

The clinical significance of CA19-9 in ovarian mature cystic teratoma

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Summary

Objective: To evaluate the clinical significance of CA19-9 in patients with ovarian mature cystic teratoma (MCT). **Materials and Methods:** A retrospective study was performed on 65 patients with pathologically-confirmed MCT and 80 patients with benign epithelial ovarian tumors. Serum tumor markers for all patients and tissue CA19-9 for MCTs were measured. The relationships between clinical characteristics of MCTs and CA19-9, as well as the correlation between serum and tissue level of CA19-9 in MCTs, were evaluated. **Results:** The mean serum level of CA19-9 in MCTs was significantly higher than that in benign ovarian epithelial tumors (49.9 ± 73.4 IU/ml vs. 17.08 ± 24.8 IU/ml). CA19-9 was the only tumor marker with a mean serum level above the cut-off value and the elevation rate was 30.76% in MCTs. The positive tissue expression rate of CA19-9 in MCT patients were 50.9 % and were higher than that of preoperative serum levels (50.9% vs. 32.7%). **Conclusion:** Serum CA19-9 has the highest positivity rate among other tumor markers in MCT. Elevated serum CA19-9 is not an uncommon finding MCT and could be used as a marker in the differential diagnosis of MCT in patients with pelvic mass.

Key words: Mature cystic teratoma; Ovarian epithelial tumor; CA19-9; Tumor marker.

Introduction

Mature cystic teratoma (MCT) or dermoid cysts are the most common type of ovarian tumor accounting for 10-20% of all primary ovarian tumors [1]. MCTs generally occur during reproductive years with a mean age of 33 years and are commonly unilateral (about 85% of cases) [2]. Most cases present as an asymptomatic adnexal mass incidentally detected on routine pelvic examination. 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 [3].

Serum tumor markers have been used in the management of pelvic masses and ovarian cancer. Clinical usefulness of tumor markers including CA125 and CA19-9 in patients with MCTs has been evaluated in few studies only [4-7]. CA19-9 is a powerful and independent prognostic factor in patients with pancreatic carcinoma [8]. However, the relationship of CA19-9 with MCTs is not well established. The current data are insufficient and includes few trials and mostly case reports [9-11]. In patients with MCTs, increased serum levels of CA19-9 have been reported [2, 11-13] and CA19-9 could be used at postoperative follow-up investigation in benign diseases and as a marker for examining MCTs recurrence [14].

This article aimed to evaluate the serum levels of tumor markers (particularly CA19-9) in patients with MCTs with respect to the clinical characteristics, and the correlation between serum and tissue level of CA19-9 in MCTs.

Materials and Methods

The authors reviewed 65 patients diagnosed with MCTs of the ovary and 80 cases with benign epithelial ovarian tumors who were treated in the First Affiliated Hospital, Guangxi Medical University, Department of Gynecology between January 2013 and December 2013. They obtained the data from the reports of patients as age, average diameter of the tumor, site of the tumor (right or left ovary), bilaterality, menopausal status, and the levels of serum tumor markers. Serum tumor markers most frequently analyzed were CA125, CA19-9, alpha-fetoprotein (AFP), carcino-embryonic antigen (CEA), and squamous cell carcinoma antigen (SCCA). All the blood samples were obtained preoperatively and were determined using enzyme immunoassay technique. In patients diagnosed with MCTs of ovary with elevated serum CA19-9, blood sample was obtained again postoperatively within three to five days. The cut-off values for CA19-9, CA125, AFP, CEA, and SCCA were accepted in the present hospital as 37 IU/ml, 35 U/ml, 11 ng/ml, 5 ng/ml, and 1.5 ng/ml, respectively.

Average tumor size was determined by the review of operative records, gross pathologic description, and preoperative imaging studies. Cases which were diagnosed as MCT preoperatively but could not be confirmed by histopathology reports were excluded from the study.

Oophorectomy, cystectomy, or hysterectomy with unilateral or bilateral salpingo-oophorectomy was performed as treatment modality according to the presence of normal residual ovarian tissue, age, fertility desire, or presence of other pathology.

According to serum level of CA19-9 patients with MCT were divided into an elevated level group (group 1) and a normal level group (group 2). Groups were compared in terms of clinical characteristics and serum tumor markers. Immunohistochemical staining for CA19-9 in tissue from 55 patients with MCT and the

Table 1. — Characteristics of patients with elevated and normal CA19-9 in patients with MCT.

| | Group 1 n=20 | Group 2 n=45 | <i>p</i> |
|----------------------|-----------------|-----------------|----------|
| Age (mean ± SD) | 31.3 ± 10.5 | 33.02±12.82 | 0.831 |
| Diameter (mean ± SD) | 6.92 ± 2.0 | 5.2±2.3 | 0.003 |
| Bilaterality n (%) | 4 (20) | 9 (20) | 1.000 |
| Menopause n (%) | 2 (10) | 6 (13.34) | 1.000 |
| CA125 (mean±SD) | 55.34 ± 46.90 | 18.98 ± 17.52 | 0.000 |
| CEA (mean ± SD) | 1.83 ± 1.16 | 1.45 ± 0.98 | 0.710 |
| AFP (mean ± SD) | 37.43 ± 112.28 | 2.76 ± 1.48 | 0.315 |
| SCCA (mean ± SD) | 1.12 ± 0.57 | 0.81 ± 0.38 | 0.361 |
| CA19-9 (mean ± SD) | 131.44 ± 88.49 | 13.73 ± 9.66 | 0.000 |
| Elevated CA125 n (%) | 11 (55) | 6 (13.3) | 0.000 |

correlation of positive rate to serum level of CA19-9 was performed.

Statistical analysis was performed with SSPS (version 18.0). 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.

Results

For the patients with MCT, the mean age was 32.5 ± 12.1 years (median 28; range 15–71). Tumor size ranged from 2.3 to 12 cm in diameter, with a median and mean ± SD, 5.6 cm and 5.8 ± 2.33 cm, respectively. The overall bilaterality rate was 20%. Unilateral tumors were more abundantly observed on the right side (29 patients, 55.7%) than the left (23 patients, 44.2%).

There was no statistically significant difference in terms of patient age, menopause, and bilaterality between groups 1 and 2. The mean tumor diameter of group I was significantly greater than group 2 (6.92 ± 2 vs. 5.18 ± 2.3 cm, $p = 0.003$). The mean serum CA125 levels and the rate of elevated CA125 were significantly high in group 1. There was a weak positive correlation of CA19-9 levels to diameter of tumor ($r = 0.43$, $p = 0.001$) in all patients. In group 1 there was a moderate positive correlation of CA19-9 levels to the diameter of the tumor ($r = 0.48$, $p < 0.05$) (Table 1).

Postoperative assessment of CA19-9 levels in 20 patients of group 1, who had elevated levels preoperatively revealed that mean CA19-9 level was decreased from 131.44 ± 88.5

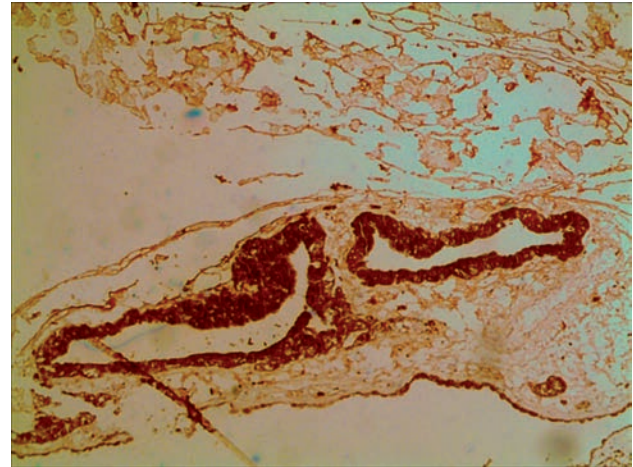


Figure 1. — Diffuse cytoplasmic CA 19-9 expression in the mucinous epithelium in MCT of ovary (IHC stain × 400).

IU/ml to 66.9 ± 32.64 IU/ml, and the difference was statistically significant ($p < 0.01$).

Among the four tumor markers, CA19-9 was the only tumor marker with the mean serum level above the cut-off value and had the highest positive rate among other tumor markers in MCT. The mean serum levels and positive rate of CA19-9 in patients with MCT were significantly higher when compared to the patients with benign epithelial ovarian tumors (49.9 ± 73.41 U/ml vs. 17.08 ± 24.81 U/ml, 30.76% vs. 8.75%, respectively) ($p < 0.01$). Meanwhile, the difference in CA125, CEA, AFP, and SCCA in patients with MCT and benign epithelial ovarian tumor group was not statistically significant ($p > 0.05$) (Table 2).

Immunohistochemical investigation of the teratoma was done in 55 patients with MCT. Immunoreactivity to CA19-9 was recognized as brown staining within cells (Figure 1). The positive expression rate of CA19-9 in tissues of MCT (28/55, 50.9%) was higher than the elevated rate in serum (18/55, 32.7%) and the difference attained statistical significance ($p < 0.01$) (Table 3).

Discussion

Results of the present study have shown that CA19-9 is more frequently elevated than CA125 and hence could be

Table 2. — Tumor markers in patients with MCT and benign epithelial ovarian tumors.

| Tumor marker | Cut-off value | n | MCT | | n | Benign epithelial ovarian tumor | | <i>p</i> |
|--------------|---------------|----|------------------|---------------------------|----|---------------------------------|---------------------------|----------|
| | | | mean ± SD | Elevated rate (n / total) | | mean ± SD | Elevated rate (n / total) | |
| CA19-9 | 37 | 65 | 49.94 ± 73.4 | 30.76% (20/65) | 80 | 17.08 ± 24.8 | 8.75% (7/80) | 0.00 |
| CA125 | 35 | 65 | 30.5 ± 34.25 | 27.6% (18/65) | 80 | 32.95 ± 82.6 | 18.7% (15/80) | 0.59 |
| AFP | 11 | 65 | 13.42 ± 63.3 | 4.61% (3/65) | 80 | 3.55 ± 7.6 | 6.25% (5/80) | 0.73 |
| SCCA | 1.5 | 65 | 0.90 ± 0.46 | 7.69% (5/65) | 80 | 0.81 ± 0.6 | 8.75% (7/80) | 0.36 |
| CEA | 5.0 | 65 | 1.56 ± 1.04 | 0% (0/65) | 80 | 1.38 ± 0.8 | 0% (0/80) | 0.06 |

Table 3. — CA19-9 tissue staining in MCT patients with elevated and normal serum level of CA19-9.

| CA19-9 tissue staining | Serum CA19-9 (IU/ml) | | Total |
|------------------------|----------------------|------|-------|
| | > 37 | ≤ 37 | |
| Positive | 16 | 12 | 28 |
| Negative | 2 | 25 | 27 |
| Total | 18 | 37 | 55 |

a more useful marker in MCT. In literatures, elevated rate of CA19-9 varies between 31.9% to 59% and extreme levels up to 1430 U/ml have been reported [5, 9, 13]. CA19-9 was elevated in 30.76% of patients with MCT in this study with the highest positivity rate among other tumor markers.

The present authors also demonstrated increased levels of mean serum CA19-9 in patients with MCT compared to the patients with benign epithelial ovarian tumor (49.9 ± 73.4 IU/ml vs. 17.08 ± 24.8 IU/ml, $p < 0.01$). Pre-operative serum CA19-9 levels were elevated in 30.76% (20/65) MCT patients, whereas only 8.75% (7/80) patients with benign epithelial ovarian tumor had elevated levels of serum CA 19-9. Therefore the authors suggest that CA19-9 may be a better predictor in the diagnosis of MCT as compared to other tumor markers and elevated serum CA19-9 may be suggestive of MCT in patients with a pelvic mass, the nature of which could not be determined by ultrasonography alone.

To the best of the authors' knowledge, this study is the first to evaluate the correlation between serum and tissue level of CA19-9 in MCT. The present preliminary data analysis showed that majority of tissues of MCT contain CA19-9 and the percentage of positive CA19-9 tissue staining is significantly higher than that of preoperative elevated CA19-9 serum levels (50.9% vs. 30.76%, $p < 0.01$). This imbalance between serum and tissue level of CA19-9 indicates that there may be some mechanisms that prevent the access of CA19-9 into the circulation.

Studies have shown that CA19-9 has been immunohistochemically demonstrated in the bronchial mucosa and glands of MCT and it has been shown to be secreted into the cystic cavity of the lesions [15]. The mechanism of an elevated CA19-9 in MCT is principally the leakage from cystic cavity into the blood stream, possibly due to weakening of cyst wall following the cyst enlargement, or any inflammations or ruptures of the dermoid cysts [15]. Direct serum excretion via epithelial surface could be another cause of increased serum levels of CA19-9. Elevation of CA19-9 therefore might be anticipated with larger MCT since leakage into the bloodstream is more probable in this condition. In the literature, data regarding association between serum CA19-9 levels and certain clinical features other than malignant transformation are very limited and few studies have addressed this issue.

The present results indicate that tumor size was the only clinical finding that correlated with elevated CA19-9 levels, which is similar to Cho *et al.*'s report [2]. Diameters of the MCTs are significantly larger in patients with increased levels of CA19-9 and there is moderate correlation of CA19-9 levels to tumor size. This may be mainly due to weakened cyst wall and CA19-9 leakage from cystic cavities into the blood circulation. However bilaterality is not associated with elevated serum CA19-9 levels. This is in contrast to the study of Dede *et al.* in which elevated CA19-9 was associated with high rate of bilaterality with a likelihood ratio of 2.8 [4].

Ugur *et al.* evaluated the change of serum CA19-9 in 33 patients with MCT pre-and postoperatively and demonstrated that the elevated rate of CA19-9 decreased to 0% after surgery [15]. In the present study the authors demonstrated a postoperative decrease in levels of serum CA19-9 in 20 patients with MCT who had elevated levels before the surgery. The findings suggested that serum CA19-9 could be used as a useful marker for examining mature cystic teratoma recurrence in follow-up.

In summary, serum CA19-9 has the highest positivity rate among other tumor markers in MCT and they will be decreased postoperatively. The present authors suggest that in addition to ultrasonography, serum CA19-9 levels could be a useful tumor marker in the diagnosis of MCT as a supporting diagnostic tool. The positive tissue staining rate of CA19-9 is higher than the elevated rate of serum CA19-9 in patients with MCT, indicating that not all the tissue containing CA19-9 in MCTs excrete CA19-9 into bloodstream. There may be some mechanisms preventing the access of CA19-9 into the circulation.

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