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Original Article

Reactivity of CA19-9 and CA125 in Histological Subtypes of Epithelial Ovarian Tumors and Ovarian Endometriosis

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Previous reports have shown that some ovarian endometrioid adenocarcinomas and ovarian clear cell adenocarcinomas derive from ovarian endometriosis (OE), and that endocervical-like mucinous borderline ovarian tumors are associated with OE. We examined the relationship between the staging and histological subtypes of OE or epithelial ovarian tumors (EOT) and the serum levels of carbohydrate antigen 19–9 (CA19–9) and carbohydrate antigen 125 (CA125) to evaluate the potential of these markers for preoperative diagnosis. First, we analyzed the preoperative serum levels of CA19–9 and CA125 in 195 patients who were histopathologically diagnosed with OE or EOT. We then performed a case-control study in which 308 women were enrolled, the 195 women described above and 113 healthy women as control subjects. Serum CA19–9 and CA125 levels were found to be useful in differentiating between OE and serous adenocarcinoma, but not between OE and other EOT. Moreover, serum CA19–9 levels were useful for preoperative assessment between OE and stage I mucinous borderline ovarian tumors, with or without the interstitial infiltration. In addition, considering that the serum CA19–9 levels in stage I mucinous borderline ovarian tumors were elevated via the interstitial infiltration of leukocytes and that precancerous lesions are associated with a cancerous glycosylation disorder in the process of inflammatory carcinogenesis, the CA19–9 level may be considered a suitable biomarker for estimating drug susceptibility.

Key words: ovarian endometriosis, epithelial ovarian tumors, histological subtype, carbohydrate antigen 19–9, carbohydrate antigen 125

The histological type and stage of tumors that were surgically resected by using laparotomy or laparoscopy are important prognostic factors in the definitive diagnosis of ovarian tumors [1–5]. For preoperative diagnosis, a range of tools are used, including inquiry, internal examination, various imaging modalities, and supplementary tests such as with tumor markers. The diagnostic accuracy of imaging modalities for malignant tumors (MT) is reported to vary within the range of 82–93% [6, 7]. To determine the appropriate operative procedure, differential diagnosis between benign and malignant tumors is conducted through histological examination, along with the aid of tumor markers such as carbohydrate antigen 125 (CA125) [8]. CA125, a representative tumor

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marker of ovarian cancer, is one of the markers used to evaluate the effectiveness of drug therapies [9]. However, elevated CA125 levels are not always observed in patients with ovarian clear cell adenocarcinoma (CCA) and ovarian mucinous adenocarcinoma (MA), or in patients with other epithelial ovarian cancers [10, 11]. Moreover, CA125 levels are affected by menstruation and pregnancy, since this antigen is produced by epithelial cells of the peritoneum, pleura, and endometrium, and are elevated in patients with ovarian endometriosis (OE) and pelvic inflammatory diseases [12].

Carbohydrate antigen 19–9 (CA19–9) levels are used as a diagnostic marker of gastrointestinal cancers such as pancreatic cancer and cholangiocarcinoma, in which they exhibit a high positivity rate [13, 14]. Even higher CA19–9 positivity rates have been reported in gynecological tumors such as MA, ovarian endometrioid adenocarcinoma, and mucinous borderline ovarian tumors (MBT) [15, 16]. However, elevated CA19–9 levels have also been reported in patients with benign tumors, including OE and mature cystic teratoma, and CA19–9 levels vary markedly among Lewis blood types in healthy individuals [17–20]. Thus, the application of these tumor markers for differentiating ovarian cancer requires extreme caution.

Recent reports have shown that some ovarian endometrioid adenocarcinomas and CCA derive from OE, and that endocervical-like mucinous borderline ovarian tumors (ELMBT) are associated with OE [21]. In Japan, the incidences of CCA and ELMBT are significantly higher than those in Europe and the United States [22–24]. Therefore, we examined the relationship between the stage and histological subtype of OE or epithelial ovarian tumors (EOT) and the CA19–9 and CA125 levels in order to confirm the usefulness of these antigens as preoperative diagnostic markers.

Materials and Methods

Subjects. The study subjects included 195 patients who were histopathologically diagnosed with OE or EOT at the Kurashiki Central Hospital from January 2008 to December 2012. The serum CA19–9 and CA125 levels of the subjects were measured as a preoperative test. Patients with ruptured ovarian tumors were excluded because they showed marked increases in CA19–9 and CA125 levels [25]. The International Federation of Gynecology and Obstetrics (FIGO) stage and World Health Organization histological classifications were utilized in the tumor staging [26, 27]. Ovarian tumors were classified into 8 histological subtypes, namely, OE, serous cystadenoma, mucinous cystadenoma, ELMBT, intestinal type mucinous borderline ovarian tumor (ITMBT), serous adenocarcinoma (SA), MA, and CCA. The SA cases were all high-grade serous adenocarcinomas. The FIGO stages were classified into 4 categories, namely I, II, III, and IV. Interstitial infiltration of cancer cells and leukocytes in stage I ovarian tumors were categorized as present or absent. As healthy controls, 113 healthy women who showed no abnormalities in liver function, renal function, glycolipid metabolism, or abdominal and transvaginal ultrasonography upon medical examination were selected and requested to undergo measurements of serum CA19-9 and CA125 levels in the Comprehensive Health Center of our hospital. The institutional review board approved this case-control study (No. 1062).

Measurement of serum CA19–9 and CA125 levels. Serum CA19–9 and CA125 levels were measured by using ARCHITECT i 2000 with special reagents, ARCHITECT CA19–9 XR and CA125 II (Abbott Laboratories, Abbott Park, IL, USA). All serum samples were assayed within 2 h after centrifugation, following the manufacturer's instructions. Because the CA19–9 levels of Lewis (a–b–) patients have been reported to be < 1.1 U/ml [28], we excluded subjects with serum CA19–9 levels < 1.1 U/ml.

Statistical analysis. Data are expressed as the median values with range. Statistical analysis was performed by using EZR Ver. 1.25 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [29]. Comparisons between the 2 groups were performed by using the Mann-Whitney U test. For comparisons involving multiple groups, the Kruskal-Wallis test was used with post hoc comparisons according to the Steel-Dwass method. The chi-squared test was used to compare positive rates between the groups, and Fisher's exact test was used when the number of samples was small. The multiple comparison test was done with Bonferroni correction. Statistical significance was defined as $p < 0.05$. Only significant p-values are given in the Tables. CA19–9 and CA125

cutoff values of 37.0 and 35 U/ml, respectively, were assumed in this study.

Results

Patient characteristics. The number of patients, patient age, FIGO stage, histological subtype of the ovarian tumors, and characteristics of the healthy controls are shown in Table 1. Ages were expressed as the median with range. Interstitial infiltration of stage I ovarian tumors was classified as present or absent.

Serum CA19-9 and CA125 levels in the healthy controls and patients according to the histological subtype of the ovarian tumors. Serum CA19-9 and CA125 levels in the healthy controls and the patients according to the histological subtype of the ovarian tumors are shown in Table 2. Serum CA19-9 levels (median, range U/ml) were significantly higher in the patients with OE (36.8, 2.7-471.8), MBT (24.6, 6.1-6,222.3), and MT (18.5, 1.1-14,417.0) than in the healthy controls (8.0, 1.4-31.7). Moreover, serum CA19-9 levels were significantly lower in the patients with serous cystadenoma (7.7, 2.0-31.4), mucinous cystadenoma (11.9, 1.5-76.9), and SA (11.2, 1.1-1,102.9) than in the patients with OE. For CA19-9, the positivity rate in patients with OE (50%) was significantly higher than that in patients with SA (11%), but the positivity rates were not significantly different between patients with other histological subtypes and those with SA. The positivity rates in serous cystadenoma (0%) and mucinous cystadenoma (17%) were significantly lower than that in patients with OE.

Serum CA125 levels were significantly higher in the patients with OE (51.0, 9-226), MBT (41.0, 7-1,630), and MT (277.0, 9-22,470) than in the healthy controls (10.0, 5-32). Serum CA125 levels were significantly lower in the patients with OE, serous cystadenoma (14.0, 6-30), mucinous cystadenoma (15.0, 4-69), ELMBT (47.0, 14-889), ITMBT (31.0, 7-1,630), MA (22.0, 9-114), and CCA (46.0, 11-2,899) than in the patients with SA (1,847.0, 58-22,470). For CA125, the positivity rates of patients with OE (73%), serous cystadenoma (0%), mucinous cystadenoma (11%), ITMBT (47%), MA (40%), and CCA (57%) were significantly lower than that of patients with SA (100%). The positivity rates for serous cystadenoma and mucinous cystadenoma were significantly lower than that for OE.

Serum CA19-9 and CA125 levels according to the histological subtypes and FIGO stage of

Table 1 Patient characteristics

		Age	FIGO stage			
		Median	I	II	III	IV
	n	Median (range)	Interstitial infiltration (absent, present)			
Healthy control	113	51.0 (32-68)				
Ovarian endometriosis	52	34.0 (22-69)				
Epithelial ovarian tumors						
Benign tumor	68	52.0 (22-91)				
Serous cystadenoma	33	49.0 (24-91)				
Mucinous cystadenoma	35	55.0 (22-81)				
Borderline tumor						
Mucinous borderline tumor	24	48.0 (25-82)	22 (17, 5 [a])	1	0	1
Endocervical-like mucinous borderline tumor	7	42.0 (26-81)	6 (3, 3)	1	0	0
Intestinal type mucinous borderline tumor	17	50.0 (25-82)	16 (14, 2)	0	0	1
Malignant tumor	51	59.0 (20-86)	19 (0, 19 [b])	2	27	3
Serous adenocarcinoma	27	65.0 (38-80)	0 (0, 0)	1	23	3
Mucinous adenocarcinoma	10	39.5 (20-86)	10 (0, 10)	0	0	0
Clear cell adenocarcinoma	14	54.0 (34-74)	9 (0, 9)	1	4	0

a, For the stage I mucinous borderline tumors, interstitial infiltration was consisted of only leukocytes; b, For the stage I malignant tumors, iInterstitial infiltration was consisted of only cancer cells.

Table 2 Serum CA19–9 and CA125 levels in the healthy controls and patients according to the histological subtype of the ovarian tumors

	Serum CA19–9 levels			Serum CA125 levels		
	n	Median (range)	Positive rate (%)	n	Median (range)	Positive rate (%)
Healthy control	100	8.0 (1.4–31.7) [c,d,e]	0	113	10.0 (5–32) [c,d,e]	0
Ovarian endometriosis	48	36.8 (2.7–471.8) [a,b,d,f]	50[$]	52	51.0 (9–226) [a,b,d,g,j]	73[$]
Epithelial ovarian tumors						
Benign tumor	56	8.5 (1.5–76.9) [c,e]	9	68	14.0 (4–69) [c,d,e]	6
Serous cystadenoma	27	7.7 (2.0–31.4) [e]	0[#]	33	14.0 (6–30) [e,i,j,k,l]	0[#,$]
Mucinous cystadenoma	29	11.9 (1.5–76.9) [e]	17[#]	35	15.0 (4–69) [e,g,j]	11[#,$]
Borderline tumor						
Mucinous borderline tumor	20	24.6 (6.1–6,222.3) [a,b]	35	24	41.0 (7–1,630) [a,b,d]	54
Endocervical-like mucinous borderline tumor	7	39.1 (11.5–4,533.2)	57	7	47.0 (14–889) [j]	71
Intestinal type mucinous borderline tumor	13	16.0 (6.1–6,222.3)	23	17	31.0 (7–1,630) [f,g,i,j]	47[$]
Malignant tumor	49	18.5 (1.1–14,417.0) [a,b,e]	31	51	277.0 (9–2,2470) [a,b,c,e]	77
Serous adenocarcinoma	27	11.2 (1.1–1,102.9) [e]	11[#]	27	1,847.0 (58–22,470) [f,g,h,i,k,l]	100[#]
Mucinous adenocarcinoma	9	56.4 (2.5–14,417.0)	56	10	22.0 (9–114) [f,j]	40[$]
Clear cell adenocarcinoma	13	39.0 (2.6–132.0)	54	14	46.0 (11–2,899) [f,j]	57[$]

Serum CA19–9 levels, cut off value 37.0 U/ml; serum CA125 levels, cut off value 35 U/ml

The Kruskal-Wallis test was used with post hoc comparsions according to the Steel-Dwass method.

a, $p < 0.05$ vs. healthy control; b, $p < 0.05$ vs. benign tumor; c, $p < 0.05$ vs. mucinous borderline tumor; d, $p < 0.05$ vs. malignant tumor; e, $p < 0.05$ vs. ovarian endometriosis; f, $p < 0.05$ vs. serous cystadenoma; g, $p < 0.05$ vs. mucinous cystadenoma; h, $p < 0.05$ vs. endocervical-like mucinous borderline tumor; i, $p < 0.05$ vs. intestinal type mucinous borderline tumor; j, $p < 0.05$ vs. serous adenocarcinoma; k, $p < 0.05$ vs. mucinous adenocarcinoma; l, $p < 0.05$ vs. clear cell adenocarcinoma

The Chi-squared test or Fisher's exact test was used with Bonferroni correction for the comparison of positive rates.

#, $p < 0.05$ vs. ovarian endometriosis; $, $p < 0.05$ vs. serous adenocarcinoma.

the ovarian tumors. Serum CA19–9 and CA125 levels according to the histological subtypes and FIGO stages of the ovarian tumors are presented in Table 3. Most of the cases of ELMBT, ITMBT, MA, and CCA were categorized as stage I or II, early-stage cancers; and most of the cases of SA were categorized as stage III or IV, advanced cancers.

Serum CA19–9 levels were significantly higher in the patients with OE (36.8, 2.7–471.8) than in the patients with stage III SA (16.3, 1.1–1,102.9). Markedly elevated CA19–9 levels were observed in the patients with ELMBT, which involved interstitial infiltration of leukocytes, and in those with MA, which involved interstitial infiltration of cancer cells. For CA19–9, the positivity rate of stage III SA (16%) was significantly lower than that of OE (50%).

Serum CA125 levels were significantly higher in the patients with stage III SA (2,073.0, 58–22,470) than in the patients with OE (51.0, 9–226). Serum CA125 levels were significantly lower in the patients with stage I ELMBT (43.5, 14–889), stage I ITMBT (30.5, 7–200), stage I MA (26.0, 9–114), and stage I CCA (33.0, 11–119) than in the patients with stage III SA. For CA125, the positivity rate of OE (73%) was significantly lower than that of III SA (100%). Moreover, the positivity rates of stage III and IV EOT were 100% of CA125.

Serum CA19–9 and CA125 levels according to interstitial infiltrates in the patients with stage I epithelial ovarian tumors and ovarian endometriosis. The serum CA19–9 and CA125 levels according to interstitial infiltrates in the patients with stage I EOT and OE are shown in Table 4. For stage I MBT, the serum CA19–9 levels, as well as the positivity rate of CA19–9, were significantly higher in the patients with interstitial infiltration of leukocytes (218.8, 39.1–3,303.3; 100%) than in those with OE (36.8, 2.7–471.8; 50%) and without interstitial infiltration (14.2, 6.1–33.9; 0%). Serum CA19–9 levels, as well as the positivity rate with CA19–9, were significantly lower in the patients with stage I MBT without interstitial infiltration of leukocytes than in the patients with OE. In particular, the positivity rate of stage I MBT with interstitial infiltration was 100% of CA19–9.

In the patients with stage I MT with interstitial infiltration of cancer cells, the serum CA19–9 levels, as well as the positivity rate of CA19–9, did not differ significantly from those in the patients with OE. However, 10 patients with stage I MT showed ele-

Table 3 Serum CA19-9 and CA125 levels according to the histological subtypes and FIGO stage of the ovarian tumors

A

	n	Serum CA19-9 levels	Positive rate (%) Median (range)			
			FIGO stage			
			I	II	III	IV
Ovarian endometriosis	48	50 (24/48) 36.8 (2.7-471.8) [b]				
Epithelial ovarian tumors						
Mucinous borderline tumor	20		28 (5/18) 18.1 (6.1-3,303.3)	100 (1/1) 4,533.2	—	100 (1/1) 6,222.3
Endocervical-like mucinous borderline tumor	7		50 (3/6) 35.8 (11.5-3,303.3)	100 (1/1) 4,533.2	—	—
Intestinal type mucinous borderline tumor	13		17 (2/12) 15.3 (6.1-524.9)	—	—	100 (1/1) 6,222.3
Serous adenocarcinoma	27		—	0 (0/1) 20.6	12 (3/23) [#] 16.3 (1.1-1,102.9) [a]	0 (0/3) 8.3 (2.8-9.6)
Mucinous adenocarcinoma	9		56 (5/9) 56.4 (2.5-14,471.0)	—	—	—
Clear cell adenocarcinoma	14		63 (5/8) 41.7 (4.2-126.1)	0 (0/1) 11.9	50 (2/4) 67.8 (2.3-132.0)	

B

	n	Serum CA125 levels	Positive rate (%) Median (range)			
			FIGO stage			
			I	II	III	IV
Ovarian endometriosis	52	73 (38/52) 51.0 (9-226) [b]				
Epithelial ovarian tumors						
Mucinous borderline tumor	24		50 (11/22) 35.5 (7-889) [b]	100 (1/1) 289.0	—	100 (1/1) 1,630
Endocervical-like mucinous borderline tumor	7		67 (4/6) 43.5 (14-889) [b]	100 (1/1) 289.0	—	—
Intestinal type mucinous borderline tumor	17		44 (7/16) 30.5 (7-200) [b]	—	—	100 (1/1) 1,630
Serous adenocarcinoma	27		—	100 (1/1) 86.0	100 (23/23) [#] 2,073.0 (58-22,470) [a]	100 (3/3) 1,515.0 (807-1,729)
Mucinous adenocarcinoma	10		40 (4/10) 26.0 (9-114) [b]	—	—	—
Clear cell adenocarcinoma	14		44 (4/9) 33.0 (11-119) [b]	0 (0/1) 29.0	100 (4/4) 379.5 (53-2,899)	

(**A**) For serum CA19-9 levels, cut off value 37.0 U/ml.
(**B**) For serum CA125 levels, cut off value 35 U/ml.
The Kruskal-Wallis test was used with post hoc comparsions according to the Steel-Dwass method.
a, $p < 0.05$ vs. ovarian endometriosis; b, $p < 0.05$ vs. serous adenocarcinoma stage III
The Chi-squared test or Fisher's exact test was used with Bonferroni correction for the comparison of positive rates.
#, $p < 0.05$ vs. ovarian endometriosis.

vated CA19-9 levels higher than the cutoff value, and 9 of the 10 had interstitial infiltration of cancer cells.

For stage I MBT, the serum CA125 levels, as well as the positivity rate with CA125, were significantly lower in the patients without interstitial infiltrate (30.0, 7-9; 41%) than in the patients with OE (51.0, 9-226; 73%).

For stage I MT, the serum CA125 levels, as well as the positivity rate with CA125, were significantly lower in the patients with interstitial infiltrates (30.0,

Table 4 Serum CA19–9 and CA125 levels according to interstitial infiltrates in the patients with stage I epithelial ovarian tumors and ovarian endometriosis

		Serum CA19–9 levels	Positive rate (%) Median (range)			Serum CA125 levels	Positive rate (%) Median (range)	
			Interstitial infiltration				Interstitial infiltration	
	n		absent	present	n		absenct	present
Ovarian endometriosis	48	50 (24/48) 36.8 (2.7–471.8)			52	73 (38/52) 51.0 (9–226)		
Mucinous borderline tumor								
FIGO stage I	18		0 (0/13) [#] 14.2 (6.1–33.9) [a]	100 (5/5) [$] 218.8 (39.1–3,303.3) [a,b]	22		41 (7/17) [#] 30.0 (7–95) [a]	80 (4/5) 90.0 (14–889)
Malignant tumor								
FIGO stage I	17			59 (10/17) 44.3 (2.5–14,417.0)	19			42 (8/19) [#] 30.0 (9–119) [a]

Serum CA19–9 levels, cut off value 37.0 U/ml; serum CA125 levels, cut off value 35 U/ml.
The Mann-Whitney U test or the Kruskal-Walls test was used with post hoc comparsions according to the Steel-Dwass method.
a, $p < 0.05$ vs. ovarian endmetoriosis; b, $p < 0.05$ vs. intersititial infiltration absence.
The Chi-squared test or Fisher's exact test was used with Bonferroni correction for the comparison of positive rates.
#, $p < 0.05$ vs. ovarian endmetoriosis; $, $p < 0.05$ vs. intersititial infiltration absence.

9–119; 42%) than in the patients with OE.

Discussion

In this study, we examined the relationship between the FIGO stage and histological subtype of OE or EOT and the serum CA19–9 and CA125 levels to confirm the usefulness of these antigens as preoperative diagnostic markers.

According to the recent carcinogenesis model of the ovary, ovarian cancer can be divided into types I and II using a new classification based on morphological, molecular and biological analyses, and each type of tumor shows a different mode of progression in carcinogenesis [30, 31]. Low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, which are often confined to the ovary at the time of diagnosis, are classified as type I and considered to be genetically stable without TP53 mutations [32, 33]. In contrast, type II tumors, including high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas, are more aggressive and genetically highly unstable [34–36]. Despite a relatively good prognosis in early-stage disease, MA and CCA frequently have poorer responses to chemotherapies and survival than serous ovarian cancers [37–39]. MBT, which are generally characterized as having low malignant potential, without interstitial infiltration of cancer cells, present with peritoneal implants, lymph node metastases, and recurrence after resection [40–42].

In the histological subtype classification in our study, the serum CA19–9 levels and positivity rate of CA19–9 were significantly higher in patients with OE than SA, but those of CA125 were significantly lower in OE than in SA. For CA125, the positivity rates in subjects with OE, serous cystadenoma, mucinous cystadenoma, ITMBT, MA, and CCA were significantly lower than that in subjects with SA.

Several studies have described the positive rates of ovarian cancer and OE by using CA19–9 and CA125 levels as diagnostic markers. Kataoka *et al.* [15] reported that both CA19–9 and CA125 could be used to determine the histological type, because different positivity rates of CA19–9 and CA125 were observed according to the histological types of ovarian cancer. In other studies, one half of patients with localized (stage I) ovarian cancer and 90% of patients with advanced disease (stages II–IV) had increased serum CA125 levels [43]. For the revised American Society for Reproductive Medicine classification of endometriosis, the positivity rates of stage III and IV endometriosis were approximately 40% and 60% of CA19–9 and 50% and 80% of CA125, respectively [44].

In the present study, there were no significant differences between the positivity rate of CA19–9 and that of CA125 in either ovarian cancer or OE. The difference in the positivity rate of serum CA19–9 and CA125 among histological types of ovarian cancer was thought to depend on the diversity of histological types and the mechanism of production of these antigens in

type I and II ovarian cancer. Serum CA19-9 and CA125 levels were suggested to depend on the subtype of MBT, as well as the histological type of ovarian cancer. The positivity rate and serum levels of CA125 were significantly higher in SA than in other ovarian cancers.

CA19-9, the carbohydrate antigen sialyl Lewis a, is not a cancer-specific antigen, but a differentiation antigen [45]. Furthermore, epigenetic suppression of gene expression, including DNA methylation and histone deacetylation associated with carcinogenesis, has previously been reported to be the underlying cause of the induction of sialyl Lewis a carbohydrate expression in early-stage cancers [46-49]. In addition, disialyl Lewis a carbohydrate, which is highly expressed in normal epithelial cells, serves as a specific carbohydrate ligand of sialic acid-binding immunoglobulin-like lectin-7, and has been shown to mediate the interactions between leukocytes and epithelial cells in the normal mucosa [47]. Thus, disialyl Lewis a carbohydrate is considered to play an important role in the maintenance of immunological homeostasis [47].

In this study, for stage I MBT, the serum CA19-9 levels and positivity rate in the patients with interstitial infiltration of leukocytes were significantly higher than in those without interstitial infiltration and in those with OE. Therefore, the elevation of serum CA19-9 levels was considered to depend on the interstitial infiltration of leukocytes in MBT. In contrast, all the patients with stage I MT in this study had interstitial infiltration of cancer cells, but there were no significant differences in the serum levels of CA19-9 between stage I MT and OE, or in the positivity rates of CA19-9. Furthermore, the patients with stage I MT in this study did not include any histological types such as SA and endometrioid adenocarcinoma other than MA and CCA. However, 10 patients with stage I MT showed elevated CA19-9 levels above the cutoff value, of whom 9 had interstitial infiltration of cancer cells. These elevated serum CA19-9 levels in MT were considered to be due to the differences in the degree of interstitial infiltration of cancer cells and histological type. The mechanism of the elevation of CA19-9 levels in ovarian cysts has been well documented in a number of studies of mature cystic teratomas. Ito *et al.* [18] reported that leakage of CA19-9 from the cystic cavity into the bloodstream might be the main mechanism of elevation of the serum CA19-9 level.

Therefore, the mechanism of the elevation of serum CA19-9 levels involves the leakage of CA19-9 into the bloodstream from the cyst cavity via interstitial infiltration. CA19-9 levels are also elevated in patients with MBT with interstitial infiltration of leukocytes. These phenomena suggest that abnormalities in the expression of the carbohydrate moiety on the cell surface might be responsible for the carcinogenesis process. Therefore, in the immediate future, there is need of genome-wide analyses of the histological types of various ovarian cancers. With this information in hand, the CA19-9 level could become a tool for estimating drug susceptibility and prognosis.

In conclusion, serum CA19-9 and CA125 levels were useful in differentiating between OE and SA, but not between OE and EOT. Moreover, serum CA19-9 levels were useful for preoperative assessment between OE and stage I MBT, with or without interstitial infiltration. In addition, considering that the serum CA19-9 levels in stage I MBT were elevated via the interstitial infiltration of leukocytes and that precancerous lesions are associated with a cancerous glycosylation disorder in the process of inflammatory carcinogenesis, the CA19-9 level may be considered as a suitable biomarker for estimating drug susceptibility in the future.

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