Do high levels of CA 19-9 in women with mature cystic teratomas of the ovary warrant further evaluation?

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Summary

Purpose: To evaluate the serum levels of tumor markers (particularly CA 19-9) in patients with ovarian mature cystic teratomas (MCT) with respect to age, size, bilaterality, menopause, presence of adhesions, complications and the postoperative levels. *Methods:* We evaluated clinical characteristics and tumor markers of 157 patients with MCT of the ovary operated at our clinic. *Results:* CA19-9 was the only tumor marker with a mean serum level (46.95 ± 101.11 U/ml) above the cut-off value and the elevated rate was 33.1%. Tumor size, presence of adhesions and CA 125 levels were significantly higher in patients with elevated CA 19-9. Bilaterality rate was 10.8%. The most common complication was torsion (6.4%). *Conclusion:* We suggest that elevated levels of CA 19-9 may be expected in MCTs of the ovary and that they will probably be decreased postoperatively. Therefore, postponing evaluation of other possible sources of CA 19-9 elevation in asymptomatic and young patients is more common sense.

Key words: Tumor markers; CA 19-9; Mature cystic teratoma; Ovary; Adhesion.

Introduction

Mature cystic teratomas (MCT) or dermoid cysts are germ cell tumors of the ovary. They are the most common type of ovarian tumor accounting for 27-44% of all primary ovarian tumors [1]. A vast majority of these tumors are benign and in about 1% of MCTs, one tissue element shows malignant transformation, most often to squamous cell carcinoma [2]. MCTs generally occur during reproductive years with a mean age of 32 years and are commonly unilateral (about 88% of cases) [1].

Quite discrete surgical approaches in MCTs and malignant tumors emphasize the need for making a differential diagnosis of patients with ovarian tumors, and serum tumor markers have been shown to be useful in providing additional information [3-6]. There are few studies concerning the clinical value of tumor markers in the diagnosis and management of MCT [4, 5, 7-9]. Almost all studies have suggested that CA 19-9 may be the only tumor marker with clinical significance.

In this study, our aim was to evaluate the serum levels of tumor markers (particularly CA 19-9) in patients with ovarian MCTs with respect to age, size, bilaterality, menopause, presence of adhesions, complications and the postoperative levels.

Materials and Methods

Patients with MCT of the ovary, who underwent surgery in Gaziantep University, Faculty of Medicine, Department of Obstetrics and Gynecology between November, 2001 and August, 2010 were reviewed through hospital charts and pathology archives. Ultrasound examinations were performed with a 3.5-MHz transabdominal sector probe and/or a 7.5-MHz transvaginal probe (Applio, Toshiba, Japan). MCTs were typically diagnosed when there was a homogeneous ovarian hyperechoic mass with regular capsule and posterior shadowing or a heterogenous mass with irregular hypo- and hyperechoic appearance with posterior shadowing without any septa [10].

Age of the patients, average tumor size (according to operative records and gross pathologic descriptions), bilaterality, preoperative and postoperative serum tumor marker levels [including CA 19-9, CA 125, CA 15-3, alpha-fetoprotein (AFP), and carcino-embryogenic antigen (CEA)], presence of any adhesions and complications observed during surgery were all recorded.

No further imaging and endoscopic procedure had been performed in patients in order to rule out any possible gastrointestinal tract disease.

The determination methods and cut-off values were immunoassay for AFP (11.3 ng/ml), CA 19-9 (37 U/ml), CA 125 (35 U/ml) and CA 15-3 (30 U/ml) and enzyme immunoassay for CEA (3.4 ng/ml). Analyses were performed on the Modular Analytics E170 module (Roche Laboratory Systems, Mannheim, Germany).

Surgeries performed for MCTs were cystectomy, oophorectomy or hysterectomy with unilateral or bilateral salpingo-oophorectomy according to age, desire of future fertility or presence of other pathology.

According to serum level of CA 19-9 patients were divided into an elevated level group (Group I) and a normal level group (Group II). Groups were compared in terms of clinical characteristics and preoperative or postoperative serum tumor markers. Also the correlation of diameter of tumor to CA 19-9 levels was analyzed.

Statistical analysis was performed with SSPS 13 software (SSPS Inc, Chicago, IL). Statistical evaluation of the data was performed by the chi-square test, Student's *t*-test, Mann-Whitney U test and Pearson's test. Differences were considered significant when $p < 0.05$ for the two-tails.

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Results

There were 157 patients with MCT of the ovary who underwent an operation in our clinic. The mean age of all patients was 37.45 ± 14.90 years (median 35; range 15-84). Overall, 33 patients (21%) were in the postmenopausal period. Tumor size ranged from 2.5 to 28 cm in diameter, with a median and mean ± SD, 7 cm and 7.88 ± 3.62 cm, respectively. The overall bilaterality rate after pathologic examination was 10.8%. Unilateral tumors were more abundantly observed on the right side (77 patients, 49%) than the left (63 patients, 40.1%). Intraoperative adhesions were detected in seven patients (4.5%). The most commonly observed complication was torsion, followed by infection, rupture and malignant transformation, observed in ten patients (6.4%), six patients (3.8%), one patient (0.6%) and one patient (0.6%), respectively. Infection resulted in a tubo-ovarian abscess in one patient who had a CA19-9 level of 60.9 U/ml. The malignant transformation was reported as squamous cell carcinoma in a 67-year-old woman who had only preoperative serum CA 125 level evaluated, which was 7.82 U/ml.

Preoperative serum CA 125 (157 patients), CA19-9 (148 patients), CA 15-3 (53 patients), AFP (25 patients) and CEA (52 patients) levels of the patients were: 19.59 ± 22.01 U/ml, 46.95 ± 101.11 U/ml, 21.45 ± 8.66 U/ml, 2.37 ± 2.54 ng/ml and 2.60 ± 3.96 ng/ml, respectively. CA19-9 was the only tumor marker with a mean serum level above the cut-off value. Elevated rates of serum tumor markers from most common to least were CA 19-9 (33.1%), CA 125 (19.1%), CA 15-3 (18.9%), CEA (15.4%) and AFP (4%).

As shown in Table 1, there was no difference in terms of patient age, menopause and bilaterality of tumor between groups I and II. The mean tumor diameter of group I was significantly greater than group II (p = 0.001). We determined a weak positive correlation of CA 19-9 levels to diameter of tumor (r = 0.33, $p < 0.001$) in all patients. In group I there was a moderate positive correlation of CA 19-9 levels to diameter of tumor (r = 51, $p < 0.001$) (Figure 1) but there was no such correlation in group II (r = 0.04, p = 0.687). There was a significant difference in terms of adhesions between groups (p = 0.003). Also, tumor marker levels of groups are also shown in Table 1.

When complications were reviewed, torsions observed in the patients of group I and II were three (6.2%) and seven (7.1%), respectively (p = 0.829). Also, no significant difference was revealed between the groups, as there was one patient with a complication of infection in group I (2.0%) and four patients in group II (4.0%) (p = 0.528). There was only one patient with rupture and again only one patient with malignant transformation in group I, with no such complications in group II (p = 0.155).

Postoperative assessment of CA 19-9 levels in 33 patients of group I revealed that elevated rate was decreased to 0%, and mean CA 19-9 level was decreased from 157.28 ± 172.78 to 15.11 ± 10.48 U/ml ($p < 0.001$).

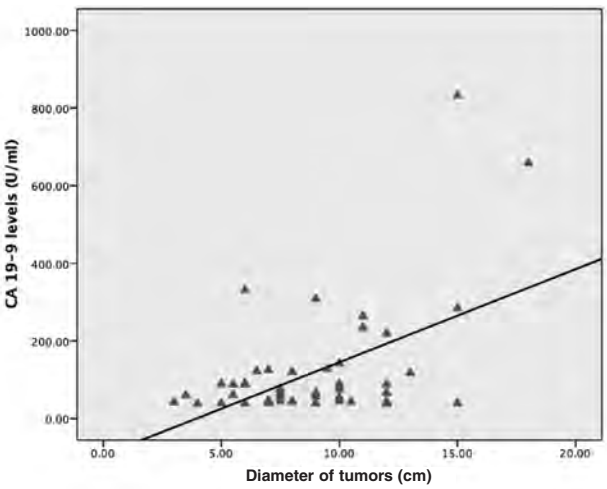

Figure 1. — Correlation of serum CA 19-9 levels and diameter of tumors in group I.

Table 1. — *Clinical characteristics and preoperative serum levels of tumor markers of groups*.

Clinical characteristics	Group I n	Group I mean ± SD	Group II n	Group II mean ± SD	p
Age (years)	49	38.54 ± 15.04	99	36.41 ± 14.82	0.422
Diameter of tumor (cm)	49	8.95 ± 3.21	99	7.10 ± 3.13	0.001
		n, (%)		*n, (%)*	
Menopause	49	12 (24.5%)	99	19 (19.2%)	0.458
Bilaterality	49	6 (1.2%)	99	10 (10.1%)	0.694
Intraoperative adhesions	49	6 (1.2%)	99	1 (0.01%)	0.003
Serum levels of tumor markers		*mean ± SD*		*mean ± SD*	
CA 19-9 (U/ml)	49	120.36 ± 151.06	99	10.67 ± 11.45	< 0.001
Elevated rate (%)	49	100.0%	0	0.0%	< 0.001
CA 125 (U/ml)	49	25.94 ± 15.20	99	17.37 ± 24.97	0.029
Elevated rate (%)	18	36.7%	12	12.1%	< 0.001
CA 15-3 (U/ml)	16	21.14 ± 9.00	37	21.59 ± 8.63	0.865
Elevated rate (%)	3	18.7%	7	18.9%	0.989
AFP (ng/ml)	8	1.87 ± 0.53	17	2.60 ± 3.06	0.515
Elevated rate (%)	0	0.0%	1	5.9%	0.493
CEA (ng/ml)	13	2.69 ± 1.23	39	2.58 ± 4.54	0.932
Elevated rate (%)	2	15.3%	6	15.4%	1.00

SD: standard deviation, AFP: Alpha-fetoprotein, CEA: Carcino-embryonic antigen.

Similarly, postoperative mean CA 125 level of 14 patients, who had elevated levels preoperatively, was decreased from 60.91 ± 49.37 U/ml to 21.78 ± 14.25 U/ml (p = 0.001).

Discussion

MCTs constitute about 58% of the benign ovarian tumors and are mainly encountered in women of reproductive age [2, 11, 12]. Consistently, median age of patients with MCT of the ovary was 35 in our study and only 21% were postmenopausal women.

Mean tumor diameter of MCTs range between 6.4 and 8.8 cm in the literature, and in accordance mean tumor diameter was 7.9 cm in our study [13, 14]. MCTs of the ovary can be reliably diagnosed with ultrasound [3, 10].

MCTs of the ovary consist of a combination of peculiar kinds of tissues due to their origin in parthenogenetic development of germ cells and therefore, increased levels of certain tumor markers can be detected. There are few reports concerning the usefulness of tumor markers in clinical management, especially CA 19-9, in patients with MCT of the ovary [4, 5, 7].

CA 19-9 is a tumor associated cancer antigen with a glycolipid structure [15]. Initially, CA 19-9 was described in gastrointestinal adenocarcinomas particularly of the pancreas but its specificity extends to any tissue malignancy [11].

In the literature, elevated rate of CA 19-9 varies between 59% and 31.9% and extreme levels up to 1430 U/ml have been reported [7, 14, 16]. We found that a considerable portion (33.1%) of patients in our study had an elevated rate of CA 19-9, which is of clinical significance. Larger tumor size was reported to be associated with increased serum levels of CA 19-9 [5-7], whereas no significant correlation was reported in other studies [4, 8]. Our results support that diameter of MCTs are significantly larger in patients with increased levels of CA 19-9 and there is a moderate correlation of CA 19-9 levels to tumor size. This may be mainly due to a weakened cyst wall and CA 19-9 leakage from cystic cavities into the blood circulation [17].

Similar controversy is true for the relation of CA 19-9 and bilaterality of MCTs. Dede *et al*. [4] reported a significant relation but other studies including our present study did not agree with this finding [5-7].

A complication rate of 20% is expected in MCTs, which may present as torsion, rupture, infection and malignant transformation [18]. Total complication rate was 11.5% in our study and torsion (6.4%) was the most common one as expected. Kyung *et al*. [7] reported that elevated CA 19-9 levels were correlated with higher torsion rates, however, we did not find such a relation with torsion or any other complications with elevated CA 19-9 levels.

Concerns may raise thoughts about postoperative evaluation of CA 19-9 for follow-up of increased levels in MCTs but there are no such data in the literature. We demonstrated a postoperative decrease in CA 19-9 levels in 33 patients.

To the best of our knowledge, this study is the only one that has investigated the association of elevated CA 19-9 levels and intraoperative presence of adhesions. Although there was a significant difference, only seven patients could be evaluated from this perspective, which is a limitation of our study.

CA 125 is the most widely investigated ovarian tumor marker in ovarian cancer and may be elevated in about 1% of healthy women [19]. In accordance with the literature, elevated rate of CA 125 was 19.1% in our study, as varying elevated levels between 28.0% and 12.7% have been reported [8, 14]. CA 125 alone cannot be considered as useful in the diagnosis. We also observed a postoperative decrease of these elevated serum CA 125 levels, which is noteworthy.

The value of CA 19-9 in asymptomatic patients is a more dubious issue. In a study concerning diagnostic value of CEA, CA19-9 or AFP in asymptomatic individuals with slightly elevated tumor markers, despite continuous and repeated meticulous examinations, no specific pathology was revealed to explain these increases [20]. In the literature, there are reports regarding abnormally high elevations of CA 19-9 with MCTs of the ovary, but no gastrointestinal or other pathology could be detected [5, 21]. We suggest that especially in asymptomatic young women with MCTs of the ovary that can be demonstrated by ultrasound, elevated rates of CA 19-9 should not warrant further evaluation, which may be complicating matters for clinicians, a cause of anxiety for patients and a reason for unnecessary and expensive further clinical examinations such as colonoscopy, complex imaging techniques and so forth.

Conclusion

We suggest that there may be a relation between elevated levels of CA 19-9 and diameter of tumor and presence of adhesions. Because elevated levels of CA 19-9 may be expected in some patients with MCTs of the ovary that will probably be decreased postoperatively, postponing evaluation of other possible sources of this elevation to the postoperative period is more common sense.

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