Fig. 2).

Immunohistochemistry was negative in all control sections. As seen in Table Ⅷ, positive immunohistochemistry was also observed in 50-75 % cases of other gynecologic malignancies although the immunohistochemical positive rate in other gynecologic



A : CA 54/Cervical Cancer | B : CA 61/Endometrial Cancer
C : CA 54/Serous OCACa | D : CA 61/Mucinous OCACa

Fig. 2 Localization of CA54/61-uterine and ovarian carcinoma

malignancies did not show good correlation with the respective serum levels of CA54/61.

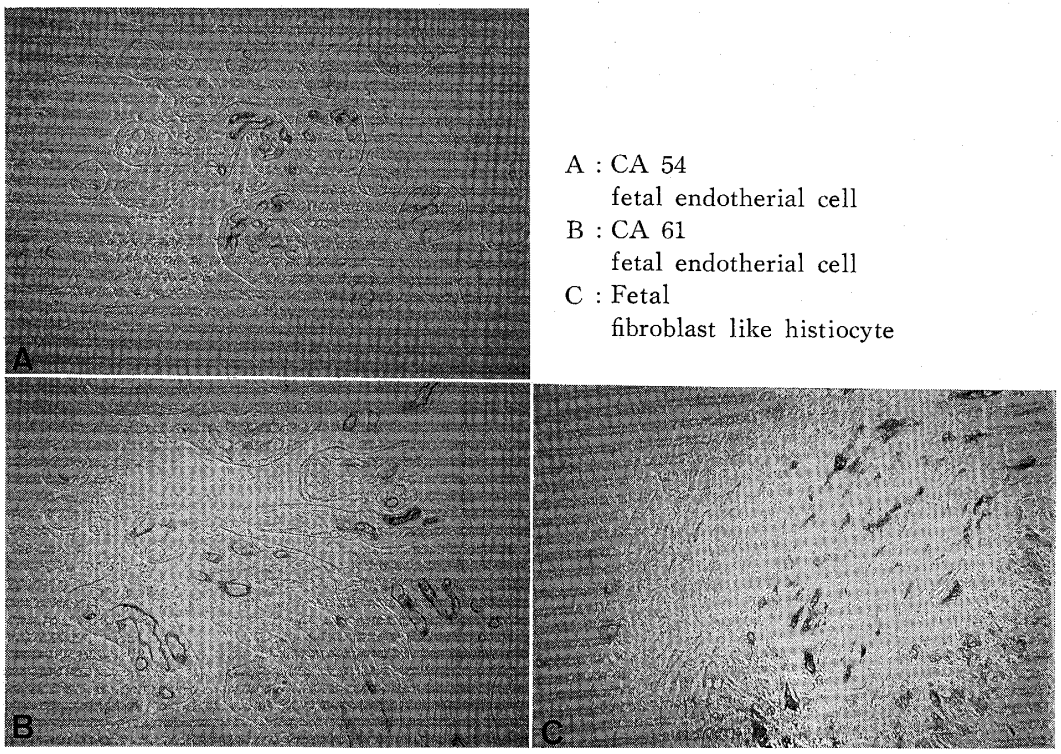
6) Immunohistochemical detection of CA54/61 in human term placentae

An immunohistochemical investigation was also performed in normal placenta (8 cases) obtaind after full-term delivery. The immunohistochemical reaction of MA54 and MA61 were observed clearly in intravillous fetal endothelium and that of MA61 was also seen in the fibroblast-like histiocyte in the fetal membranes (Fig. 3). Immunohistochemistry showed a negative result in other villous and reflected chorionic trophoblasts, amnion and decidua and control sections.

IV. Discussion

The significance of tumor marker has been markedly increasing recently in the diagnosis of gynecologic malignancies. Gynecologic malignancies are mainly classified into cervical cancer, endometrial cancer, choriocarcinoma and ovarian cancer. For cervical and endometrial cancer, direct collection of tissue samales has brought about a dramatic advancement in early detection and treatment. For choriocarcinoma, the specific marker, hCG, has also helped to achieve major improvement in its diagnosis and treatment. However, it is still difficult to detect ovarian cancer in early stage although the incidence of ovarian cancer has been increasing year by year. The ovaries form very special organ and tumors of different origins can be involved in ovarian cancer. In addition, they exsist in a deep area in the pelvic cavity so it is difficult to examine them by palpation or visual modalities. These features may be one of a reason for the difficulty in early detection of ovarian cancer. However, various tumor markers for ovarian cancer such as CA125[4] and CA19-9[5] has been clinically used and their usefullness in the diagnosis or therapeutic management of ovarian cancer has been established.

CA54/61 are glycosylated antigens which are distinguished by the two monoclonal antibodies, MA54 and MA61 originated from mice immunized with the human pulmonary adenocarcinoma cell line (C-1509)[8]. Using DDA-EIA techinique which



A : CA 54
fetal endotherial cell
B : CA 61
fetal endotherial cell
C : Fetal
fibroblast like histiocyte

Fig. 3 Localization of CA54/61-human term placentae

utilize MA54 and MA61, antigens recognized by these monoclonal antibodies (CA54/61) were assayed in sera and amniotic fluid.

As shown in Table I the serum CA54/61 level was higher in women than in men, decreased in the luteal phase in ovulating women and increased slightly in menopausal women. Nozawa et al reported the localization of CA54/61 in the entometrium in the luteal phase[16], and CA54/61 have been shown to be kinds of endometrial antigens. This finding and the data from this study suggest the possibility that sex steroid hormones may be involved in the production of CA54/61.

The serum CA54/61 level was slightly higher in pregnant women thoughout all trimesters than in non pregnant ovulating women, but the difference was not significant. The CA54/61 level was low in umbilical arterial and venous blood and, despite this, the level in amniotic fluid was extremely high. There is a report concerning the localization of CA54/61 in fetal erythcocytes.[16] Therefore, CA 54/61 may be considered to be an oncofetoplacental antigen. However, this assumption appears to contradict the finding that the level in umbilical arterial and venous blood was lower than that in the maternal blood, and further investigation are thought necessary to determine the origin of CA54/61 in amniotic fluid. The CA54/61 level in postpatum maternal blood was slightly higher than the prepartum level. A finding which is the same as this has also been reported with CA125 or tissue polypeptide antigen (TPA)[17]. Therefore it is considered that it can be explained by the effect of outflow of amniotic fluid or retroplacental pooling blood which contain a large amount of CA54/61[18].

The pertherapeutic serum assay demonstrated a CA54/61 positive rate of 33.3 % in the case of ovarian carcinoma although the positive rate was 19 % or lower in cases of cervical and endometrial carcinoma. In paticular, in the case of mucinous OCACa, 66.7 % of patients were positive for CA54/61. In the case of benign gynecologic disease including uterine myoma, benign ovarian neoplasms and endometriosis, the pretherapeutic serum assay gave a mean CA54/61-positive rate of 2.2 % and this positive rate indicated the higher specificity of CA54/61 in benign gynecologic disease than that of TPA.[19]

According to the literature, the sensitivities of

already clinically used tumor markers in the diagnosis of ovarian cancer are 60.0-82.2 % with CA125[4,20-22], 30.4 % with CA19-9, 13 % with cancer antigen 50 (CA50)[23], 40.0 % with TPA[9], 41.4 % with sialyl TN antigen (STN)[24], 33.3 % with cancer antigen 72-4 (CA 72-4)[25] and 26.0 % with stage specific embryonic antigen I (SLX)[26]. Cancer antigen 130 (CA130) which is said to exist in the same molecule as that of CA125[27] has also shown a high sensitivity of 87 % in pretherapeutic samples[28]. However, CA125 and CA130 showed a high false positive rate (38-73 %) in benign gynecologic disease[29,21] and this has weakend the diagnostic value of these tumor markers. To improve such an assay defect using a single tumor marker, combination assay has currently been attempted. As the principle of combination assay, tumor markers to be combined should show a low correlation and they should be complementary in sensitivity and specificity. There are also requirements from the cost-benfit efficiency point of view.

In the present investigation, the correlation coefficient between CA125 and CA54/61 was as low as 0.38 and the results suggested the possibility that this combination assay avoided the high false positive rate with CA125 alone and increased the sensitivity in gynecologic malignancies. In this investigation, the combination assay for CA54/61 and CA125 achieved a sensitivity of as high as 66.7 % in mucinous OCACa which supported the findings by Inaba et al[30,31]. as well as Nozawa et al.[32].

In stage I ovarian cancer, the CA54/61-positive rate shown by the pretherapeutic serum assay was 20.0 % , suggesting that this tumor marker alone may not be suitable enough for screening of early ovarian cancer. Hower, since the CA54/61-positive rate given by the pretherapeutic serum assay tended to increase with the advancement in ovarian cancer stage (Table V), these antigens were suggested to be produced in tumor cells and to be chracterized by dependency on mass. In fact, the immunohistochemistry of MA54 and MA61 showed positive rate of 83.3 % in samples of mucinous OCACa (Table Ⅷ) which was consistent with the high positive rate shown by the pretherapeutic serum assay (66.7 %). From the immunohistochemical findings it is also considered that CA54/61 is produced in the stroma of cancer cells, the majority of the antigens produced remain in the stroma and some of the antigens transfer into the cell membrane or leak out of the cells. In other gynecologic malignancies, immunohistochemistry for CA54/61 showed high positive rates (50-75 %), while serum assay showed rather low positive rates (Tables Ⅳ and Ⅷ), and this result suggested that, among the different types of cancer, there had to be variations in the degree of transfer of antigens into blood from the cancer cells producing them[33].

It is known that some cancer-derived tumor markers can be produced in fetal organ or in placenta[34] and that, in contrast, antigen substances[37] specific to fetuses[35] or placenta[36] can be produced in cancer cells. This appears to be taken into consideration in the development of new tumor markers[39]. For MA54 and MA61, the intravenous fetal endothelium was shown to be clearly positive and the stroma of the fibroblast-like histiocytes of the fetal membrane were also shown to be positive for MA61 (Fig. 3). The reaction of MA54 and MA61 were not seen in other placenta components. These findings may infer the CA54 is an oncofetal antigen and CA61 is an oncofetoplacental antigen. However, the CA54/61 level in amniotic fluid was extremery high, while the level was low in umbilical arterial and venous blood. These findings appeard to be inconsistent with immunohistochemical findings. Additionally, CA 54/61 was also detected in serum from nonpregnant momen and nonpathologic individuals. Therefore, a closer investigation involging an assessment of the uterine endometrium[16] should be necessary.

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要　旨

ヒト肺腺癌由来細胞株培養上清抽出物を免疫して得られた2種のモノクローナル抗体（MA54, MA61）が認識する腫瘍マーカー cancer antigen 54/61（CA54/61）について，産婦人科領域における基礎的臨床的検討を行ない，以下の成績を得た。なお，血中値測定は，double determinant sandwich enzyme immnunoassay 法にて，又免疫組織学的検索は，avidin-biotin immunoperoxidase 法によった。1）正常人104名における血中平均値は6.98u/ml（SD:4.56u/ml）で，正常上限は，mean+3SD より20.0u/ml に設定された。2）妊娠各期を通じて血中 CA54/61 値は非妊娠時に比べ上昇を認めなかったが羊水中では平均220.9u/ml の異常高値であった。3）婦人科良性疾患91例における治療前血中陽性率は2.2%に留まったが，特に粘液性嚢胞癌では66.7%であった。臨床進行期が進むにつれて陽性率の上昇傾向が見られた。また CA 125とのコンビネーションアッセイにおいて，陽性率が上昇し，両腫瘍マーカー間での低い相関係数（r=0.38）と考え合わせ，卵巣腫瘍における CA54/61, CA125のコンビネーションアッセイの臨床的有用性が示された。4）MA54, 61共に各種悪性疾患において50%以上の局在率が得られ，粘性嚢胞腺癌では83.3%の高局在率で，組織局在，血中値間で乖離は認められなかった。5）胎盤では絨毛内胎児血管内皮細胞に，卵膜内組織球に明瞭な陽性所見が得られ，CA54/61 が oncofetoplacental antigen である可能性が示唆された。

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