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CLINICAL ARTICLE

A retrospective analysis of the clinicopathologic characteristics of uterine cellular leiomyomas in China

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ABSTRACT

Objective: To investigate the clinicopathologic features of uterine cellular leiomyomas (CLs) by comparing them with those of uterine leiomyosarcomas (LMSs). *Methods:* A case–control study comparing 78 cases of CL with 10 cases of LMS was conducted. The patients' records were reviewed to abstract information on tumors features and treatment, immunohistochemical findings, and disease prognosis. *Results:* The mean age at diagnosis was 45.3 ± 8.41 years in the CL group. The main clinical CL manifestations were menstrual abnormalities (56.4%), abdominal pain or distension (14.1%), and pelvic pressure (8.9%). Abdominal pain or distension was significantly more common in the LMS than in the CL group ($P<0.05$). Generally, CL tumors were smaller in diameter than LMS tumors ($P<0.05$). Moreover, lower levels of Ki-67 and PCNA expression were measured in CL than in LMS tumors ($P<0.05$). There were no cases of malignant transformation or metastasis in 41 patients with CL who adhered to long-tern follow-up. *Conclusion:* No symptoms were found to be specifically associated with CL, and management of CL does not need to differ from that of ordinary leiomyoma. In contrast to malignant disease, CL has a favorable long-term prognosis. However, given its "borderline" pathologic nature, patients with CL require clinical surveillance.

1. Introduction

Uterine leiomyomas, which are benign tumors of myometrial origin, are the most common gynecological neoplasms, with an estimated prevalence of 25% in women older than 30 years [1]. They are the leading cause of hysterectomy [1,2]. Although the diagnosis of ordinary uterine leiomyoma is usually unproblematic, the tumor's morphologic variants may create challenges for the pathologist and may be misinterpreted as leiomyosarcoma (LMS). Of all the histologic variants—cellular, epithelioid, myxoid, atypical, mitotically active, and lipoleiomyomatous—the cellular variant seems to be the most common.

Cellular leiomyoma (CL) exhibits hypercellularity and may have the potential for malignant transformation and metastasis [3,4]. Several reports indicate that ordinary leiomyoma, CL, and LMS can coexist in the uterus [5]. It is not clear whether CL is a borderline or intermediate smooth muscle tumor constituting a transition between leiomyoma and leiomyosarcoma. It is important for pathologists and gynecologists to fully understand the differences in clinical presentation, pathologic features, and biologic behavior that characterize ordinary uterine leiomyoma, CL, and LMS. Taran et al. [6] presented a case–control study in which CLs were compared with ordinary leiomyomas and concluded that CLs had a clinical phenotype distinct from that of ordinary leiomyomas, with some characteristics in common with LMSs.

The purpose of the present study was to compare the clinicopathologic characteristics of CL with those of LMS.

2. Materials and methods

The present retrospective study was conducted between January 1, 2000, and December 31, 2010, at the Department of Gynecology of the Second Military Medical University Hospital, Shanghai, China, with 78 women with CL. Ten women treated for LMS during the same period acted as controls. The study was approved by the Medical Ethics Review Board of Changhai Hospital, Second Military Medical University School.

All histologic sections were reviewed according to the criteria of the 2003 WHO classification of tumors to confirm diagnoses [7], and LMSs were assessed according to the 2009 FIGO staging guidelines [8]. Five of the control patients had stage I, 2 had stage II, 2 had stage III, and 1 had stage IV LMS (1 patient had epithelioid LMS, a morphologic variant of LMS).

We abstracted from the patients' records any information on the clinical features, treatment, prognosis, and immunohistochemical characteristics of their tumors. The presence of both Ki-67 protein and proliferating cell nuclear antigen (PCNA) was assessed by immunohistochemistry from paraffin-embedded tissue sections. Follow-up telephone

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interviews were conducted with 48 participants, 41 case and 7 control patients, to obtain information toward prognosis. Forty case patients were lost to follow-up.

Comparisons between the case and the control groups were performed using *t* tests, χ^2 tests, and nonparametric tests. All statistical analyses were performed using SPSS version 17.0 (IBM, Armonk, NY, USA). $P<0.05$ was considered significant.

3. Results

All participants were Chinese and 86 (97.7%) were ethnic Han. The clinical characteristics of the 2 groups combined are presented in Table 1.

For the 78 participants in the CL group, age ranged from 27 to 71 years (mean age, 45.3 ± 8.41 years). The main clinical manifestations of CL were menstrual abnormalities (n = 44 [56.4%]), abdominal pain or distension (n = 11 [14.1%]), and pelvic pressure (n = 7 [8.9%]). Some patients (n = 24 [30.8%]) did not feel any discomfort and their uterine masses were discovered on physical examination or ultrasound. Abdominal pain or distension was significantly more common in the LMS group (n = 5 [55.6%]).

Five (6.4%) patients with CL were postmenopausal. Three of these patients complained of an enlarging leiomyoma and/or postmenopausal bleeding. The lesions were diagnosed incidentally for the 2 other patients, during surgery for uterine prolapse or ovarian neoplasms.

In the CL group, the surgical procedures consisted of 48 total hysterectomies, 12 subtotal hysterectomies, and 18 myomectomies (performed abdominally, laparoscopically, or hysteroscopically). The mean diameter of the CL masses was 7.56 ± 4.08 cm (range, 2.0–20.0 cm), which was significantly smaller than that of the LMS masses (10.75 ± 5.18 cm). Clinically, 4 (5.1%) of the CLs had lost their whorled pattern. These looked fleshy and soft with irregular margins, whereas the remaining CLs were macroscopically similar to ordinary leiomyomas. Histologically, the number of mitotic figures per 10 high-power fields (MF/10 HPF) ranged from 0 to 5. No mitotic figures were observed in 30 (38.5%) of the 78 tissue samples; 2 or fewer were observed in 44 samples (56.4%); and 3 to 5 were observed in 4 samples (5.1%) (Fig. 1). In the LMS group, the coexistence of CL and LMS was identified in 1 patient.

In the CL group, 41 patients were followed up for a median of 72 months (range, 10–126 months). There were no cases of recurrence or metastasis in the 27 patients who underwent total or subtotal hysterectomies. Of the 14 who underwent myomectomies, 4 (28.6%) experienced recurrence. Of these, 2 (14.3%) had a second myomectomy or total hysterectomy because of the recurrence. The median time to recurrence was 4.2 years. One patient had a CL recurrence 5 years after an abdominal myomectomy and underwent total abdominal hysterectomy.

Immunohistochemical analysis showed Ki-67 expression in 23 (76.7%) of the available CL and 8 (100%) of the available LMS lesions, and PCNA expression in 21 (87.5%) of the available CL and 5 (100%) of the available LMS lesions. The results of the immunohistochemical analysis are summarized in Table 2.

Table 1
Characteristics of the 88 study participants.[a]

Variable	Cellular leiomyoma group	Leiomyosarcoma group	*P* value
Age, y	45.3 ± 8.41	50.0 ± 8.82	0.11 [b]
<40 y	15.4 (12/78)	0 (0/10)	0.35 [c]
Postmenopausal	6.4 (5/78)	30.0 (3/10)	0.04 [c]
Menstrual abnormalities [d]	56.4 (44/78)	77.8 (7/9)	0.38 [e]
Abdominal pain or distension [f]	14.1 (11/78)	55.6 (5/9)	0.01 [e]
Pelvic pressure	8.9 (7/78)	22.2 (2/9)	0.23 [c]
Anemia [g]	42.3 (33/78)	33.3 (3/9)	<0.001 [i]
Mild	12.8 (10/78)	11.1 (1/9)	
Moderate	23.1 (18/78)	22.2 (2/9)	
Severe	6.4 (5/78)	0 (0/9)	
Sonographic features of the largest mass			0.06 [c]
Hypoechoic	74.3 (55/74)	62.5 (5/8)	
Isoechoic	8.1 (6/74)	0 (0/8)	
Hyperechoic	12.2 (9/74)	0 (0/8)	
Mixed echoic	5.4 (4/74)	37.5 (3/8)	
Solitary mass	34.8 (24/69)	62.5 (5/8)	0.25 [e]
Diameter of the largest leiomyoma [h], cm	7.56 ± 4.08	10.75 ± 5.18	0.05 [b]
Survival rate	100 (41/41)	42.9 (3/7)	0.002 [c]

[a] Values are given as mean ± SD or percentage (number per total number in the subgroup).
[b] By the 2-sample *t* test.
[c] By the Fisher exact test.
[d] Menstrual abnormalities included menometrorrhagia, menorrhagia, and abnormal menstrual cycle intervals.
[e] By the continuity adjusted χ^2 test.
[f] Abdominal pain or distension did not include dysmenorrhea.
[g] Anemia was classified on the basis of hemoglobin concentration as mild (9.0–10.9 g/dL), moderate (6.0–8.9 g/dL), or severe (<6.0 g/dL).
[h] Information was available for 71 women in the CL group and 8 women in the LMS group.
[i] By the Mann–Whitney nonparametric test.

4. Discussion

Uterine cellular leiomyoma is a special type of leiomyoma that accounts for less than 5% of uterine leiomyomas [7,9]. Histologically, CL resembles malignant neoplasms and may be misdiagnosed. Moreover, CL may have some clinical behaviors that are associated with malignancies. Cases of malignant transformation and metastasis of CL have been reported [3,4]. The present case–control study provides data on the clinicopathologic characteristics of CL and outlines statistically significant clinicopathologic differences between CL and the LMS tumors.

Most LMSs occur in women older than 40 years [8]. On average, women with CLs are younger than women with LMS. Postmenopausal women account for a relatively small proportion (6.4%) of all women with CL. The most frequent symptoms of uterine CL are menstrual abnormalities, a pelvic mass, abdominal pain, and pelvic pressure. Signs and symptoms of CL are similar to those of LMS, but abdominal pain or distension is much more common in women with LMS. Tumor growth or bleeding may accompany CL, especially in postmenopausal women, and these can be signs of malignancy.

Almost all CLs are diagnosed during hysterectomy or myomectomy at the time of frozen section analysis of resection specimens. These tumors are generally smaller in diameter than LMSs. However, CLs can undergo rapid growth and enlargement. In this study, the largest uterus in the CL group was similar in size to a 7-month-pregnant uterus. Macroscopically, CLs resemble ordinary leiomyomas but they sometimes lack the whorled pattern and irregular margins. In the present study, the number of mitotic figures ranged from 0 to 2 per MF/10 HPF for 94.9% of all CLs and ranged from 3 to 5 MF/10 HPF for only 5.1% of the CLs.

Immunohistochemistry is currently an essential tool for biomarker detection even in clinical practice. Many tumor-associated antigens, such as squamous cell carcinoma antigen and cancer antigen 125, have been used not only in the differential diagnosis of gynecologic tumors but also as prognostic tools, to assess therapeutic response and detect recurrence [10]. Immunohistochemistry offers some assistance in differentiating between CL and malignant disease. The Ki-67 protein and PCNA are regarded as indicators of cell proliferation [11,12]. In this study, the levels of Ki-67 and PCNA expression were lower in CL than in LMS tumors. These findings are consistent with those of previous studies [11–13] and suggest that PCNA and Ki-67 can be used as immunohistochemical markers for differential diagnosis. Furthermore, the immunohistochemical detection of p53, of the smooth muscle markers desmin and smooth muscle actin, and of the estrogen and progesterone receptors can be useful in differentiating CL from LMS