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CA19-9 elevation in ovarian mature cystic teratoma: Discrimination from ovarian cancer – CA19-9 level in teratoma

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Background: We aimed to identify clinical characteristics of ovarian mature cystic teratoma (MCT) in association with CA19-9 elevation, and to determine if CA19-9 is a useful marker in discrimination of MCT from ovarian cancer (OC).

Material/Methods: Medical records of 322 women with pathologically-confirmed MCT or OC (stage 1 or 2) were reviewed retrospectively. The relationships between the characteristics of MCT (mean diameter, bilaterality, and pathologic components) and elevated CA19-9 were evaluated. Tumor markers in MCT were compared to those in OC.

Results: MCTs with CA19-9 elevation were correlated with a larger diameter (8.53±3.84 cm *vs.* 6.95±3.97 cm, p=0.002) and presence of fat component (67.1% *vs.* 32.9%, p<0.001), compared to those with normal CA 19-9. Although the incidence of CA19-9 elevation was not different between patients with MCT and OC (p=0.700), the mean value of CA19-9 was higher in those with OC (114.66±20.66 U/mL *vs.* 508.58±261.63 U/mL, p=0.013). In addition, simultaneous elevation of CA125 and CA19-9 was associated with a higher probability of malignant neoplasm (p<0.001; odds ratio: 23.7; 95% confidence interval: 8.863–63.576) than single elevation of CA 19-9.

Conclusions: CA19-9 could be an important tool in the diagnosis of ovarian mature cystic teratoma. CA19-9, in combination with CA125, might be a useful marker in discrimination of MCT from cancer.

Key words: CA 19-9 • CA 125 • mature cystic teratoma • ovary cancer • tumor marker

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Background

Mature cystic teratoma (MCT) is one of the most common benign neoplasms, accounting for 10–20% of all ovarian tumors [1]. Most women with MCT present with an asymptomatic adnexal mass, incidentally detected on routine pelvic examination or imaging studies. However, about 20% of patients with MCT can have complications, such as torsion, rupture, infection, and malignant transformation, which is why MCT should not be disregarded.

Histologically, MCT is an admixture of 1 or more of the 3 primary tissue layers: ectodermal, endodermal, and mesodermal tissue derivatives. Therefore, various tumor markers, including CA125 and CA19-9, are often elevated in ovarian MCT. Specifically, CA19-9, a monosialoganglioside associated with mucins in gastrointestinal adenocarcinomas, has been suggested as a potential marker in diagnosing ovarian MCT [2–6].

Although the characteristics of ovarian MCT in ultrasound have been well established, the nature of MCT could not be determined by imaging study alone. Moreover, if serum CA19-9 is elevated, it is not easy to rule out ovarian cancer (OC).

We aimed to identify clinical characteristics of ovarian MCT in association with CA19-9 elevation, and to determine if CA19-9 is a useful marker in discrimination of MCT from OC.

Material and Methods

We retrospectively reviewed clinical features of 239 patients with pathologically-confirmed MCTs at Seoul National University Bundang Hospital between 2003 and 2010, focussing especially concerning on tumor markers. Patients for whom CA 19-9 or CA 125 was not measured preoperatively were excluded from the study group. Characteristics of MCT, including the mean diameter, bilaterality, and pathologic components, were obtained from medical records and pathology reports. For comparison with MCT patients, tumor markers of 83 patients with pathologically-confirmed ovarian cancers (OC) were extracted from the cancer registry of Seoul National University Bundang Hospital between 2003 and 2010. All the patients with OC were stage 1 or 2. Almost all patients in the OC group had epithelial ovarian cancer, except for 1 patient with carcinosarcoma (malignant mixed Müllerian tumor) and 1 with granulosa cell tumor. Characteristics of patients with OC are shown in Table 1.

Pathologic findings of MCTs were analyzed by 5 pathologists, in terms of the following tumor characteristics: mean diameter; bilaterality; and the presence of pathologic components, including fat, calcification, solid portion, septation (gross findings on section), and soft tissue (on histologic examination).

Table 1. Relationships between CA19-9 elevation and clinical characteristics of mature cystic teratoma (MCT) were described. Mean diameter of the tumor and the presence of fat were associated with CA19-9 elevation.

Characteristics	
Age, yr	
Median	50
Range	25–89
FIGO stage, n	
1a	16
1b	4
1c	46
2a	3
2b	2
2c	12
Histology, n	
Epithelial ovarian cancer	81
Serous	26
Mucinous	18
Endometrioid	14
Clear cell	15
Transitional cell carcinoma	1
Others	7
Granulosa cell tumor	1
Carcinosarcoma	1

Absence of those pathologic components was defined as absolute invisibility on gross findings or histologic examination.

All the blood samples used for checking tumor markers were obtained preoperatively. The serum level of CA 19-9 and CA 125 were determined by radioimmunoassay on the Modular Analytics E 170 module (Roche Laboratory systems, Mannheim, Germany). The cut-off values for CA19-9 and CA 125 are 37 U/mL and 35 U/mL, respectively. All patients preoperatively underwent transvaginal or transabdominal sonography as part of the gynecologic examination.

The treatment modality was decided by considering patient age, desire to maintain fertility, and the presence of other pathologies. The treatment modality included oophorectomy, cystectomy, and hysterectomy with unilateral or bilateral salpingo-oophorectomy.

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Table 2. The frequency of CA19-9 elevation was similar between the 2 groups. On the other hand, elevated CA125 was more frequently observed in patients with cancer.

Clinical characteristics	Normal CA19-9 (N=134)	Elevated CA19-9 (N=105)	P-value
Mean diameter (cm)	6.95±3.97	8.53±3.84	0.002
Bilaterality			0.369
Unilateral	116 (57.4%)	86 (47.6%)	
Bilateral	18 (48.6%)	19 (51.4%)	
CA125			0.350
Normal	125 (57.1%)	94 (42.9%)	
Elevated	9 (45.0%)	11 (55.0%)	
Pathologic component			
Fat			< 0.001
Negative	107 (68.2%)	50 (31.8%)	
Positive	27 (32.9%)	55 (67.1%)	
Calcification			0.237
Negative	103 (58.5%)	73 (41.5%)	
Positive	31 (49.2%)	32 (50.8%)	
Soft tissue			1.000
Negative	96 (56.1%)	75 (43.9%)	
Positive	38 (55.9%)	30 (44.1%)	
Solid portion			1.000
Negative	125 (56.1%)	98 (43.9%)	
Positive	9 (56.3%)	7 (43.8%)	
Septation			1.000
Negative	121 (56.0%)	95 (44.0%)	
Positive	13 (56.5%)	10 (43.5%)	

Statistical analysis was performed using SPSS for Windows (version 18.0, SPSS Inc.). Statistical evaluation of the data was performed by Chi-square test, Fisher's exact test, and Student's t test. For all statistical tests, a P value less than 0.05 was considered significant.

Results

The mean age of patients with MCT was 33.4 years (range 5–73). Tumor size ranged from 2 cm to 30 cm in diameter with a mean (±SD) of 7.6 (±3.9) cm. The rate of bilaterality was 15.5% (37/239).

The relationships between CA 19-9 elevation and clinical characteristics of MCT are shown in Table 2. The mean diameter of MCT with CA 19-9 elevation was significantly greater than those without CA19-9 elevation (8.53±3.84 cm *vs.* 6.95±3.97 cm, p=0.002). Likewise, the presence of fat component at pathologic finding was more frequently observed in MCT with CA 19-9 elevation (67.1% *vs.* 32.9%, p<0.001). There were no significant differences in terms of CA 125 elevation, rate of bilaterality, and the presence of calcification, soft tissue, solid portion, and septation at pathologic findings. Multivariate analysis revealed that presence of fat components in MCT was an independent factor of CA19-9 elevation (HR 4.579, 95% CI 2.546–8.234, p<0.0001) (Table 3).

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Table 3. Multivariate analysis revealed that presence of fat component in MCT was an independent correlating factor of CA19-9 elevation (95% CI 2.546–8.234).

Clinical characteristics	Hazard ratio	(95% CI)	P-value
Bilaterality			0.478
Bilateral	1.318	(0.614–2.829)	
Unilateral	1		
CA125 level			0.200
Elevated	1.898	(0.713–5.050)	
Normal	1		
Pathologic component			
Fat			< 0.0001
Positive	4.579	(2.546–8.234)	
Negative	1		
Calcification			
Positive	1.363	(0.725–2.563)	0.337
Negative	1		
Soft tissue			0.498
Positive	1.238	(0.668–2.295)	
Negative	1		
Solid portion			0.616
Positive	0.754	(0.250–2.274)	
Negative	1		
Septation			0.865
Positive	0.921	(0.358–2.368)	
Negative	1		

The distribution of tumor markers in patients with MCT and OC is shown in Table 4. Although the mean value of serum CA 19-9 was higher in patients with OC than MCT (114.6±20.66 *vs.* 508.58±261.63 U/mL, p=0.013), the rate of CA 19-9 elevation was not different between the 2 groups (43.9% *vs.* 40.9%, p=0.700). Interestingly, single elevation of CA19-9 was more frequent in patients with MCT than OC (39.3% *vs.* 10.8%). On the other hand, the mean value of serum CA 125 was higher (24.71±4.16 *vs.* 483.6±159.6 U/mL, p<0.001). The elevation of CA 125 was more frequently observed in patients with OC than MCT (68.7% *vs.* 8.4%, p<0.001). Normal CA 125 was significantly associated with MCT than OC (91.6% *vs.* 31.3%, p<0.001).

Subgroup analysis of patients with elevated CA19-9 revealed that simultaneously elevated CA125 was associated with a higher probability of malignant neoplasm (p<0.001) (Table 5). The odds ratio for CA125 elevation was 23.7 (95% confidence interval 8.863–63.576). In other words, the negative predictive value and positive predictive value of CA125 was 91.3% and 69.4%, respectively, for cancer discrimination in patients with elevated CA19-9.

Discussion

Despite the specific features of MCT, including fat component and calcification by pelvic imaging studies, making a differential diagnosis is sometimes very difficult. According to a report by Mais et al., nearly 30% of MCT may not be apparent in sonography, due to the presence of associated pelvic abnormalities (e.g., endometriomas, large fibromas, or large contralateral ovarian masses) or intrinsic sonographic characteristics of MCTs [7]. Actually, 80% of cystic teratomas were reported to have an echo pattern that should suggest malignancy [8]. In addition, other features of MCT, such as a very large tumor size and significantly elevated tumor markers could make the diagnosis more difficult. Because the surgical procedure performed

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Table 4. Simple comparison between teratoma and cancer patients, regarding CA125 /CA19-9 elevations revealed that normal CA125 level was more frequent in patients with teratoma than those with cancer (91.6% *vs.* 31.3%, p<0.001). In addition, single elevation of CA19-9 was more frequently observed in patients with teratoma than those with cancer (39.3% *vs.* 10.8%).

	Teratoma (N=239)	Cancer (N=83)	*P*-value
CA125 & CA19-9			<0.001
All normal	125 (52.3%)	17 (20.5%)	
CA19-9 only elevated	94 (39.3%)	9 (10.8%)	
CA125 only elevated	9 (3.8%)	32 (38.6%)	
All elevated	11 (4.6%)	25 (30.1%)	

Table 5. Single elevation of CA19-9 in addition to normal CA125 was correlated with a higher rate of teratoma, with likelihood ratio of 23.7 (95% CI 8.863–63.576).

CA125	Teratoma	Cancer	P- value	Odds ratio	95% CI*
Normal	94 (91.3%)	9 (8.7%)	<0.001	23.7	8.863–63.576
Elevated	11 (30.6%)	25 (69.4%)			

* CI – confidence interval.

is quite different for benign and malignant tumors, differential diagnosis is very important for women with an ovarian mass.

As a tool to assist in the diagnosis of MCT, the importance of serum CA19-9 level has been proposed in many studies [4–6]. CA19-9 is a sialylated Lewis A antigen, which is associated with mucins in gastrointestinal adenocarcinomas and is frequently expressed in the mucinous histotype of OC [3]. It is not surprising that CA19-9 is commonly elevated in patients with MCT, considering the histological feature of MCT, which contains various kinds of tissue.

According to our results, CA 19-9 was more frequently elevated than CA 125 and thus could be a more useful marker in MCT. The rate of CA19-9 elevation in MCT has been reported to be from 39% to 59% [9,10]. In our data, CA19-9 was elevated in 43.9% of patients with MCT. The negative predictive value and positive predictive value of CA19-9 for MCT was 26.8% and 75.5%, respectively. Thus, CA19-9 testing alone is not sufficient for the diagnosis of MCT. However, when the nature of a pelvic mass cannot be determined by imaging study alone, CA19-9 testing might be a potent tool assisting MCT diagnosis.

The relationship between CA19-9 elevation and clinical characteristics of MCT has not been well documented. There have been only a few reports elucidating the relationship between serum CA19-9 level and characteristics of MCT. In a retrospective study evaluating 163 patients with ovarian MCT, the authors concluded that CA 19-9 elevation appears to correlate with a larger tumor diameter and higher rate of ovarian torsion [6]. Likewise, another retrospective study evaluating 215 patients with ovarian MCT concluded that serum CA19-9 levels were correlated with larger tumor size, although they failed to show a positive relationship between bilaterality and CA19-9 elevation [9]. The above study results are compatible with our own results. However, to the best of our knowledge, ours is the only study showing significant correlation between CA19-9 elevation and the presence of fat component in MCT.

The presence of CA19-9 in the bronchial mucosa and glands of MCT has been demonstrated by immunohistochemical stains [11] and the secretion of CA19-9 into the cystic cavity of the lesion has been revealed [11]. According to those findings, the principal mechanism of the elevation of CA19-9 in MCT is thought to be leakage from the cystic cavity into the blood stream [11]. Therefore, in the more probable conditions of leakage into the blood stream, such as larger or bilateral MCT, serum CA19-9 elevation might be expected. Similarly, our results indicate that CA19-9 elevation is correlated with larger tumor size, but we could not find a significant correlation between CA 19-9 elevation and bilateral MCT. In contrast to the present study, Dede et al suggested that CA19-9 elevations were associated not with tumor size, but with bilaterality in 2.8 of likelihood ratio [4]. Additionally, they reported that bilateral MCTs showed a significantly higher rate of ectodermal component than that shown by unilateral MCTs. Considering the secretion mechanism of CA 19-9 from bronchial mucosa and glands in MCT, it appears to be reasonable that there should be a positive correlation between endodermal tissue components in MCT and CA 19-9 elevation. However, in the present study, CA19-9 elevation was significantly associated with a fat component, which is a mesodermal tissue derivative. We did not categorize the tissue components of MCT as

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ectoderm, mesoderm, and endoderm, thus we could not exactly determine the presence and proportion of each component in each MCT. According to prior reports, all 3 tissue components are present in over 90% of MCTs [12], but there is little information about the quantity and proportion of each component in ovarian MCT. We can only assume that there might be more endodermal tissue components in MCT, if there are fat components that can be easily detected at gross pathology examination.

Comparison of tumor markers between patients with MCT and OC revealed that the rate of CA19-9 elevation was not different between the 2 groups. In contrast, CA125, which is the most widely used marker for OC, was more frequently elevated in the OC group. In accordance with previous reports, CA125 was elevated in approximately 70% of the stage 1 and 2 OC cases [13,14].

CA125 is known to be expressed in coelomic epithelium, including Müllerian epithelium, peritoneum, pleura, and pericardium [15]. Considering the wide distribution of CA 125 expression, elevations of serum CA125 in various benign and inflammatory conditions, including MCT, are not unexpected. Even though the combination of CA125 level and imaging studies raised the early detection rates of ovarian malignancy, sometimes more information is required to distinguish MCT from OC [16,17]. Difficulty in the differential diagnosis of MCT from OC usually stems from the morphologic and serologic characteristics of MCT, including large size and elevations of various tumor markers.

Although there was a study that compared various tumor markers in MCT, there is no English literature regarding discrimination of MCT from OC in elevated CA19-9 [9]. Therefore, we evaluated the correlation between elevated CA125 and OC in patients with elevated CA19-9 by subgroup analysis.

According to our results, if the nature of a pelvic mass with elevated CA19-9 is not determined by imaging study alone, serum CA125 should be checked for the differential diagnosis between MCT and OC. Although our study was a very simple comparison of patients with OC and MCT, we can say that CA125 can provide useful information in determining the nature of a pelvic mass with elevated CA19-9.

Conclusions

Serum CA19-9 has clinical importance as a tool to assist in the diagnosis of MCT, even though it is not sufficient as a single tool. In combination with imaging studies and CA125, CA19-9 could offer valuable information in diagnosing MCT. In other words, when we encounter an obscure pelvic mass in an imaging study and serum CA19-9 is elevated, CA125 could provide useful information. If the serum CA125 level is normal, there is a high probability of MCT. In addition, CA19-9 elevation in patients with MCT was correlated with the presence of fat component in the tumor at gross pathology findings. The biochemical mechanisms of CA19-9 elevation and tissue component of MCT should be clarified in future studies.

This study was a retrospective comparison without matching and has some limits, including a relatively small study group size, and possible bias at pathology findings owing to the involvement of different pathologists. In the future, a large-scale, randomized controlled trial comparing various tumor markers between MCT and OC should be conducted.

Disclosure statement

The authors report no conflict of interest.

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