The role of tumor markers in predicting mature cystic teratoma of the ovary

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Abstract

Objective. The objective of this study was to evaluate size, torsion rate, bilaterality, histopathologic origin, and the serum levels of some tumor markers in patients with mature cystic teratomas of the ovary. **Methods.** Retrospective study of 110 patients operated at Department of Obstetrics and Gynecology, Bakirkoy Dr. Sadi Konuk Turkey, between January 1998 and December 2003 was performed. The patients were divided into two groups according to cut off levels of each cancer antigens (CA) 19-9 and CA 125. Statistical analysis of the data was performed by Student's t test, Pearson's chi-square test and Mann-Whitney rank sum test. **Results.** The mean age was 36.01 ± 12,403 years (range 15-78). The mean tumor diameter was 67.83±32.049 mm (range 27-211mm). The mean serum tumor markers of CA 19-9 and 125, carcinoembryogenic antigen and a-fetoprotein levels were 101.2±179.7 IU/mL, 32.0±37.8 U/mL, 1.46±1.20 ng/mL and 2.7±3.0 ng/mL. The bilaterally rate was 6.4% in the normal CA19-9 group and 5.4% in the normal CA125 group. There was no bilaterally in both of the elevated CA19-9 and CA125 groups. The histopathologic component of the teratomas were sebum (70%), hair (62.7%), keratin (20%), cartilage (16.3%) and teeth (3.6%). The torsion rate was 11.5% in the normal CA19-9 group, 15.20% in the normal CA125 group and 15.6% in the elevated CA19-9 group. There was no patient with torsion in the elevated CA125 group. **Conclusion.** Our study shows that there was no statistical significance between the two analyzed groups in respect to relation between tumor markers and the mean tumor size, bilaterally or torsion rate.
Keywords: ectoderm, mature teratoma, ovary, tumor markers.

Introduction

Mature cystic teratoma (MCT) is defined as a tumor that contains elements of mesoderm, endoderm and ectoderm. The content of this cystic formation may include sebum, hair, skin and occasionally teeth as well[1,2]. MCT is the most common germ cell tumor of the ovary in young women and accounts for 5-25% of all ovarian tumors. The malignant transformation of MCT is rare and the reported incidence is 1-3%[3,4]. MCT usually presents as an asymptomatic adnexal mass incidentally detected on routine pelvic examination. Having in the view that the ultrasonographic features comprising the tumor are various in which can make it difficult to distinguish MCT from other ovarian neoplasms[5,6], additional diagnostic tools are required.

Ovarian MCT contains various types of tissues in which some tumor markers are expected to be positive and may be helpful in differential diagnosis of pelvic masses[7]. Among others, cancer antigens (CA) 19-9, CA125, alpha-fetoprotein (AFP) and carcino-embryogenic antigen (CEA) are the most important tumor markers for predicting the diagnosis of ovarian neoplasms.

In this study, we aimed to evaluate serum levels of tumor markers and their relations with the mean tumor size, torsion rate and bilaterally in patients with MCT, and additionally we also evaluated the relation between tumor markers and histopathological components like sebum, hair, cartilage and teeth.

Methods

Before the onset of data collection, approval was obtained from the institutional review board of Bakirkoy Dr. Sadi Konuk Teaching and Research Hospital, Istanbul. From a number of 126 patients with histopathologically confirmed MCT of the ovary between January 2007 and December 2011 in our department, only 110 of these patients were included into the study. The other 16 patients were emergent cases and the data for the tumor markers were not available. The parameters analyzed were age, gravity, parity, ultrasonographic findings and laboratory results. We used radioimmunoassay methods for detection of AFP, CA 19-9, CA 125 and CEA.

All the blood samples were obtained preoperatively and the analysis performed in Architect C16200 integrated systems (Abbott Laboratories, Abbott Park, IL, USA). The cut off values for AFP, CEA, CA 19-9 and CA 125 were 11.3ng/ml, 3.4 ng/ml, 37 U/mL and 35 U/mL. Furthermore, all patients underwent transabdominal and/or transvaginal ultrasound examinations before the operations. General Electric Medical Systems 200 (Milwaukee, WI, USA) with a 3.5-MHz transabdominal sector probe and a 6.5-MHz transvaginal probe were used. Oophorectomy, cystectomy, or hysterectomy with unilateral or bilateral salpingo-oophorectomy was performed as treatment modality according to age, fertility desire, and experience of the surgeon and presence of other pathologies. In our daily practice we evaluate AFP, CEA, CA 19-9 and CA125 for the patients with suspicious adnexal masses. In this study we want only to compare the mostly reported tumor markers

for MCT, CA 19-9 and CA 125 respectively, by using their normal and elevated values. The patients were divided into two groups according to elevated and normal values of the tumor markers, CA 19-9 and CA 125. The cut off level for the CA 19-9 group was 37 and the cut off level for the CA 125 group was 35.

The mean tumor size was categorized and ranged from less than 4 cm, 4-6 cm, 6-8 cm, 8-10 cm, and over 10 cm. The parameters such as age, the mean tumor size, laterality of the tumors, torsion rate and histopathologic components were compared with the elevated rate of CA19-9 and CA125.

The statistical analysis was performed by using NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) among the two groups. Geometric mean was used for mean values of CA 125 and CA 19-9 because of the heterogenous distribution of these markers. Statistical analysis included the Student's t test, Pearson's chi-square test and Mann-Whitney rank sum test where appropriate. P value less than 0.05 was considered as significant.

Results

The mean age, gravity and parity of 110 patients was 36.01±12.403 (range 15-78), 2,52±2,324 (range 0-12) and 1,98±1,751 (range 0-9) respectively. The mean tumor diameter was 67.83±32.049 mm (range 27-211mm). The mean tumor size was categorized and ranged from less than 4 cm, 4-6 cm, 6-8 cm, 8-10 cm and over 10 cm to find out the relation between tumor size and tumor markers. The bilaterally rate was 6.4% in the normal CA 19-9 group and 5.4% in the normal CA125 group. There was no bilaterally in both of the elevated CA 19-9 and CA 125 groups.

The mean serum CA 19-9 level was 77.25±323.89 IU/mL and there was 78 (70.9%) patients with normal and 32 (29.1%) patients with elevated CA 19-9 levels. The mean serum CA125 level was 27.87±33.48U/mL and was 92 (83.6%) patients with normal and 18 (16.4%) patients with elevated CA 125 levels. The mean serum AFP level 2.46±1.23ng/mL and mean serum CEA level was 1.60±1.22 ng/mL. Among these tumor markers, CA 19-9 was with the highest elevation rate 32 (29.1%), however there was no patient with elevated AFP level (Table 1). Both of the tumor markers, CA19-9 and CA125, were elevated only in 6 patients (5.5%). CA19-9 levels were
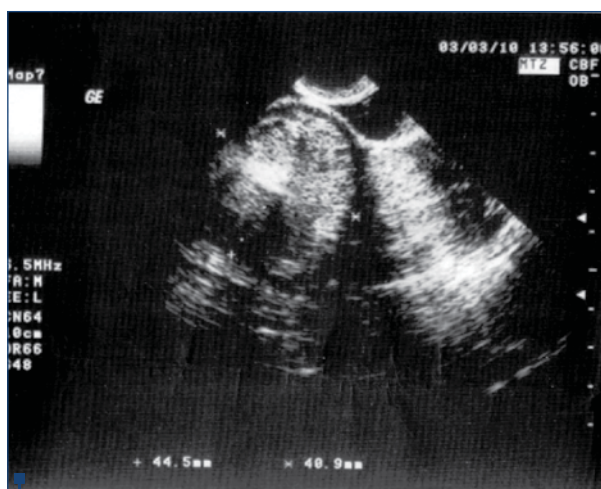

Figure 1. Transvaginal ultrasonography showing complex mass with echogenic components

greater than 100 IU/mL in 10 patients (9.1%) and greater than 500 IU/mL in only 2 patients (1.8%). Table 2 shows the clinical characteristics of women with elevated and normal levels of CA19-9 and CA 125.

There was no statistical significance considering: mean age, bilaterally, tumor size, rate of ovarian torsion between the two groups. The relation between final histopathological results and tumor markers were evaluated and there was no statistical significance in both of the elevated and normal groups of CA19-9 and CA125 (Table 2). The relation between tumor markers and tumor component was also evaluated. The pathological component of the teratomas was keratin, sebum, hair, cartilage, teeth. We found a statistical significance between CA 19-9 elevation and teeth or keratin component (P value of 0.039 and 0.021 respectively) (Table 3). Figure 1 shows the trans-vaginal ultrasonography findings.

Discussion

Ovarian MCT accounts for 5-25% of all ovarian tumors[8]. Although some women complain of lower abdominal pain, vaginal bleeding or other symptoms[9,10] it is difficult to accurately diagnose of teratoma with given symptoms and/or ultrasonography. It is particularly difficult to differentiate MCT from endometrioma, tubo-ovarian abscess, hemorrhagic corpus luteum cyst, and other malignant diseases[11]. The difficulty in diagnosing MCT of

Table 1	Distribution of serum tumor markers in ovarian MCT				
Tumor markers	**n**	**Cut-off value**	**Mean±SD**	**Range**	**Elevated rate n (%)**
CA125	110	35	27.87±33.48	2.3-248	18 (%16.4)
CA 19-9	110	37	77.25±323.89	0.01-3269.3	32 (%29.1)
CEA	110	3.4	1.60±1.22	0.01-9.73	8 (%7.27)
AFP	110	8.1	2.46±1.23	0.68-7.95	0 (%0)

Table 2 Clinical characteristics of women with elevated and normal levels of CA 19-9 and CA 125

		Normal CA 19-9		Elevated CA 19-9		P value	Normal CA125		Elevated CA125		P value
Age		37.33±12.88		34.72±12.23		0.329	36.51±12.69		36.89±13.06		0.909
Gravidity		2.67±2.47		2.28±2.2		0.446	2.62±2.36		2.22±2.63		0.522
Parity		2.12±1.84		1.88±1.72		0.528	2.11±1.84		1.72±1.64		0.408
		n	%	n	%		n	%	n	%	
Size	<4 cm	13	16.7	2	6.3	0.122	13	14.1	2	11.1	0.714
	4-6 cm	35	44.9	12	37.5		40	43.5	7	38.9	
	6-8 cm	14	17.9	5	15.6		17	18.5	2	11.1	
	8-10 cm	9	11.5	10	31.3		14	15.2	5	27.8	
	>10 cm	7	9	3	9.4		8	8.7	2	11.1	
Side	Bilateral	5	6.4	0	0	0.316	5	5.4	0	0	0.117
	Right	44	56.4	18	56.3		48	52.2	14	77.8	
	Left	29	37.2	14	43.8		39	42.4	4	22.2	
Torsion	Torsion (-)	69	88.5	27	84.4	0.559	78	84.8	18	100	0.076
	Torsion (+)	9	11.5	5	15.6		14	15.2	0	0	

Table 3 Histopathological components of mature cystic teratoma in the elevated and normal CA 19-9 and CA 125 groups

Tumor compound	Normal CA 19-9		Elevated CA 19-9		P value	Normal CA125		Elevated CA125		P value
	n	%	n	%		n	%	n	%	
Sebum	52	66.7	25	78.1	0.234	64	69.6	13	72.2	0.822
Hair	48	61.5	21	65.6	0.687	57	62	12	66.7	0.705
Keratin	20	25.6	2	6.3	*0.021	18	19.6	4	22.2	0.797
Cartilage	14	17.9	4	12.5	0.483	13	14.1	5	27.8	0.152
Teeth	1	1.3	3	9.4	*0.039	3	3.3	1	5.6	0.634

the ovary therefore necessitates additional diagnostic tools, such as tumor markers. CA19-9, CA125, AFP and CEA are the most important tumor markers for the diagnosis of ovarian neoplasms, especially CA19-9 which has been used to identify gastrointestinal tract tumors in practice[12,13], and CA125 the most studied ovarian cancer-associated marker.

It is well known that CA19-9 is active in the bronchial mucosa and glands of MCT and it has been shown to be secreted into the cystic cavity of the lesion. The mechanism of an elevated CA19-9 in MCT is principally the leakage from cystic cavity into the blood stream[14-17]. The CA125 is expressed in coelomic epithelia such as müllerian epithelium, peritoneum, pleura and pericardium[18]. Serum CA125 assay is a useful preoperative test for prediction of epithelial ovarian cancer and provides additional data to help discriminate between benign and malignant adnexal masses[19-22]. Clinical application of CA125 in ovarian cancer also includes monitoring disease response to

treatment, detecting disease recurrence and estimating prognosis. In differential diagnosis of adnexal masses AFP and CEA are also studied before[23]. Elevated serum AFP levels occur in hepatocellular carcinoma, pregnancy, hepatitis, liver cirrhosis, and other malignancies such as tumors of gonadal origin and the gastrointestinal tract[24]. High levels of CEA expression have been noted on a variety of gastrointestinal epithelial tumors and it is usually used to differentiate gastrointestinal tumors from gynecological malignancies[25].

One study showed CA19-9 to be the only marker for ovarian MCT and commonly elevated in women with these tumors[26]. In this study we found only 32 (29.1%) of women who had elevated CA19-9 levels which is the highest elevation rate among the other tumor markers, being in correlation with the other studies[7,9,23]. In patients with MCT, the elevated level of CA125 was 18 (16.4%), a higher value in respect to 12.7% value found by Mikuni et al.[27].

We evaluated also AFP and CEA markers for the patients with suspicious adnexal masses. Interestingly, AFP was not elevated and showed similar results with that reported by Kawai et al.[28]. The elevated rate of CEA was seen in 8 (7.27%) of the patients which had the same prognostic like in Dede et al.[23] study.

Moreover, we categorized the mean tumor size to find out if there is a relation between tumor markers and elevated tumor size. Kyung et al.[29] reported a number of 163 patients with MCT and they concluded that elevated CA19-9 levels appear to correlate with larger tumor diameters. Despite of the other studies reported before, in our cases there was no statistical significance between tumor size and tumor markers (P=0.122 and P=0.714 for normal and elevated CA19-9 and CA125 groups). Studies reported by Dede et al.[23] are also in good correlation with our results, without any statistical significance[23].

Ovarian MCT occurs more frequently on the right side than on the left, and it is bilateral in about 10% of the patients[30]. In our study 68 (56.2%) of the patients had adnexal mass in the right side, and 48 (39.7%) of them in the left side which is similar to the literature. There was only 5 (4.1%) of patients with bilateral ovarian teratoma. In contrast to Dede et al.[23] results, serum CA19-9 and CA125 levels were not significantly related to bilaterality in our study and that can be due to our small number of sample size.

The torsion rate in ovarian MCT is higher than in other ovarian tumors datorated to adipose tissues, which are abundant in MCT, which increase the fluidity in the pelvic cavity[9].

Kyung and contributors[29] reported that the rate of ovarian torsion in women with elevated CA19-9 levels was significantly higher than that in women with normal CA19-9 levels due to larger tumor diameters. In our study there was no statistical significance between elevated tumor markers and ovarian torsion rate (P=0.559 and P=0.076 for normal and elevated CA19-9 and CA125 groups).

Kikkawa et al.[26] assessed the value of CA19-9, CA125, and CEA in making a differential diagnosis between MCT and squamous cell carcinoma arising from MCT. In 92 patients with MCT, they found that CA19-9 was the only marker, the mean level of which was above the cut off value. In our study there was one squamos cell cancer differentiated from MCT and serum CA19-9 and CA125 levels were surprisingly normal.

MCTs are composed of well-differentiated tissues derived from the three germ-cell layers (ectoderm, mesoderm, and endoderm). In a retrospective study of 501 cases, Ayhan et al.[9] reported that an ectodermal and a mesodermal tissue were present in all cases, whereas only 3.5% of teratomas had an endodermal tissue. In our study histopathologic component of the tumors were sebum (70%), hair (62.7%), keratin (20%), cartilage (16.3%) and teeth (3.6 %). The results of our study were similar to Ayhan et al.[9] which showed that ectodermal and mesodermal tissues were the most common components of MCT. Surprisingly we found a statistical significance between CA19-9 elevation and both of teeth and keratin component (P= 0.039 and P=0.021, respectively), but we cannot conclude that as a certain results and the data has to be supported with larger series.

Conclusions

CA19-9 could be the only important marker in the diagnosis of MCTs. CA19-9 may be useful as an adjunct tool for the diagnosis of ovarian teratoma, but it has to be combined with imaging studies. Moreover, CA19-9 and CA125 tumor markers could be elevated in both benign and malignant conditions, and the interpretation of these findings must be made in the clinical condition of the patient point of view. Further, larger prospective studies are required to confirm these results. ∎

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