

Serum CA-125 is a good predictor of benign disease in patients with postmenopausal ovarian cysts

E. Dikensoy¹, M.D.; O. Balat¹, M.D.; M.G. Ugur¹, M.D.; A. Ozkur², M.D.; S. Erkilic³, M.D.

¹Department of Obstetrics and Gynecology, ²Department of Radiology, ³Department of Pathology, Gaziantep University, Gaziantep (Turkey)

Summary

Aim: To determine whether serum CA-125 levels, in addition to tumor size and ultrasonographic findings can help in differentiating benign ovarian cysts from malignant disease.

Methods: All postmenopausal women who had undergone explorative laparotomy for a preoperative diagnosis of an adnexal cyst between January 1999 and February 2006 were included if serum CA-125 levels were below 50 IU/ml.

Results: Ninety-three patients with ovarian cysts and serum CA-125 levels lower than 50 IU/ml were included. Seventy-five (80%) of the patients (53 unilocular, 22 multilocular) had ovarian cysts < 13 cm. Of 18 patients with ovarian cysts > 13 cm, seven had unilocular and 11 had multilocular cysts. All the patients (n = 77) with a serum CA-125 level < 35 IU/ml had benign histopathology regardless of the tumor size or ultrasonic features. Among 16 patients with CA-125 levels between 35 and 50 IU/ml, two with unilocular cysts > 13 cm and nine with multilocular cysts (3 < 13 cm, 6 > 13 cm) had borderline histopathology.

Conclusion: We concluded that when unilocular ovarian cyst size is < 13 cm and serum CA-125 levels are below 35 IU/ml in a postmenopausal woman, the possibility of a benign etiology is most likely.

Key words: Menopause; Ovarian cyst; CA-125; Ultrasonography.

Introduction

Unilocular ovarian cysts, smaller than 10 cm in diameter, in asymptomatic postmenopausal women or women ≥ 50 years of age are associated with minimal risk for ovarian cancer [1]. In contrast, complex ovarian cysts with wall abnormalities or solid areas are associated with a significant risk for malignancy [2, 3].

Serum CA-125 is frequently used to differentiate benign adnexal masses from malignant ones, and in the follow-up of patients with ovarian cancer. Elevated levels of serum CA-125 can be encountered in gynecological and non-gynecological malignancies, and also in some benign conditions. The reference value of 35 IU/ml is accepted as the cut-off level for the differentiation of benign from malignant tumors, higher being in favor of malignancy [4]. Only 1% of healthy women and 6.3% of women with benign disease have been reported to have values above that level [5, 6]. On the other hand, the positive predictive value of serum CA-125 levels over 65 IU/ml in postmenopausal women with ovarian cancer is very high [7].

In this study, we aimed to determine whether serum CA-125 is helpful in differentiating benign and malignant ovarian cysts in postmenopausal women with multilocular or unilocular ovarian cysts.

Materials and Methods

This study was carried out between January 1999 and February 2006 in the Obstetrics and Gynecology Department of Gaziantep University hospital. All consecutive patients who were over 48 years of age and had undergone explorative laparotomy for a preoperative diagnosis of adnexal cyst were included in the study if the serum CA-125 level was ≤ 50 IU/ml. Transvaginal ultrasonography was performed and serum CA-125 levels were measured in all patients.

Ultrasonographic examinations were carried out with Siemens Sonoline SL-1 ultrasound system equipped with a 7 MHz transvaginal transducer by an experienced radiologist in the lithotomy position. According to the gray scale ultrasound image, each mass was classified as follows: unilocular cyst (a cyst without septa and without solid parts or papillary excrescences), a multilocular cyst (a cyst with a septum or septa but no solid parts or papillary excrescences), a unilocular solid cyst (a cyst containing solid parts or papillary excrescences but no septa), a multilocular solid tumor (a tumor with a septum or septa and solid parts or papillary excrescences) or a solid tumor (a tumor where the solid components comprised 80% or more of the tumor) [8].

The indications for surgery were: 1) Postmenopausal unilocular or multilocular persistent adnexal cyst larger than 5 cm and without any solid component; 2) Serum CA-125 level under 50 IU/ml. During the surgery, upon exploration of the abdomen and pelvis, any fluid in the peritoneal space was aspirated and sent for cytology. The abdomen and pelvis were examined for morphologic abnormality and biopsies were obtained from any abnormal-appearing areas. When an adnexal cyst was detected, unilateral salpingo-oophorectomy was performed and the specimens sent for rapid histological analysis of frozen section slides during the surgery. Patients with benign ovarian cysts on frozen section underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. All specimens were sent for histopathological examination at the end of surgery. Patients were evaluated for ultrasonographic findings, serum CA-125 levels, tumor size and histopathological results.

All data are presented as mean ± SD (standard deviation) unless otherwise stated. All data were analyzed with a Sigma Stat V3.0 software program (San Rafael, CA, USA). Fisher's exact test was used for the comparison of the ratios; p < 0.05 was considered significant.

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Results

Total abdominal hysterectomy was performed on 93 consecutive patients. The demographic characteristics of the subjects enrolled in the study are shown in Table 1.

While 50 patients (53.7%) were asymptomatic, 15 patients (16.1%) had pelvic pain, 13 patients (13.9%) had abdominal mass and, 15 patients (16.1%) had vaginal bleeding or discharge.

Table 1. — Demographic data, serum CA-125 levels and ultrasonographic findings.

| Characteristics | Mean ± SD |
|-------------------------------|----------------------|
| Age (yrs) | 54.35 ± 5.33 (47-67) |
| Duration of menopause (yrs) | 5.56 ± 4.29 (1-18) |
| Operative time (min) | 36.50 ± 7.05 (22-51) |
| Hospital days | 1.98 ± 0.37 (1-3) |
| Tumor size (cm) | 9.96 ± 3.55 (5-28) |
| Serum CA-125 (IU/ml) | 33.17 ± 9.25 |
| Symptoms | N (%) |
| Asymptomatic | 50 (53.7%) |
| Pelvic pain | 15 (16.1%) |
| Palpable abdominal mass | 13 (16.9%) |
| Vaginal bleeding or discharge | 15 (16.1%) |
| Multilocular cyst | 35 (37.6%) |
| Unilocular cyst | 58 (62.4%) |
| Underlying medical disease | 7 (0.07%) |
| Previous abdominal surgery | 10 (10.7%) |

Seven patients (13.4%) had diabetes mellitus or hypertension. Ten patients (19.2%) had previous pelvic surgery for the following reasons: tubal ligation, ectopic pregnancy and cesarean/section.

According to the gray scale ultrasonographic evaluation, none of the cysts included papillary excrescences or solid areas. The mean tumor size on ultrasound was 9.96 ± 3.55 cm (5-28 cm). Thirty-three of 93 patients had multilocular cysts (35.9%) and 59 patients had unilocular cysts (64.1%).

Two patients with unilocular and nine patients with multilocular cysts had borderline tumors. Histopathological diagnoses of the patients with unilocular or multilocular ovarian cysts are shown in Table 2.

Table 2. — Ultrasonographic findings and percentage of pathological diagnoses.

| Unilocular cysts (n = 60) | Multilocular cysts (n = 33) |
|---|--|
| Serous cystadenoma 34 (56.6%) | Serous cystadenoma 8 (24.4%) |
| Mucinous cystadenoma 16 (26.6%) | Mucinous cystadenoma 13 (39.3%) |
| Paraovarian cysts 8 (14.7%) | Serous borderline ovarian tumor 2 (0.6%) |
| Serous borderline ovarian tumor 2 (0.3%) | Mucinous borderline ovarian tumor 7 (21.2%) |
| | Pelvic adhesion (pseudocyst) 1 (0.3%) |
| | Paraovarian cysts 2 (0.6%) |

All of the 69 patients (100%) with ovarian cysts < 13 cm and serum CA-125 levels < 35 IU/ml had benign histopathology regardless of the ultrasonographic features of the tumor. However, three of six patients (50%) with ovarian cysts < 13 cm and serum CA-125 levels between 35 and 50 IU/ml had borderline tumors, while the other three had benign histopathology (p = 0.000). All of the eight patients (100%) with ovarian cysts > 13 cm and serum CA-125 levels < 35 IU/ml had benign histopathology. While eight of ten patients (80%) with ovarian cysts > 13 cm and serum CA-125 levels between 35 and 50 IU/ml had borderline tumors, another two had benign histopathology (p = 0.001) (Table 3).

Table 3. — Tumor size, ultrasonographic findings and pathological results.

| Tumor size | Serum CA-125 | Diagnosis of Pathology | | | | N | p value |
|------------|--------------|------------------------|--------------|--------------|--------------|----|---------|
| | | Benign % | Borderline % | Borderline % | Borderline % | | |
| < 13 cm | ≤ 35 IU/ml | 69 | 100 | 0 | 0 | 69 | 0.000 |
| | 35-50 IU/ml | 3 | 50 | 3 | 50 | 6 | |
| > 13 cm | ≤ 35 IU/ml | 8 | 100 | 0 | 0 | 8 | 0.001 |
| | 35-50 IU/ml | 2 | 20 | 8 | 80 | 10 | |
| Total | | 82 | 88.2 | 11 | 11.8 | 93 | |

All of the 53 patients (100%) with unilocular ovarian cysts < 13 cm had benign histopathology. Three of 22 patients (13.6%) with multilocular ovarian cysts < 13 cm had borderline ovarian tumors (p = 0.023). Two of seven patients (28.6%) with unilocular ovarian cysts > 13 cm had borderline ovarian tumors. Six of 11 patients (54.5%) with multilocular ovarian cysts > 13 cm had borderline ovarian tumors (p = 0.278) (Table 4).

Sensitivity and specificity of serum CA-125 levels of < 35 IU/ml to rule out malignancy were 93.9% and 100%, respectively.

Table 4. — Comparison of tumor size, serum CA-125 levels and pathological results.

| Tumor size | Ultrasonographic findings | Pathological diagnosis | | | | N | p value |
|------------|---------------------------|------------------------|--------------|--------------|--------------|----|---------|
| | | Benign % | Borderline % | Borderline % | Borderline % | | |
| < 13 cm | Unilocular | 53 | 100 | 0 | 0 | 53 | 0.023 |
| | Multilocular | 19 | 86.4 | 3 | 13.6 | 22 | |
| > 13 cm | Unilocular | 5 | 71.4 | 2 | 28.6 | 7 | 0.278 |
| | Multilocular | 5 | 45.5 | 6 | 54.5 | 11 | |
| Total | | 82 | 88.2 | 11 | 11.8 | 93 | |

Discussion

The results of this study revealed that all the patients with ovarian cysts and serum CA-125 levels < 35 IU/ml had benign disease regardless of tumor size and ultrasonic features of the tumor. When tumor size and ultrasonic features are considered alone, among patients with a cyst size smaller than 13 cm, all the patients with unilocular ovarian cysts had benign disease, however three of 22 patients (13.6%) with multilocular ovarian cysts had borderline ovarian tumors. When tumor size was larger than 13 cm, two of seven patients with unilocular cysts and six of 11 patients with multilocular cysts had borderline ovarian tumors.

It has been reported that unilocular ovarian cysts, the majority of which are less than 5 cm in diameter, occur in approximately 3% of asymptomatic postmenopausal women [1]. The frequency of these cysts decreases progressively with age, and most resolves spontaneously [9]. Documentation of the presence of papillary projections or solid areas extending from the tumor wall into the lumen of the cyst is important for the evaluation of the malignant potential of small cystic tumors of the ovary. In the absence of wall abnormalities, the risk of malignancy in small cystic ovarian tumors is virtually nonexistent [10]. Some authors have recommended that if the volume of the unilocular tumors continues to increase, or if wall abnormalities develop, immediate operative removal is indicated during the follow-up [10, 11]. All the patients in the present study had unilocular or multilocular cysts without any wall abnormalities such as solid components or papillary excrescences, which might be consistent with malignant disease.

Although there have been a number of tumor markers associated with ovarian cancer, CA-125 is the most reliable [12]. Serum levels of CA-125 are elevated (> 35 IU/ml) in approximately 50% of patients with Stage I epithelial ovarian cancer and in more than 90% of those with advanced cancer [12]. Calculations based on progressively rising serum CA-125 levels were able to increase the sensitivity of ovarian cancer detection from 62% to 86% [13]. In a large multicenter Italian study, a serum CA-125 value of 65 IU/ml accurately differentiated 83% of benign from malignant ovarian tumors. When combined with pelvic ultrasound this diagnostic accuracy increased to 94% [14].

The results of our study revealed that postmenopausal multilocular or unilocular pure cystic adnexal masses are benign in nature even if they are above 10 cm in diameter when serum CA-125 levels are below 35 IU/ml.

In clinical practice, the presence of even a relatively simple ovarian cyst in postmenopausal women is considered as ominous and a source of anxiety for the patient. However women with unilocular cystic tumors less than 10 cm in diameter and a normal serum CA-125 are reported to be essentially at no risk for malignancy [15]. The results of this study showed that all the patients with an ovarian cyst had benign histopathology when serum CA-125 level was lower than 35 IU/ml regardless of the cyst size and the ultrasonic appearance. When serum CA-125 levels were between 35 and 50 IU/ml, 50% of those who had ovarian cysts smaller than 13 cm and 80% of those who had ovarian cysts larger than 13 cm had borderline tumors ($p = 0.000$, $p = 0.001$, respectively).

If the size of the ovarian cyst was smaller than 13 cm, there was no statistically significant difference between the ratios of multilocular and unilocular cysts with the histopathology of borderline tumors. Similarly, when the cyst size was > 13 cm, the ratio of borderline tumors was higher in multilocular tumors than that in unilocular tumors, but the difference was not statistically significantly (28.6%, 54.5%, respectively, $p > 0.05$).

When the patient had a multilocular ovarian cyst and a

serum CA-125 level between 35-50 IU/ml, we assume that the possibility of malign disease is very high. Thus a thorough understanding of the size, morphology and marker profile of an adnexal mass is crucial in selecting the appropriate treatment for each patient.

In conclusion, we suggest that a serum CA-125 level below 35 IU/ml reflects benign disease regardless of the size and the ultrasonographic appearance of the tumor in postmenopausal women with ovarian cysts.

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Address reprint requests to:
E. DIKENSOY, M.D.
Department of Obstetrics and Gynecology
Gaziantep University
Gaziantep (Turkey)