Potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma

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Summary

Purpose: Most comparisons between uterine leiomyoma and uterine leiomyosarcoma have been based on postoperative pathological or molecular analyses. Very few reports have investigated preoperative differentiation between uterine leiomyoma and uterine leiomyosarcoma.

Methods: Between January 1990 and December 2003, 42 consecutive patients with uterine leiomyosarcoma treated at index hospitals were analyzed. Meanwhile, 84 patients with uterine leiomyomas were used as controls. The diagnostic performance of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma using receiver operating characteristic (ROC) curves was evaluated. Data presentations were categorized into premenopausal and postmenopausal groups. Diagnostic efficiency was calculated as the sensitivity multiplied by the specificity.

Results: Values of preoperative serum CA125 were significantly higher in the uterine leiomyosarcoma group than those in the uterine leiomyoma group. There was significant overlapping of preoperative serum CA125 between the uterine leiomyoma group and early-stage uterine leiomyosarcoma. For both the premenopausal and postmenopausal group, there was a significant difference in the distribution of preoperative serum CA125 in early-stage and advanced-stage uterine leiomyosarcoma. The optimal cutoff values of serum CA125 for the premenopausal group and postmenopausal group was 162 U/mL and 75 U/mL, respectively.

Conclusion: These findings demonstrated that preoperative serum CA125 had a potential role in the differential diagnosis between early-stage and advanced-stage uterine leiomyosarcoma. Further investigation with a larger sample size at adequate power is necessary to verify the current study.

Key words: Uterine leiomyoma; Uterine leiomyosarcoma; CA125.

Introduction

Uterine leiomyomas are benign clonal tumors that arise from the smooth muscle cells of the human uterus. They are clinically apparent in about 25% of women, and with newer imaging techniques, the true clinical prevalence may be higher [1]. For uterine leiomyoma, ultrasonography is typically used to confirm the diagnosis and exclude the possibility of associated ovarian neoplasm. Magnetic resonance imaging (MRI) gives better visualization of individual myomas, but for most clinical indications the extra cost is not justified [2, 3]. Several factors determine the treatment modality of uterine leiomyomas, including the size and location of the myomas, the presenting symptoms, the age and reproductive desires of the patient [4-6].

Uterine leiomyosarcomas are rare malignant smooth muscle tumors with an annual incidence of 0.64 per 100,000 women. They account for 25% to 36% of all uterine sarcomas and only 1.3% of all uterine malignancies in a Western female population [7]. In the majority of cases, leiomyosarcomas arise de novo. However, in 5% to 10%, they may arise via sarcomatous degeneration of a preexisting leiomyoma [8]. Uterine leiomyosarcoma is one of the most difficult neoplasms to treat because of its aggressive behavior, manifested by rapid tumor growth and high propensity to recur both locally and, more often, at distant sites [9, 10].

The number of women treated with GnRH analogs for uterine leiomyomas is growing consistently [11]. On the one hand, many women diagnosed with uterine leiomyoma in the reproductive age who wish to preserve their fertility and those who in the perimenopausal stage would prefer to avoid an operation, but on the other hand, uterine leiomyosarcoma is difficult to treat, to some extent, by the fact that it often cannot be distinguished preoperatively from uterine leiomyoma, hence the importance of distinguishing between leiomyosarcoma and leiomyoma is imperative [12, 13]. However, preoperative diagnosis of leiomyosarcoma is unreliable in spite of endometrial sampling and imaging techniques [14-17]. Goto *et al.* have used MRI for the diagnosis of leiomyosarcoma. The expressions in MRI images were unique and could be used to suggest the diagnosis of leiomyosarcoma [18]. Indeed, as there are no convincing imaging features with good diagnostic accuracy for

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leiomyosarcoma, the routine use of high-cost MRI for the differential diagnosis is not justified at present.

The tumor-associated antigen CA125 has a role in the monitoring of treatment, in the detection of recurrence, and as a prognostic marker in women with epithelial ovarian carcinoma [19, 20]. The value of preoperative serum CA125 has never been investigated for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma in the literature.

The current study was intended to evaluate the diagnostic performance of preoperative serum CA125 for the differential diagnosis between uterine leiomyosarcoma and uterine leiomyoma.

Materials and Methods

The present study was approved by the hospital research ethics committee. Forty-five consecutive patients with pathologically proven uterine leiomyosarcoma, with available pretreatment serum CA125, treated at the Veterans General Hospital, Taipei, Taiwan between January 1990 and December 2003 were recruited in this retrospective analysis. The pathological diagnosis of uterine leiomyosarcoma was confirmed by a senior pathologist according to O'Connor and Norris [21]. Meanwhile, 84 patients diagnosed with uterine leiomyoma treated between 2002 and 2003 at the index hospital with available CA125 data were selected as controls. The study patients were further categorized into two groups: premenopausal group and postmenopausal group. In the premenopausal group, uterine leiomyomas and uterine leiomyosarcomas were matched with respect to age, body mass index, and tumor size. In the postmenopausal group, uterine leiomyomas and uterine leiomyosarcomas were matched with respect to age and body mass index (BMI) only. Patients with uterine leiomyomas in the premenopausal group were pathologically confirmed or had at least follow-up of two years with stable tumor size by sonographic examination or other image studies. Patients with uterine leiomyomas in the postmenopausal group were not pathologically confirmed due to ethical reasons, but had at least follow-up of two years with stable tumor size by image studies.

Three patients with uterine leiomyosarcomas who had associated pelvic pathologies (2 endometriomas and 1 functional cyst) which could potentially provoke CA125 elevation were excluded. While during the selection of matched controls, patients with uterine leiomyomas who had associated pelvic or non-pelvic pathologies were also excluded. One case of surgically proven uterine leiomyoma presented with pseudo-Meigs syndrome (ascites, pleural effusion and uterine leiomyoma) had unusual elevated CA125 (873 U/ml) was also excluded.

The CA125 assay was performed by an immunoradiometric assay according to manufacturer's instructions (Abbot Diagnostics). Blood samples from patients with uterine leiomyosarcoma were collected because of suspected uterine malignancy by imaging studies.

Receiver operating characteristic (ROC) curves were constructed by calculating the sensitivities and specificities for several cutoff values. The optimal cutoff value was selected on the basis of the extreme upper left points of the ROC curves. The significance of the ROC analyses was evaluated by area tests according to the method described by Hanley and McNeil [22]. Diagnostic efficiency was calculated as sensitivity multiplied by specificity. Differences of serum CA125 between uterine leiomyoma and different stages of uterine leiomyosarcoma were compared using Kruskal-Wallis analysis of variance. The Student's t-test was used to compare means of continuous variables between the study and control groups. All p values were calculated based on two-tailed tests with $p < 0.05$ considered significant.

Results

The basic demographic features of the study population are presented in Table 1. In the premenopausal group, study patients and control patients were matched with respect to age, BMI, and tumor size. In the postmenopausal group, study patients and control patients were matched with respect to age and BMI only. The reason why tumor size could not be matched in the postmenopausal group was that we could not find adequate patients with uterine leiomyomas who had comparable tumor size to those with uterine leiomyosarcomas.

Table 1. — *Demographic characteristics of patients with uterine leiomyoma and uterine leiomyosarcoma*.*

		Uterine leiomyoma	Uterine leiomyosarcoma	p
Premenopausal group**	Total no.	60	30	
	Age	44 (39-55)	43 (39-54)	0.327
	BMI (kg/m^2)	22.6 (19.5-26.6)	22.9 (19.8-27.5)	0.249
	Tumor size***	13 (7-25)	14 (8-23)	0.103
	Stage I-II		21 (70%)	
	Stage III-IV		9 (30%)	
Postmenopausal group**	Total no.	24	12	
	Age	55 (49-61)	56 (50-64)	0.216
	BMI (kg/m^2)	23.5 (20.5-25.9)	23.9 (20.9-26.7)	0.328
	Tumor size***	7 (4-12)	11 (8-18)	0.016
	Stage I-II		5 (41.7%)	
	Stage III-IV		7 (58.3%)	

*Values are given as mean (range) or number (%).
**Uterine leiomyoma and uterine leiomyosarcoma were age, BMI and tumor size matched in the premenopausal group, whereas age and BMI were matched in the postmenopausal group.
***Tumor size denotes the single largest diameter of the tumor by sonographic examination or measurement of surgical specimen.

The distribution of CA125 among patients with uterine leiomyomas and patients at different stages of uterine leiomyosarcoma is illustrated in Figure 1 (premenopausal group) and Figure 2 (postmenopausal group), respectively. For the premenopausal group, the median value of CA125 in the uterine leiomyoma, Stage I-II uterine leiomyosarcoma, and Stage III-IV uterine leiomyosarcoma was 78 U/ml, 107 U/ml ($p = 0.048$, vs uterine leiomyoma) and 209 U/ml ($p < 0.001$, vs uterine leiomyoma; $p = 0.018$, vs Stage I-II uterine leiomyosarcoma), respectively. For the postmenopausal group, the median value of CA125 in the uterine leiomyoma, Stage I-II uterine leiomyosarcoma, and Stage III-IV uterine leiomyosarcoma was 38 U/ml, 95 U/ml ($p < 0.001$, vs uterine leiomyoma), and 447 U/ml ($p < 0.001$, vs uterine leiomyoma), respectively. A significant overlapping in the distribution of serum CA125 between uterine leiomyoma and early stage uterine leiomyosarcoma can be seen in both the premenopausal and postmenopausal groups.

Figure 3 (premenopausal group) and Figure 4 (postmenopausal group) demonstrate the ROC curves for pre-

Fig. 1

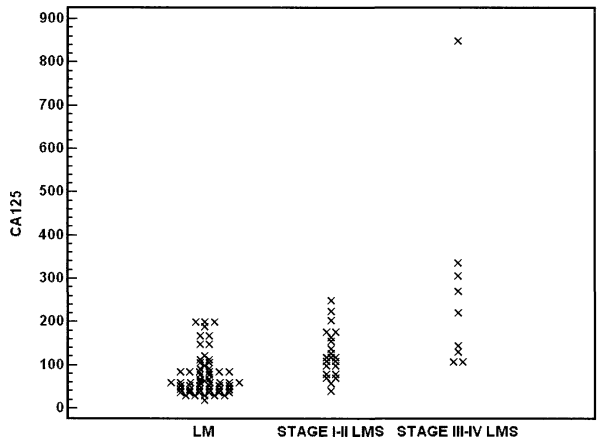


Fig.

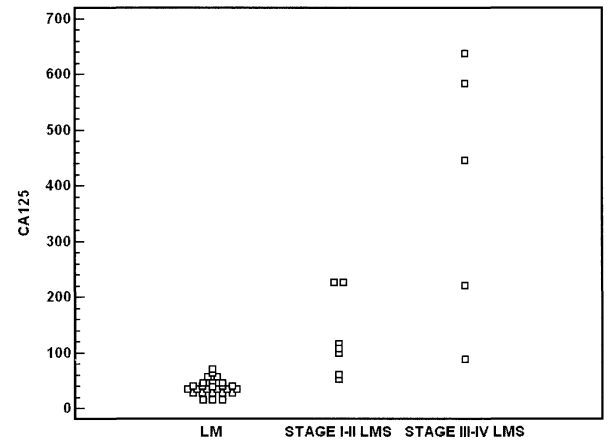
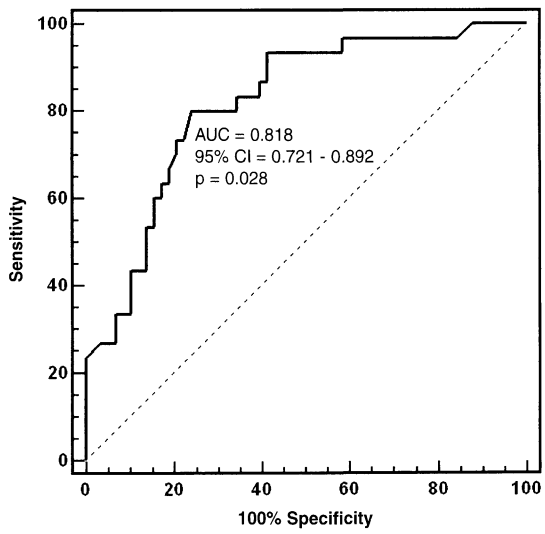


Fig. 3



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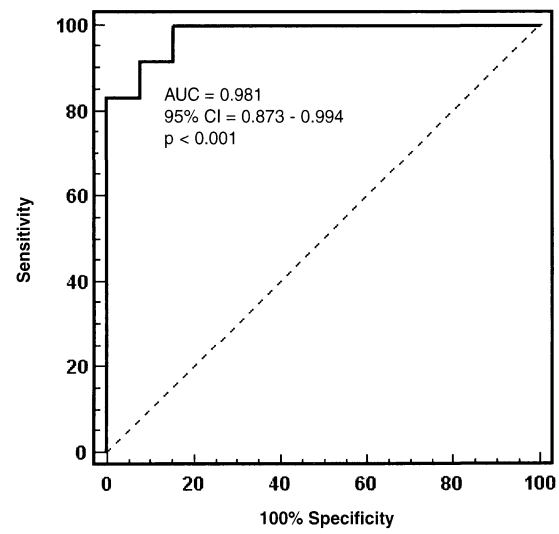

Figure 1. — Distribution of preoperative serum CA125 among patients with uterine leiomyoma and different stages of uterine leiomyosarcoma in the premenopausal group.
Figure 2. — Distribution of preoperative serum CA125 among patients with uterine leiomyoma and different stages of uterine leiomyosarcoma in the postmenopausal group.
Figure 3. — Receiver operating characteristic (ROC) curves for the levels of preoperative serum CA125 in premenopausal patients with uterine leiomyosarcoma.
Figure 4. — Receiver operating characteristic (ROC) curves for the levels of preoperative serum CA125 in postmenopausal patients with uterine leiomyosarcoma.

operative serum CA125 among the patients with uterine leiomyosarcomas; cases of uterine leiomyomas served as the ROC control group. The mean (95% CI) area under the curve (AUC) for the premenopausal group was 0.818 (0.721-0.892), and 0.981 (0.873-0.994) for the postmenopausal group. There were significant differences of AUC both in the premenopausal group and the postmenopausal group ($p = 0.028$ for the premenopausal group, $p < 0.001$ for the postmenopausal group). This suggested that preoperative serum CA125 was a candidate tumor marker for the differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma both in the premenopausal group and the postmenopausal group.

Table 2 shows the performance of optimal cutoff value of serum CA125 in each study group. For the premenopausal group, the optimal cutoff value for differentiating between uterine leiomyoma and uterine leiomyosarcoma was 75 U/ml, while the value was 162 U/ml for the postmenopausal group. In the premenopausal group, the likelihood ratio for a positive test in the premenopausal group was 5.68 which indicated that there was a 5.68 odds of occurrence of disease when the test was above the cutoff value. Likewise, the likelihood ratio for a negative result was 0.11 which indicated there was a 0.11 odds of occurrence of disease when the test was below the cutoff value. In the postmenopausal group, the likelihood ratio for a positive test in the premenopausal group was 8.0, while the likelihood ratio for a negative result was 0.05.

Discussion

The current study demonstrates that although there was significant overlapping of preoperative serum CA125 between uterine leiomyoma and early stage uterine leiomyosarcoma, there was still a significant difference in preoperative serum CA125 between early and late stage of uterine leiomyosarcoma which indicated a positive correlation between CA125 and tumor burden and spreading. To view it in another way, CA125 could potentially be used to monitor treatment efficacy and to detect disease recurrence in uterine leiomyosarcoma.

One of the major problems regarding treatment of uterine leiomyosarcoma is the difficult preoperative differential diagnosis from uterine leiomyoma. For treatment of uterine leiomyoma, there is a trend toward more conservative treatment using gonadotropin-releasing hormone agonist (Gn-RHa) to improve anemia in menorrhagic women or in an attempt to avoid hysterectomy in perimenopausal patients [23-25]. Therefore, some patients with uterine leiomyosarcoma who were misdiagnosed as having uterine leiomyoma would be treated in a conservative way leading to delayed definitive treatment [26, 27]. Accordingly, it is imperative to make a correct preoperative differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma. So far there are few reports investigating the preoperative differential diagnosis between uterine leiomyoma and uterine leiomyosarcoma in the literature [28, 29]. All of the studies used magnetic resonance imaging (MRI) as the main diagnostic instrument.

Because the incidence between uterine leiomyoma and uterine leiomyosarcoma varies greatly, routine use of MRI for the differential diagnosis between these two tumors may cause too much medical expenditure. The current study provides useful information in that when a physician faced with a seemingly benign uterine leiomyoma but with a high serum CA125, the possibility of advanced uterine leiomyosarcoma should also be put in the differential diagnosis list. However, there was still a great overlapping of distribution of serum CA125 between uterine leiomyoma and early-stage uterine leiomyosarcoma which made the differential diagnosis problematic.

One thing to note, in rare conditions, patients with uterine leiomyoma may present with massive ascites (pseudo-Meigs syndrome) and elevated serum CA125 levels. In such condition, our proposed method may fail to differentiate between the two tumors. Moreover, some patients with uterine leiomyoma would have massive uterine bleeding with resultant intraabdominal blood accumulation, which potentially induces peritoneal irritation and subsequent elevation of serum CA125. Therefore the best timing for blood collection for the differential diagnosis should be selected at the non-bleeding period.

Conclusion

In conclusion, there is increasing demand for pretreatment differential diagnoses between uterine leiomyoma and uterine leiomyosarcoma due to the modern trend of conservative treatment for uterine leiomyoma. For cases of uterine leiomyosarcoma misdiagnosed as uterine leiomyoma definitive treatment would thus be delayed. MRI is the only reported image modality for discriminating between these two tumors thus far with great expense. The current study only provided information that when treating presumed uterine leiomyoma with high preoperative serum CA125 advanced uterine leiomyosarcoma should also be included in the differential diagnosis list.

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