Clinical Characteristics Differentiating Uterine Sarcoma and Fibroids

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ABSTRACT

Background and Objectives: Uterine fibroids are a common indication for laparoscopy. Unsuspected sarcoma can pose a serious risk if morcellation is used in the procedure. We sought to determine the clinical factors associated with uterine sarcoma compared with uterine fibroids.

Methods: We conducted a case–control study of 66 women who had hysterectomy for uterine sarcoma from April 1, 2007, to March 31, 2014. Sixty-six patients who had hysterectomy for fibroids were randomly selected as controls.

Results: Women with sarcoma vs women with fibroids, tended to be older (mean $\pm$ SD 62.1 $\pm$ 10.1 vs 46.5 $\pm$ 6.6; $P < .0001$), were more likely to be postmenopausal (81.8% vs 9.2%; $P < .0001$), and were more likely to have a history of another nonuterine malignancy (16.7% vs 4.6%; $P = .02$). Women with sarcoma were more likely to have masses that were subserosal (69.4% vs 34.8%; $P < .0001$), rather than intramural (11.1% vs 37.0%; $P = .01$), and to have a solitary rather than multiple uterine mass (56.3% vs 18.5%; $P < .0001$). They were also more likely to have a history of documented rapid growth (16.7% vs 4.6%; $P = .02$).

Conclusion: Despite limitations in sample size related to infrequency of uterine sarcoma, our results suggest some preoperative clinical differences between women who have uterine sarcoma vs uterine fibroids. Further studies on such features may assist us in identifying patients who are at higher risk of having a uterine sarcoma among women with a uterine mass contemplating surgery.

Key Words: Case–control, Fibroid, Laparoscopic morcellation, Leiomyoma, Uterine sarcoma

INTRODUCTION

Uterine fibroids are common benign tumors affecting many women of reproductive age and are a main indication for uterine surgery.[1] Compared with open abdominal procedures, minimally invasive hysterectomy or myomectomy can be associated with reduced operative morbidity and rapid recovery.[2–4] However, when specimens are large, minimally invasive hysterectomy or myomectomy procedures require the fragmentation of tissue through morcellation, either with a laparoscopic power morcellator or with a scalpel for removal from the abdominal cavity.

Though uterine sarcoma is rare—with the annual incidence of leiomyosarcomas at approximately 0.4 to 0.64 per 100,000 women—it has been estimated that approximately 1:8300 to 1:352 women undergoing uterine surgery for presumed fibroids have unsuspected sarcoma.[5–14] In such cases, uncontained morcellation of the uterine mass can be associated with the risk of cancer dissemination and potentially worsened prognosis.[13]

Although the identification of malignant disease before surgery can prevent inadvertent uncontained morcellation of occult malignancy, uterine sarcomas are difficult to distinguish from uterine fibroids clinically. Some studies suggest that magnetic resonance imaging (MRI) with contrast showing certain features, such as the absence of calcifications[14,15] and diffusion-weighted MRI,[15] may be useful for identifying suspicious features in some cases. However, in general, studies on imaging modalities, including MRI, positron emission tomography (PET), computed tomography (CT), and ultrasonography, and serum markers, such as lactate dehydrogenase (LDH) and cancer antigen (CA)-125, have not been reliable in differentiating

between benign and malignant tumors.[14,16–19] Studies on clinical characteristics have suggested that certain characteristics, such as race, age, and menopausal status, may be risk factors for uterine sarcoma.[20–22] However, such studies have been limited by absence of control group comparisons or lack of detailed clinical information regarding tumor characteristics. The purpose of this study was to examine the clinical characteristics associated with uterine sarcoma compared with those of uterine fibroid tumor.

METHODS

Subjects

Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board. In this case–control study, the clinical records of women undergoing surgery for uterine mass at a tertiary academic center (the Ottawa Hospital), from April 1, 2007, through March 31, 2014, were reviewed for preoperative clinical characteristics. All women who had surgery for uterine sarcoma were included and compared with those who underwent surgery for uterine fibroid. The number of women with surgery for uterine fibroid far exceeded the number having surgery for uterine sarcoma. To ensure that our fibroid (control) group was selected from the same period as our sarcoma (case) group, we selected a random sample of patients from the same time period as patients undergoing surgery for uterine sarcoma. For patients having surgery for fibroid, patient chart numbers were selected with computer-generated random numbers.

Data Collection

The medical record numbers for these cases were identified through the Ottawa Hospital Data Warehouse, according to the International Classification of Diseases (ICD 10-CA) codes for Malignant Neoplasm of Cervix Uteri, Corpus Uteri, and Uterus Unspecified (C54*, C55*, and C53*) and Diagnosis type 4 (Morphology) codes for Sarcoma or Leiomyosarcoma (88903, 88913, and 88963), Mullerian Tumor/Carcinosarcoma (89503, 89803, and 89813), Endometrial Stromal Sarcoma (89303), Sarcoma Uterus Not Otherwise Specified (88003), and Adenosarcoma (89333). Fibroid cases were identified with ICD10-CA codes (D25*). A 1:1 match was used, and 66 fibroid cases were randomly selected as controls.

Information on patient demographics (age, gravidity, parity, menopausal status, and history of malignancy), clinical presentation (clinical symptoms and suspicion for rapid growth) were systematically collected from clinical notes. Suspicion for rapid growth of the mass was based on physician assessment and documentation in the patient chart. Ultrasonography and MRI characteristics (number, size, and location of uterine mass) were collected from radiologic reports. Tumor characteristics (type and stage of uterine sarcoma) were collected from pathology reports.

Statistical Analysis

Descriptive statistics were used to characterize the study population. Continuous variables were summarized as means and standard deviations for normally distributed data and medians and ranges for nonparametric data. Categorical variables were summarized by using frequencies and proportions. Categorical variables were compared by using χ^2 or Fisher's exact test. For continuous variables, t test was used if distribution was normal, and nonparametric statistical methods were used if distribution was skewed. A 2-sided $P < .05$ was considered significant.

RESULTS

Charts for 66 consecutive patients with sarcoma were reviewed, along with a random sample of 66 surgically managed patients with uterine fibroids as a control group. The patient characteristics of both study populations are presented in **Table 1**.

Women with sarcoma, compared with women with fibroids, tended to be older (mean $\pm$ SD 62.1 $\pm$ 10.1 vs 46.5 $\pm$ 6.6; $P < .0001$) and were more likely to be postmenopausal (81.8% vs 9.2%; $P < .0001$). They were more likely to have a history of other nonuterine malignancy (16.7% vs 4.6%; $P = .02$). Women with sarcoma were more likely to have masses that were subserosal (69.4% vs 34.8%; $P < .0001$) rather than intramural (11.1% vs 37.0%, $P = .01$), and have a solitary rather than multiple uterine mass (56.3% vs 18.5%; $P < .0001$). They were also more likely to have a history of documented rapid growth based on assessment by a healthcare provider (16.7% vs 4.6%; $P = .02$). No significant differences were detected between the groups with respect to gravidity, parity, pain or pressure, heavy menstrual or postmenopausal bleeding, or uterine size (**Table 1**).

Of the 66 cases of uterine sarcoma, 61 (92.4%) underwent surgery by a gynecologic oncologist for suspect malignancy, and 5 (7.6%) had surgery from a general gynecologist for presumed benign fibroids. Although

Table 1.
Comparison of Demographic and Clinical Characteristics of Patients with Uterine Sarcoma vs Fibroids

	Uterine Sarcoma	Uterine Fibroids	P-value
Mean age in years ± SD	62.1 ± 10.1	46.5 ± 6.6	<.0001
Menopausal status, n (%)			
Premenopausal	12 (18.2)	59 (90.8)	<.0001
Postmenopausal	54 (81.8)	6 (9.2)	
Median gravidity, n (range)	2 (0 to 8)	2 (0 to 8)	.74
Median parity, n (range)	2 (0 to 7)	2 (0 to 5)	.17
History of previous nonuterine malignancy, n (%)	11 (16.7)	3 (4.6)	.02
Patient symptoms, n (%)			
Pain or pressure	29 (43.9)	34 (51.5)	.38
Heavy menstrual bleeding	9 (13.6)	45 (68.2)	<.0001
Postmenopausal bleeding	36 (54.6)	2 (3.0)	<.0001
Ultrasound characteristics			
Number of masses, n (%)			
1	27 (56.3)	12 (18.5)	
2	9 (18.8)	4 (6.2)	
≥ 3	12 (25.0)	49 (75.4)	<.0001
Position of mass within uterus, n (%)			
Submucosal	7 (19.4)	13 (28.3)	.36
Subserosal	25 (69.4)	16 (34.8)	<.0001
Intramural	4 (11.1)	17 (37.0)	.01
Mean diameter of largest mass, cm ± SD	9.6 ± 5.6	8.5 ± 3.9	.40
Documented concern about rapid growth, n (%)	11 (16 .7)	3 (4.6)	.02

n = 66. Data are from the medical records of The Ottawa Hospital, Ontario, Canada, April 1, 2007 to March 31, 2014.

laparoscopic power morcellation was not used in any cases of uterine sarcoma, manual morcellation was used in 2 of the 5 cases performed by general gynecologists to facilitate removal of the large tumor (both leiomyosarcoma, 20 and 9 cm) through a laparotomy incision.

With respect to pathologic subtypes of uterine sarcomas (**Table 2**), 29 (43.9%) were carcinosarcoma, 19 (28.8%) were leiomyosarcoma, 9 (13.6%) were endometrial stromal sarcoma, 4 (6.1%) were adenosarcoma, 4 (6.1%) were undifferentiated sarcoma, and 1 (1.5%) were uterine rhabdomyosarcoma. The stage of the cancer ranged from I to IV with 43.6% in stage I, 18.2% in stage II, 27.3% in stage III, and 10.9% in stage IV. The mean (SD) diameter of the largest mass was 9.0 cm (±5.9 cm).

DISCUSSION

We performed this case–control study to identify clinical differences between patients with sarcoma and uterine fibroids, and we found that older age, postmenopausal status, and history of previous malignancy were associated with the presence of uterine sarcoma among women with uterine mass. Certain tumor characteristics, such as documentation of rapid growth, subserosal mass, and multiple masses also appeared to be associated.

The identified clinical risk factors are generally consistent with reports in the literature. Descriptive studies have reported high proportions of menopausal women among women with uterine sarcoma.[22,23] One recent population-based cohort study found the prevalence of sarcoma to be highly dependent on age, with more than 10-fold higher

Table 2.
Pathologic Characteristics of Consecutive Cases of Uterine Sarcoma

Pathologic Subtype, n (%)	
Carcinosarcoma	29 (43.9)
Leiomyosarcoma	19 (28.8)
Endometrial stromal sarcoma	9 (13.6)
Adenosarcoma	4 (6.1)
Undifferentiated sarcoma	4 (6.1)
Uterine rhabdomyosarcoma	1 (1.5)
Stage, n = 55, n (%)	
I	24 (43.6)
II	10 (18.2)
III	15 (27.3)
IV	6 (1.9)
Mean diameter of largest uterine mass, cm ± SD	9.0 ± 5.9

n = 66. Data are from the medical records of The Ottawa Hospital, Ontario, Canada, April 1, 2007 to March 31, 2014.

prevalence of uterine sarcoma among women older than 60 years compared with women younger than 50 years among women undergoing uterine surgery.[21] However, further detailed clinical information was not available, because the population-based study was conducted with hospital administrative data.

Our study also identified women with a history of previous malignancy as a risk factor for uterine sarcomas. Six of the 11 women in our study with a history of malignancy had a previous diagnosis of breast cancer, and 4 of these women had a documented history of tamoxifen therapy for breast cancer. Although an association between breast cancer and uterine sarcoma has not been shown, tamoxifen exposure has been reported as a risk factor for uterine sarcoma in population registries and in case reports.[24–25] One patient in our study had a history of retinoblastoma. Both retinoblastoma and uterine sarcoma are uncommon malignancies; however, the association between uterine sarcoma and specific malignancies such as hereditary retinoblastoma has also been reported in studies using population data.[26] In addition to the association with retinoblastoma, uterine sarcoma may be associated with hereditary leiomyomatosis and renal cell cancer (HL-RCC),[27–28] although none of our patients reported a history of this condition. Other nonuterine malignancies reported in the history of sarcoma patients included thyroid, colon, and ovarian cancers. Consistent with previous studies, no differences were found in pressure, pain, or bleed-

ing symptoms among women with uterine sarcoma or fibroid.

Women with pelvic mass are typically assessed by clinical pelvic examination, with pelvic ultrasonography as the first-line imaging modality. Features of leiomyosarcoma have classically been considered a rapidly growing, solitary uterine mass.[29] The finding of uterine growth in a postmenopausal woman without estrogenic or progestogenic hormonal stimulation may be of particular concern. In our examination of clinical characteristics, we found that physician assessment and documentation of rapid growth was associated with increased odds of a sarcoma diagnosis compared with fibroid. Whereas some reports have documented the association between a history of rapid growth and sarcoma diagnosis, other studies have not verified this association.[20,30] Because the definition of rapid growth has generally relied on subjective clinical assessment and the number of patients in reported studies is very small, the findings in this study have yet to be verified.

We also found that subserosal tumor was associated with uterine sarcoma, which is a rare finding. One report found sarcoma to be associated instead with intramural mass and large tumor size.[31] Further studies, using more detailed classification systems, such as the International Federation of Gynecology and Obstetrics (FIGO) leiomyoma subclassification system for location of uterine mass, may be helpful in verifying these study findings.[32]

Overall, our study provides support to the limited number of reports in the literature suggesting clinical risk factors for uterine sarcoma among women with a uterine mass. To our knowledge, our study is among the very limited number of studies that include a control group and are of a case–control study design to investigate multiple risk factors documented in patient charts. Given the infrequency of uterine sarcoma, the case–control design is appropriate. By contrast, one cohort study involving more than 10,000 women captured 48 sarcoma cases.[19] Population-based registries with greater than 200,000 cases may capture more than 200 cases of uterine sarcoma; however, such registries lack the detailed clinical information needed to perform clinically meaningful analyses.[21]

Compared with case reports and case series in the literature, the strength of this study is the inclusion of consecutively captured sarcoma cases at our institution with the availability of a suitable control group with uterine mass from the same institution and study period.[10,25,30] Because of the infrequency of uterine sarcoma, our study was limited by the small number of cases available for study

and our inability to perform subgroup or regression analyses related to sample size. In particular, subgroup analysis for leiomyosarcoma cases could not be performed due to the small sample. Also, the study was performed at a tertiary academic center that includes a gynecologic oncology consultant team. Although the concentration of complex disease at our center enabled us to achieve the sample size observed in our study, the results may not reflect that of a community hospital where uterine sarcoma is even less frequent. Finally, the information was collected retrospectively through review of patient charts, and some information, such as ethnicity, tamoxifen use among women with breast cancer, and use of other diagnostic imaging modalities, was not consistently available for the included patients.

The limitations of our study highlight the utility of a large, prospective patient registry with detailed clinical information to assist with the identification of important risk factors for sarcoma among women with uterine mass.

Despite limitations in sample size because of the infrequency of uterine sarcoma, our study suggests some preoperative clinical differences between women who have uterine sarcoma vs uterine fibroid. Further studies on such features may assist us in identifying patients who are at higher risk of having uterine sarcoma among women with a uterine mass contemplating surgery.

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