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Original Article

CA 125 and other tumor markers in uterine leiomyomas and their association with lesion characteristics

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Abstract: The aim of this study was to investigate the factors associated with serum levels of several tumor markers in a group of patients operated for uterine myoma. One hundred thirty-seven female patients operated for uterine myoma were included. Serum samples were examined for CA 125, CA 19-9, CA 15-3, carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) levels as part of routine workup. Pathological and morphological characteristics of the patients were retrieved from medical records. The mean age was 46.7 ± 8.8 years (range, 22-85 y). Abnormally high levels of CA 125, CA 19-9, CA 15-3, CEA, and AFP were found in 19.7%, 6.6%, 5.1%, 3.7%, and 1.5% of the patients, respectively. Patients with additional adenomyosis and patients with at least one large myoma (≥ 5 cm diameter) had significantly higher levels of CA 125. Multivariate analysis identified coexistence of adenomyosis (OR 7.7 [95% CI, 2.6-23.0], $p < 0.001$) and presence of at least one large myoma (OR 5.6 [1.4-22.8], $p = 0.016$) as independent predictors of abnormally high CA 125 levels. CA 125 levels are affected by the tumor size and coexistence of adenomyosis in uterine leiomyomas. Indirect mechanisms caused by large myoma size such as peritoneal irritation may be responsible for CA 125 elevations.

Keywords: Uterine leiomyoma, uterine fibroma, tumor marker, CA 125, CA 19-9, CA 15-3, carcinoembryonic antigen (CEA), alpha fetoprotein (AFP)

Introduction

Uterine leiomyomas are common benign tumors originating from uterine smooth muscle and affecting 60 to 80% of women at their reproductive age [1]. About one fifth of leiomyomas are symptomatic and may require treatment [2]. They are most commonly diagnosed with ultrasonography and magnetic resonance imaging (MRI). However, currently no serum biomarker is capable of differentiating and monitoring uterine leiomyomas [3].

Tumor markers can be used in variety of conditions including screening for a subclinical condition or risk stratification, follow-up, and treatment planning [4, 5]. A number of tumor markers are used for screening and follow-up purposes in gynaecological malignancies including CA 125, CA 19-9, CA 15-3, carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP). CA 125, or carbohydrate antigen, is elevated in substantial proportion of patients with ovarian cancer [6]. However, high levels of tumor markers may be found in benign gynaecological conditions. Although several studies failed to find an increase in CA 125 levels in association with uterine myoma [7, 8], abnormally high levels have been reported in limited number of patients [9, 10]. On the other hand, very few or no studies have focused on the alterations of other less commonly used markers in uterine myoma [11].

This study aimed to investigate the factors associated with elevated levels of several tumor markers particularly used in the screening of gynaecological malignancies, in a group of patients operated for uterine myoma.

Material and methods

Subjects

A total of 137 patients operated for uterine myoma between years 2009 and 2013 in GATA Haydarpasa Training Hospital were included in this retrospective study. Pathological examina-

tion and tumor marker records of the patients were retrospectively examined. Inclusion criteria were as follows: patients admitting with abnormal uterine bleeding, postmenopausal bleeding with or without anemia, or compression symptoms including constipation, back pain, urinary incontinence and who were diagnosed with uterine myoma based on ultrasonographic examination and operated; patients followed up for uterine myoma for 6 months and operated due to more than 50% increase in myoma size, patients with available data for pathological examination and tumor markers. All patients were operated for myoma uteri. Exclusion criteria were as follows: patients operated for premalignant or malignant cervical, endometrial, tubal or ovarian tumors. One patient operated form myoma uteri but postoperatively diagnosed with leiomyosarcoma was excluded. The study protocol was approved by local ethics committee and the study was conducted in accordance with declaration of Helsinki.

Assessments

Serum samples of the subjects were collected just prior to the operation. Levels of the tumor markers CA 125, CA 19-9, CA 15-3, CEA, and AFP protein were measured with chemiluminescent microparticle immunoassay method using Abbott Architect 12000SR device. Normal ranges were defined as follows: CA 125, 0-35 U/mL; CA 19-9, 0-37 U/mL; CA 15-3, 0-31.3 U/mL; CEA, 0-5 ng/mL; AFP, 0-8.78 ng/mL. Myoma sizes were calculated from postoperative pathological specimens.

Statistical analysis

SPSS version 21 was used for statistical analysis. Normality was tested using Kolmogorov-Smirnov test and graphical methods. For the comparison of normally distributed continuous variables, student t test for independent samples or one-way analysis of variance was used. Mann Whitney U test or Kolmogorov-Smirnov test was used for the comparison of continuous variables without normal distribution. *P* values were corrected for pair-wise comparisons where appropriate. Stepwise logistic regression was used for multivariate analysis to identify the independent predictors of abnormal marker levels. In addition, correlations between marker levels and myoma sizes were examined using Spearman's test. A *p* value smaller than 0.05 was considered an indication for statistical significance.

Results

Data from 137 female patients were analyzed (**Table 1**). The mean age was 46.7 ± 8.8 years (range, 22-85 y). Forty-eight patients (35%) underwent myomectomy and the remaining 65% underwent hysterectomy. A single myoma was present in 62 patients (45%) while 75 (55%) had multiple myoma. The mean number of myoma per patient was 3.6 ± 3.6 (range, 1-19).

The mean CA 125, CA 19-9, CA 15-3, CEA, and AFP levels of the patients were 27.3 ± 38.1 U/mL, 13.1 ± 14.3 U/mL, 16.5 ± 8.2 U/mL, 1.5 ± 1.1 ng/mL, and 2.7 ± 1.7 ng/mL, respectively. Abnormally high levels of CA 125, CA 19-9, CA 15-3, CEA, and AFP were found in 19.7%, 6.6%, 5.1%, 3.7%, and 1.5% of the patients, respectively. **Table 1** shows univariate analysis of marker levels by lesion characteristics.

Patients with additional pathologies, in particular with adenomyosis, had higher levels of CA 125 when compared with remaining patients. In addition, patients with at least one large myoma (≥ 5 cm diameter) had significantly higher levels of CA 125. Correlation analysis conducted in patients with single myoma found a moderate correlation between CA 125 levels and lesion size (by diameter, $r = +0.52$, $p > 0.001$; by volume, $r = +0.54$, $p < 0.001$).

CA 19-9 levels were significantly affected by the localization of the lesion, with significantly higher levels of CA 19-9 in intramural myomas when compared to subserosal myomas (13.6 ± 14.1 vs. 6.3 ± 7.3 U/mL, $p = 0.002$). A marginal but significant difference was detected with regard to additional pathology, with higher CA 19-9 levels in patients with an additional pathology when compared to the patents with pure leiomyoma.

Higher CEA levels were found in patients with any additional pathology when compared to pure leiomyomas ($p = 0.031$) and higher AFP levels were found in association with multiple lesions when compared to single leiomyomas ($p = 0.021$).

Multivariate analysis identified presence of adenomyosis in addition to leiomyoma (OR 7.7 [95% CI, 2.6-23.0], $p < 0.001$) and presence of

Table 1. Univariate analysis comparing marker levels by lesion characteristics

	CA 125 (U/mL)	CA 19-9 (U/mL)	CA 15-3 (U/mL)	CEA (ng/mL)	AFP (ng/mL)
Localization					
Intramural (n = 90)	28.0 ± 39.4	13.6 ± 14.1	17.0 ± 9.2	1.4 ± 1.0	2.7 ± 1.9
Subserosal (n = 20)	15.0 ± 12.4	6.3 ± 7.3	15.7 ± 6.0	1.4 ± 1.1	2.7 ± 0.9
Submucosal (n = 12)	17.1 ± 10.0	10.5 ± 7.5	15.8 ± 5.3	1.4 ± 0.8	3.0 ± 2.2
P	0.175	0.003	0.989	0.954	0.402
Number					
Single (n = 62)	29.3 ± 43.9	12.6 ± 13.4	16.1 ± 7.3	1.4 ± 0.7	2.5 ± 1.7
Multiple (n = 75)	25.7 ± 32.7	13.5 ± 15.0	16.8 ± 8.8	1.5 ± 1.3	2.9 ± 1.7
P	0.774	1.000	0.829	0.107	0.021
Additional pathologies					
Any pathology					
Absent (n = 94)	20.3 ± 22.8	11.7 ± 13.5	17.2 ± 9.0	1.3 ± 1.0	2.7 ± 1.6
Present (n = 43)	42.8 ± 56.5	16.2 ± 15.6	15.0 ± 5.7	1.7 ± 1.2	2.8 ± 1.9
P	0.007	0.047	0.089	0.031	0.662
Malignancy					
Absent (n = 134)	27.2 ± 38.1	12.7 ± 13.5	16.6 ± 8.2	1.4 ± 1.0	2.7 ± 1.7
Present (n = 3)	33.4 ± 46.7	29.0 ± 35.5	12.2 ± 3.2	2.8 ± 1.9	3.2 ± 1.7
P	0.576	0.377	0.315	0.146	0.547
Adenomyosis					
Absent (n = 108)	20.9 ± 23.1	12.4 ± 14.2	17.1 ± 8.6	1.4 ± 1.1	2.8 ± 1.9
Present (n = 29)	51.5 ± 65.1	15.9 ± 14.4	14.5 ± 5.8	1.5 ± 0.7	2.4 ± 1.0
P	0.002	0.118	0.193	0.168	0.839
Polyp					
Absent (n = 121)	27.2 ± 38.5	13.2 ± 14.7	16.5 ± 8.5	1.4 ± 1.0	2.7 ± 1.5
Present (n = 16)	28.3 ± 36.2	12.4 ± 10.8	16.2 ± 5.7	1.9 ± 1.5	3.0 ± 2.8
P	0.651	0.880	0.723	0.360	0.880
Lesion size (diameter of the largest lesion when multiple)					
Diameter					
< 5 cm (n = 38)	18.8 ± 40.0	11.5 ± 12.3	15.9 ± 7.1	1.5 ± 1.0	2.9 ± 2.4
≥ 5 cm (n = 99)	30.6 ± 37.0	13.7 ± 15.0	16.7 ± 8.6	1.5 ± 1.1	2.7 ± 1.4
P	< 0.001	0.328	0.503	0.788	0.780

at least one large myoma (OR 5.6 [1.4-22.8], p = 0.016) independent predictors of abnormally high CA 125 levels. When patients with adenomyosis are excluded from the analysis, only 13% of patients had abnormal CA 125 levels. However, none of the other factors emerged as an independent predictor of abnormally high values of any of the other markers. Thus, the relation between myoma site and CA 19-9 levels could not be confirmed with multivariate analysis.

Discussion

This study examined the factors associated with the levels of certain tumor markers in a group of patients operated for uterine leiomyoma. Coexistence of adenomyosis and large size emerged as significant independent predictors of elevated CA 125 levels. Marginal alterations in CA 199, CA 153, CEA and AFP levels in association with certain factors were found; however, none could be confirmed by multivariate analysis. To the best of our knowledge, this study for the first time examined the relations between tumor markers and clinical characteristics of uterine leiomyomas such as size, accompanying lesions, localization, and number, in such detail and on a large sample size.

Elevated levels of CA-125, a high-molecular weight glycoprotein, is found in a substantial proportion of patients with ovarian cancer [12]. On the other hand, only modest and inconsis-

tent alterations have been reported in patients with uterine leiomyomas. Several studies compared CA 125 levels between healthy controls and myoma patients [7, 8]. The study by Dawood et al, compared 51 patients with uterine myoma and 30 healthy controls but failed to find a difference between the groups in terms of CA 125 levels [7]. Similarly, no difference was found in the study by Dingiloglu when comparing CA 125 levels between 30 myoma patients and 38 healthy controls [8]. In contrast, several cases with abnormally high CA 125 levels have been reported [9, 10] and several studies have reported abnormal CA 125 levels in substantial proportion of myoma patients, although cutoff values vary. In a relatively small-scale study, Spuy et al found slightly elevated levels (> 35 U/mL) in 18% of their patients with myoma [13]. Bischof et al, reported that more than one third of the patients with uterine myoma had increased CA 125 levels before therapy [14]. Two studies set relatively high cut-off values and found remarkable rates in this context: Zhou et al. found 10% (cut-off 50 U/mL) [15] and Kimura et al. found 10% (cut-off 65 U/mL) positivity rates among women with myoma [16]. In the study by Moore et al, 26% of patients with myoma had CA 125 levels greater than 35 U/mL [17]. Although this study lacks a control group precluding direct comparison of the levels, CA 125 positivity rate is somewhat high (19.7%) consistent with the previous reports. Actually, CA 125 is a marker of nonspecific peritoneal conditions. Thus, the rise of this marker levels only in a proportion of patients suggests that factors other than main disease mechanism (such as peritoneal irritation) may play role in altered CA 125 levels in this benign condition.

This study identified the coexistence of adenomyosis as an independent predictor of elevated CA 125 levels in patients with myoma. This is somewhat expected based on several previous reports, which provide evidence that adenomyosis may be associated with even more pronounced elevations of this marker. A relatively large study compared 55 patients with adenomyosis and 20 patients with myoma with regard to preoperative serum CA 125 levels and found remarkable differences between the two groups [15]. Median CA 125 levels were more than 3 times higher in the adenomyosis groups (102.1 *vs* 34.6 U/mL). CA 125 positive rates (> 35 U/mL) were 80% and 10% in the adenomyosis and myoma groups, respectively. Authors proposed CA 125 levels as a possible tool to differentiate between these two conditions. Another study found similar results and corresponding levels for adenomyosis and myoma patients were 93.3 vs. 18.3 U/mL ($p < 0.001$) [18]. On the other hand, Halila et al did not find sufficient evidence to support the possible use of CA 125 levels as an aid in the diagnosis of adenomyosis [19]. In this study, CA 125 positive rate dropped to 13% when patients with additional adenomyosis were excluded, suggesting that a remarkable degree of elevation comes from the presence of adenomyosis. However, 13% is still a high proportion that is in line with previous reports and supports the potential contribution of uterine leiomyoma in CA 125 elevation.

Inconsistent and slight CA 125 alterations in association with benign gynecological conditions together with the known high prevalence of these conditions may hamper the potential use of this marker in the diagnosis and/or follow-up of uterine malignant conditions. Two studies examined potential use of CA 125 levels to differentiate between uterine leiomyoma and uterine sarcoma. Yilmaz et al failed to identify a potential benefit of CA 125 levels for the differential diagnosis between myoma and sarcoma and the levels were not predictive of sarcoma stages [20]. On the other hand, Juang et al found significantly higher preoperative levels of CA 125 levels in myoma patients when compared to leiomyosarcoma patients; however, there was a significant overlap between early-stage leiomyosarcoma and myoma groups [21]. Thus, a useful cut-off value could not be identified.

One of the main results of this study is the identification of a large myoma as a significant independent predictor of elevated CA 125 levels. Although only one study has directly assessed this relation, several investigators provided some clues on the possible relation between CA 125 levels and myoma sizes. Bischof et al. found a significant positive correlation between size as assessed by ultrasonography and CA 125 levels, which is in line with the findings of the present study [14]. Moreover, this study used pathological specimen size, which is a more reliable measurement. Yen et al. treated

46 uterine leiomyoma patients with laparoscopic bipolar coagulation of the uterine vessels [22]. All patients had elevated CA 125 levels. Shrinkage of myoma was more prominent in patients with decreased CA 125 levels after the operation, suggesting a positive relation with myoma size and marker levels. On the other hand, Baker failed to find a correlation between uterine size after operation (rather than the lesion size) and CA 125 levels [23].

Only one study examined a multitude of tumor markers in leiomyomas [11]. In that study, instead of examining a sample population of leiomyoma, a group of patients (n = 142) with elevated tumor markers in a screening program were examined and 12 turned out to have leiomyoma (5 also had endometriosis). Among these 12 patients, in addition to CA 125, CA 19-9 and CgA elevations were also detected. In this study, although not confirmed by multivariate analysis, a marginal relation between elevated CA 19-9 levels and coexistence of any other pathology and intramural location was found. These relations warrant further examination in larger studies with healthy controls. Similarly, the marginal effects on CA 15-3, CEA and AFP levels found in this study deserve further investigation.

In conclusion, CA 125 levels are affected by the tumor size and coexistence of adenomyosis in uterine leiomyomas. Indirect mechanisms caused by large myoma size such as peritoneal irritation may be responsible for CA 125 elevations. Nevertheless, this marker may have the potential to be used for the follow-up of treatment response, particularly in large leiomyomas.

Disclosure of conflict of interest

None.

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