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Original Article

Age-stratified analysis of tumor markers and tumor characteristics in adolescents and young women with mature cystic teratoma

Huseyin Yesilyurt, Berna Seckin*, Ayla Aktulay, Sebnem Ozyer

Department of Reproductive Endocrinology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

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Abstract

Background: Serum tumor markers are widely used for the preoperative evaluation of an adnexal mass. Elevations of cancer antigen (CA) 125 and CA 19-9 have been reported in patients with mature cystic teratoma (MCT). The aim of the study is to investigate the relation of serum tumor markers with tumor characteristics in young women with MCT.

Methods: We conducted a retrospective review of 157 patients under the age of 35 who underwent laparoscopic surgery for ovarian MCT. Patients were divided into two age groups: Group I (n = 80): adolescents/young adults (aged 13−25 years) and Group II (n = 77): women aged 26−35 years. Data were analyzed for serum tumor markers, tumor size, and bilaterality.

Results: The rates of elevated CA 125 and CA 19-9 were 10.7% and 31.5%, respectively, for Group I, and 13.9% and 26.5%, respectively, for Group II. The bilaterality rate was higher in Group II compared to Group I (19.5% vs. 8.8%, respectively, $p = 0.04$). Serum CA 125 and CA 19-9 elevations were not related to tumor size in Group I. In Group II, elevated levels of CA 125 were also unrelated to tumor size. However, significant elevation in CA 19-9 levels was observed when tumor size was larger than 4 cm in this age group ($p = 0.004$). Elevated CA 125 and CA 19-9 levels were not significantly associated with the presence of bilateral MCT in either group.

Conclusion: The results of our study indicate that elevations of CA 19-9 are associated with larger tumor size in women aged 26−35 years, but not in adolescents/young adults. However, elevated serum CA 125 levels are not related to tumor size in either age group.

Keywords: Adolescents; Mature cystic teratoma; Tumor marker; Tumor size; Young women

1. Introduction

Mature cystic teratomas (MCTs) are the most common germ cell neoplasms and account for 25%−40% of all primary ovarian tumors.[1] Although they can be seen at any age, more than 80% of MCTs are diagnosed during reproductive years.[2] Ovarian MCTs contain well differentiated ectodermal, mesodermal, and endodermal layers of germ cells. Malignant transformation in a teratoma has been reported to occur in 1−3% of cases, especially in postmenopausal women.[3] These tumors are bilateral in 10−15% of patients.[4]

Ovarian MCTs are often an incidental finding during routine pelvic examination or imaging procedures. About 20% of patients experience complications such as torsion, rupture and infection.[4] Ultrasonography is the main diagnostic tool and ultrasound features are usually pathognomonic for MCTs.[5] Additionally, serum tumor markers including cancer antigen (CA) 125 and CA 19-9 can provide additional information for the diagnosis of MCTs which is very important for surgical planning.[6−8] Since the peak incidence is reported in young women, the surgical treatment of MCTs usually focuses on preserving ovarian tissue and future fertility.[9] Laparoscopic surgery has become a widely preferred procedure in the

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Berna Seckin, Zekai Tahir Burak Women's Health Education and Research Hospital, Talatpasa Bulvarı, Hamamonu, Ankara, Turkey.

E-mail address: bernaseckin57@gmail.com (B. Seckin).

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management of MCT, especially in young women. It is a safe and effective treatment modality and provides many benefits over open surgery, including reduced risk of pelvic adhesions and operative morbidity.[10,11]

In the literature, several studies focused on the relationship between serum tumor markers and tumor characteristics in MCT.[6,8,12−16] The majority of these studies included all age groups with ovarian teratoma. However, it has been suggested that younger women with ovarian MCT may show different clinical presentations and tumor sizes when compared with older patients.[17] Furthermore, tumor markers are most often measured in older women, due to the concern of malignancy, and there is scarce data about tumor markers in young patients with MCT. The aim of this study was to investigate the levels of serum tumor markers and tumor characteristics in young age groups who underwent laparoscopic surgery because of ovarian MCT. We further analyzed the association of the tumor markers with tumor size and bilaterality.

2. Methods

This retrospective chart review study included all patients aged 35 years or younger who underwent laparoscopic surgery for MCT at the Reproductive Endocrinology Unit of Zekai Tahir Burak Women's Health Education and Research Hospital, between January 2012 and June 2016. Data were obtained from hospital records after exclusion of the following conditions: 1) pregnancy, 2) concomitant pelvic pathology such as myoma or endometriosis, 3) malignant transformation of teratoma or other types of malignant ovarian lesions, and 4) severe hepatic or renal diseases. The study was approved by the institutional review board of the hospital. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

All patients underwent preoperative pelvic ultrasonography for assessment of ovarian pathology. When sonographic findings were indeterminate, computed tomography or magnetic resonance imaging was also performed. Blood samples were taken for the determination of preoperative serum levels of CA 125, CA 19-9, alpha-fetoprotein (AFP), and carcinoembryogenic antigen (CEA) in the early stage of the follicular phase. Women with gastrointestinal symptoms and elevated CA 19-9 levels were referred to a gastroenterologist. Serum levels of CA 125, CA 19-9, AFP and, CEA were measured with the Accesss 2 Immunoassay system (Beckman Coulter Ireland, Inc. Mervue, Galway). The cut-off value for both CA 125 and CA 19-9 was 35 IU/mL. The upper normal limits for AFP and CEA were 9 ng/mL and 3 ng/mL, respectively. The intra-assay coefficients of variation for CA 125 and CA 19-9 were 1.7% and 6.4%, respectively. The inter-assay coefficient of variation was 6.0% for CA 125 and 5.7% for CA 19-9.

All operations were performed by two expert laparoscopists. Maximum tumor diameter was used for quantification of tumor size and was determined by review of the preoperative imaging studies and operative records. For cases with bilateral ovarian MCT, tumor size was calculated as the sum of the maximum diameters of left and right tumors. All patients underwent laparoscopic surgery and cystectomy was performed. Postoperatively, histopathological examination was performed by experienced pathologists and the diagnosis of MCT was confirmed. For analytical purposes, the study population was divided into two age groups. Group I consisted of adolescents/young adults (aged 13−25 years), which is consistent with the World Health Organization's definition of young people,[18] and Group II included women aged 26−35 years. The clinical characteristics including patient age, preoperative measurements of CA 125 and CA 19-9, tumor size, and bilaterality were recorded.

A sample size calculation was done according to previously published data.[12] We estimated that a total sample size of 140 patients would be required to show a 15% increase in mean tumor size in patients with elevated CA 19-9 levels (alpha of 5% and power of 90%) by using the open-source software R, version 3.0.1. Statistical analysis was performed using SPSS for Windows (version 11.5, Chicago, IL, USA). Continuous data were presented as mean ± standard deviation (SD) or median with range, and were analyzed by Mann−Whitney U test. Categorical data were expressed as number and percentage and were compared by Pearson's chi-square or Fisher's exact test when applicable. Pearson's correlation was used to evaluate the relationship between CA 19-9 levels and tumor size. A p-value < 0.05 was considered statistically significant.

3. Results

During the study period, medical records of 172 patients 35 years of age or younger who underwent laparoscopic surgery for a presumed ovarian MCT were reviewed. Of these, 8 had additional pelvic pathology (myoma or endometriosis). In 5 patients, diagnosis of dermoid cyst was not confirmed on histopathological examination and 2 had malignancy on the final pathology report. Therefore, these 15 patients were excluded and a total of 157 patients were enrolled in the study: 80 patients were in Group I and 77 were in Group II. The mean age of all patients was 25.6 ± 5.6 (range, 13−35) years and the mean tumor size was 6.6 ± 2.8 (range, 2−16) cm. The bilaterality rate was 14% (22/157). The serum levels of CA 125 were examined in 147 patients, CA 19-9 in 141 patients, AFP in 126 patients, and CEA in 127 patients. Since only a small number of patients had elevated serum levels of AFP and CEA (n = 3, 2.4% and n = 4, 3.1%, respectively), we analyzed the association of the serum levels of CA 125 and CA 19-9 with tumor size and bilaterality. There were 8 patients (10.7%) with elevated CA 125 levels in Group I and 10 (13.9%) in Group II. Elevation of CA 19-9 levels was detected in 23 patients (31.5%) in Group I and 18 (26.5%) in Group II. No statistically significant differences were found between the groups with regard to mean tumor size, serum CA 125 and CA 19-9 levels, and the rate of elevated tumor markers. However, the bilaterality rate was higher in Group II compared to Group I (19.5% vs. 8.8%, respectively, $p = 0.04$). The clinical characteristics of the groups are represented in Table 1.

Table 1
Clinical characteristics of the groups.

	Group I (Adolescents/young adults aged 13−25) (n = 80)	Group II (Women aged 26−35 years) (n = 77)	p
Tumor size (cm)[a]	6.4 ± 2.7 6 (3−16)	6.8 ± 2.8 6 (2−15)	0.41
Bilaterality[b]	7 (8.8)	15 (19.5)	0.04[c]
Total no. patients CA 125 examined	75	72	
Total no. patients CA 19-9 examined	73	68	
Serum CA 125 level (IU/mL)	17.9 ± 13.4 14.7 (3.3−89.6)	17.9 ± 13.1 13.7 (3−68.6)	0.79
Serum CA 19-9 level (IU/mL)	55.5 ± 91.7 19.3 (0.2−561.9)	40.2 ± 92.2 14.3 (0.7−700)	0.13
Elevated CA 125	8 (10.7)	10 (13.9)	0.45
Elevated CA 19-9	23 (31.5)	18 (26.5)	0.22

[a] Mean ± standard deviation with median (range).
[b] Number with (percentage).
[c] Statistically significant by Fisher's exact test.

Ovarian torsion was detected in 4 patients: 2 in Group I and two in Group II. In all of these cases, laparoscopic detorsion and cystectomy were performed to preserve future fertility. In order to compare the rate of elevated CA 125 and CA 19-9 levels with regard to tumor size, patients in both age groups were evaluated in 3 subgroups according to tumor size determined as <4, 4−10 cm, and >10 cm. These threshold values were selected according to an earlier study that demonstrated a significant association between increased tumor size and elevated tumor marker levels.[15] Elevations of CA 125 and CA 19-9 were neither related to tumor size nor bilaterality in Group I (Table 2). In Group II, CA 125 elevation was also unrelated to tumor size and bilaterality. On the other hand, CA 19-9 elevation was associated with increased tumor size in this group ($p = 0.004$). When the tumor size was larger than 4 cm, CA 19-9 levels became significantly higher than the normal range. However, the correlation between CA 19-9 levels and tumor size was not significant ($r = 0.139$, $p = 0.257$). Fig. 1 shows the scatter diagram illustrating the relationship between CA 19-9 levels and MCT size in Group II. Elevation of CA 19-9 was not related to bilaterality in women aged 26−35. The rate of elevated serum CA 125 and CA 19-9 levels with regard to the tumor characteristics of Group II are presented in Table 3.

4. Discussion

In the present study we focused on the relation of serum tumor markers with tumor characteristics in two different young age groups with MCT. Our results suggest that elevated levels of CA 19-9 are associated with tumor size in women aged 26−35, but not in adolescents/young adults. However, elevations in serum CA 125 levels are not related to MCT size in either age group.

Several different tumor markers have been widely used for investigation of adnexal masses. While CA 125 may be elevated in many conditions, it is the most commonly used tumor marker for evaluation of ovarian pathologies. Elevated CA 125 levels have been reported in 12.7%−24% of patients with MCTs.[13,16,19,20] Another commonly used tumor marker, CA 19-9, is a carbohydrate chain antigen and is associated with mucins in gastrointestinal adenocarcinomas. Increased serum levels of CA 19-9 in dermoid cysts have also been reported.[6,14,20] It has been suggested that serum CA 19-9 is produced in the respiratory glands and mucosa of MCTs, and it may be secreted into the bloodstream.[21] Elevated levels of CA 19-9 have been found in up to 50% of patients.[8,16] Elevated serum CA 125 and CA 19-9 levels have been considered to be unrelated to malignant transformation of

Table 2
The rate of elevated serum CA 125 and CA 19-9 levels with regard to tumor characteristics of adolescents/young adults (aged 13−25) (Group I).

	Elevated CA 125 (≥35 IU/mL) (n = 8)	p	Elevated CA 19-9 (≥35 IU/mL) (n = 23)	p
Tumor size (cm)				
<4	2/19 (10.5)	0.98	3/19 (15.8)	0.23
4−10	5/45 (11.1)		16/43 (37.2)	
>10	1/11 (9.1)		4/11 (36.4)	
Tumor bilaterality				
Bilateral	1 (14.3)	0.59	3 (42.9)	0.42
Unilateral	7 (9.9)		20 (29)	

Values are given as number with (percentage).

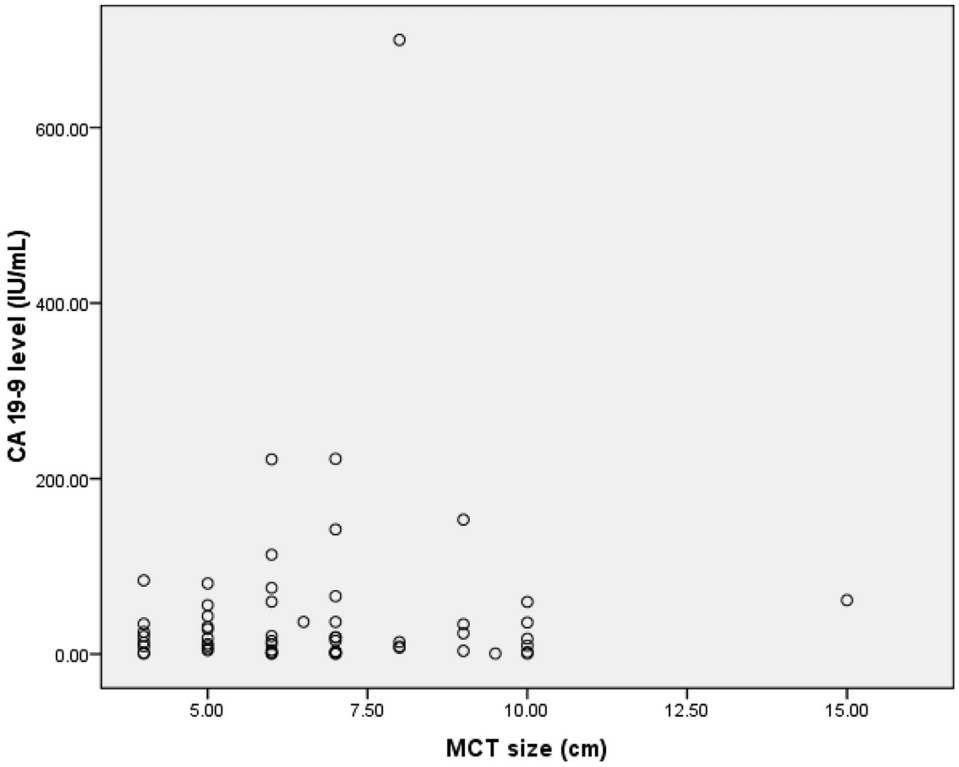

Fig. 1. Scatter diagram illustrating the relationship between CA 19-9 levels and MCT size in Group II.

MCTs.[22] It has been suggested that CA 19-9 is more commonly elevated than CA 125 and it is a more useful tumor marker for diagnosing MCT.[12]

There have been some studies about the levels of tumor markers with respect to clinical characteristics of MCTs such as tumor size and bilaterality with conflicting results.[6,8,12−16,20] Ustunyurt et al.[12] evaluated tumor markers in a large series of patients and found that CA 19-9 had the highest positivity rate among other tumor markers in MCT, and elevated serum CA 19-9 levels were correlated with larger tumor size but not with bilaterality. Similarly, Kyung et al.[13] and Cho et al.[8] each reported that larger tumor sizes were associated with elevated CA 19-9 levels. In contrast to these reports, Dede et al.[6] did not find a statistically significant association between tumor size and elevated CA 19-9 levels, but they also reported that patients with elevated CA 19-9 levels showed significantly higher rates of bilaterality. In another study, Frimer et al.[14] showed that elevated CA 19-9 was not significantly associated with tumor size or bilaterality.

However, most of these previous series included older women, a population more likely to be associated with suspicion of malignancy. In an age-focused analysis, Kim et al.[17] suggested that patients with dermoid cyst have different clinical features by age; younger patients revealed larger tumors compared to older women and the incidence of malignant transformation was highest after the age of 40 years. In our study, we found that there was no association between elevated CA 125 and CA 19-9 levels in adolescents/young adults. On the other hand, CA 19-9 elevation was associated with increased tumor size in the older age group. Similarly, the majority of the already published studies reporting an association between CA 19-9 levels and tumor size indicated a higher median age.

In a previous study from our clinic, the relationship between serum tumor marker panels and tumor size in

Table 3
The rate of elevated serum CA 125 and CA 19-9 levels with regard to tumor characteristics of women aged 26−35 years (Group II).

	Elevated CA 125 (≥35 IU/mL) (n = 10)	*p*	Elevated CA 19-9 (≥35 IU/mL) (n = 18)	*p*
Tumor size (cm)				
<4	3/18 (16.7)	0.81	1/16 (6.2)	0.004[a]
4−10	6/42 (14.3)		10/41 (24.4)	
>10	1/12 (8.3)		7/11 (63.6)	
Tumor bilaterality				
Bilateral	1 (6.7)	0.35	4 (28.6)	0.51
Unilateral	9 (15.3)		14 (25)	

Values are given as number with (percentage).
[a] Statistically significant by chi-square test.

Table 4
Summary of previous studies on serum CA 19-9 levels and tumor size.

Studies	No. of cases	Age range	Results
Ustunyurt et al.[12]	215	13−80 years	Elevated CA 19-9 levels are correlated with larger tumor size ($p = 0.01$).
Var et al.[15]	160	17−42 years	Elevated CA 19-9 levels are associated with larger tumor size. As the tumor becomes bigger, this relationship becomes more distinct. ($p = 0.001$).
Cho et al.[8]	239	25−89 years	Elevated CA 19-9 levels are associated with larger tumor size ($p = 0.002$).
Kataoka et al.[20]	435	6−81 years	Significant correlation between CA 19-9 and tumor size ($p < 0.0001$)
Dede et al.[6]	80	15−69 years	No significant relation between elevated CA 19-9 levels and tumor size
Frimer et al.[14]	139	all age groups (%59 were ≥40 years old)	No significant relation between elevated CA 19-9 levels and tumor size

reproductive age women with ovarian MCT was investigated.[15] In that study, patient age ranged from 17 to 42 years, and it was shown that the most important parameter that affects CA 19-9 elevation was the tumor size, and CA 19-9 levels were significantly elevated when the tumor size reached 4 cm. Table 4 summarizes previous studies in the literature that have investigated the relation of elevated serum CA 19-9 levels with MCT size.

In our current study, the analysis was restricted to younger patients (≤35 years old) with ovarian MCTs, and patients were investigated in two age subgroups. The most striking finding of our study is a statistically significant elevation in CA 19-9 levels with larger tumor sizes in women aged 26−35, but not in adolescents/young adults. Although serum CA 19-9 levels became significantly higher than the normal range when the tumor size was larger than 4 cm, we could not find a significant correlation between CA 19-9 levels and tumor size in women aged 26−35 years. In agreement with the literature, we found that 29.1% of patients had elevated levels of CA 19-9, and the bilaterality rate was 14%. Although, the presence of bilaterality was more frequent in women aged 26−35 compared to adolescents/young adults, elevated tumor marker levels were not related to bilaterality in this age group.

It has been suggested that CA 19-9 is secreted into the cystic cavity by the mucinous epithelium of the MCT and large size or any inflammation of cyst tissues could be possible causes of CA 19-9 leakage into the bloodstream.[23] Furthermore, ovarian torsion in MCT may cause significant elevation in serum CA 19-9 levels due to the inflammation and necrosis.[13,24] In our case series, ovarian torsion was detected only in 4 patients and these patients did not have elevated levels of tumor markers, so we assume that the study results were not affected.

The main limitation of the present study is its size. In this study, we focused on adolescents and young women with MCT. Therefore, the study included a relatively small number of patients in the subgroups determined by tumor size and elevations of CA 125 or CA 19-9. Also, we were unable to investigate the histopathological contents of the MCTs due to the retrospective nature of the study. Some tissue components of MCTs may cause elevated serum tumor markers. Therefore, it is possible that the composition of the MCTs affected the relationship between serum tumor markers and tumor characteristics.

In conclusion, consistent with previous reports, findings of the present study support the clinical importance of CA 19-9 in MCT of the ovary. Additionally, our case series provides further evidence that CA 19-9 elevation is related to larger tumor size in women aged 26−35, but not in adolescents/young adults. The reason for the difference in the older age group is hard to explain and a definitive conclusion can not be reached with the present data. On the other hand, considering the association of elevated serum levels of CA 19-9 with larger tumor size in MCT, it might be a valuable parameter in diagnostic workups of older women within the reproductive period. But, it seems reasonable to conclude that the relation of tumor markers with tumor size has limited diagnostic value in adolescents/young adults. Validation of our findings needs to be confirmed in further studies with larger study group sizes and evaluations of histopathological contents.

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