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Leiomyosarcoma of the Uterus: Ultrasonography and Serum Lactate Dehydrogenase Level

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Key Words

Leiomyosarcoma
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Abstract

Between January 1, 1979, and September 30, 1990, a total of 1,886 patients in the National Defense Medical College Hospital, a self-referred population, had a hysterectomy because of signs and symptoms presumably resulting from uterine myomas. After hysterectomy with presumed benign disease, a histologic diagnosis of leiomyosarcoma was made in 7 patients (0.37%). Preoperative diagnosis of leiomyosarcoma was not made in any of the 7 patients. However, serum lactate dehydrogenase levels were abnormally elevated in 3 of them, and degenerative changes were found within the tumor by ultrasonography in 5 of them. Furthermore, increased lactate dehydrogenase levels and degenerative changes within the tumor were found in 3 of the patients whose tumors had 10 or more mitoses per 10 high-power fields. The prognosis for the leiomyosarcomas with increased mitotic rates is very poor. Therefore, a degenerative change within the uterine mass and an increased lactate dehydrogenase level, when present, should suggest the diagnosis of leiomyosarcoma.

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Introduction

Leiomyosarcoma of the uterus is an uncommon, malignant neoplasm. On the other hand, uterine myoma, a benign neoplasm, is the most common solid tumor of the female genital tract. Recently, conservative therapy with the gonadotropin-releasing hormone analogue (GnRH-a) has been applied to women with uterine myoma, and it has been effective in decreasing uterine size in some of them [1-3]. Although removal of a uterus, the size of a 14-week gestation, was justified in the past based on the size alone, the introduction of GnRH-a therapy may change previous indications for hysterectomy. However, it is not uncommon for a patient with a uterine mass to undergo hysterectomy with a preoperative diagnosis of benign myoma only to have a sarcoma found on pathologic examination. In order to obtain further insight into the various clinical aspects of leiomyosarcoma of the uterus, which may possibly aid the management of this tumor, a retrospective study was undertaken in women who had a hysterectomy because of signs and symptoms presumably resulting from uterine myomas.

Materials and Methods

The records of all patients who underwent hysterectomy for presumed leiomyomas between January 1, 1979, and September 30, 1990, at the National Defense Medical College Hospital were

Table 1. Clinicopathologic data in7 women with uterine leiomyosarcoma

Patient No.	Age year	Symptoms	Uterus size gestational weeks	Uterine weight, g	Location of the tumor
	46				
	63				
	56				
	43				
	43				
	34				
	33				

reviewed. The histologic criteria used for the diagnosis of leiomyosarcoma were similar to those of Hendrickson and Kempson [4] and Zaloudek and Norris [5]: (1) > 10 mitoses per 10 high-power fields (HPF) with 40 fields counted, or (2) mitotic rate of 5-9 per 10 HPF, with 40 fields counted, in conjunction with nuclear atypia or metastasis. During the 11-year and 9-month period, 1,886 patients were operated on for presumed symptomatic uterine myomas. Seven patients (0.37%) had a final diagnosis of leiomyosarcoma. The clinical and biochemical data, ultrasonographic and pathologic findings were recorded for each of the patients with leiomyosarcoma. Furthermore, the biochemical data and ultrasonographic findings were also reviewed in 91 consecutive patients who underwent hysterectomy and had a final diagnosis of leiomyoma of the uterus between January 1, 1990, and September 30, 1990. The determination of lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) was performed using the Technicon SMAC system (Technicon Instruments Corp, Tarrytown, N.Y., USA) based on the method of Morgenstern et al. [6].

Table 2. Serum LDH and ALP levels, degenerative changes identified by ultrasonography, and the number of mitoses per 10 HPF in women with uterine leiomyosarcoma

Patient No.	LDH IU/1	ALP IU/1	Degenerative change	Mitoses per 10 HPF
390	71	+		10
390	80	+		62
424	92	+		16
145	59	+		8
172	49	o		9
205	62	0		5
187	71	+		6
	(140-205)a	(32-105)a		

a 95 % confidence limits for 91 women with uterine leiomyoma.

Results

The mean age of the 7 patients with uterine leiomyosarcoma was 45.5 years. The youngest and oldest patients were 33 and 63 years old, respectively, with a median age of 43 (table 1). Two were postmenopausal. Two of the seven patients were obese, but none of them had hypertension or diabetes mellitus. Uterine enlargement was common to all patients. Six patients had a uterus larger than the size of a 13-week-gestation. The uterus was of the 12-week size in 1 patient. All patients had cervical cytology performed preopera-tively. None suggested the presence of leiomyosarcoma. A preoperative dilatation and curettage was performed in 4 patients who showed hypermenorrhea or uterine bleeding. The dilatation and curettage procedure was negative in all 4 patients. All patients underwent pelvic ultraso-nography. The ultrasonographic findings were interpreted
as uterine myoma with degeneration in 5 and uterine myoma without degeneration in the other 2 (table 2). Thus, the preoperative diagnosis of leiomyosarcoma was not made in any of the 7 patients.

The 2 postmenopausal patients underwent total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). In 1 of the 5 premenopausal patients, suspicion of malignancy arose from the gross features of the tumor intraoperatively, and TAH/BSO was performed. The other 4 premenopausal patients underwent TAH only. None of the patients had metastases identified at the time of surgery (table 3). Two patients had a leiomyosarcoma in a uterus where leiomyomas were also present. In 5 patients the leiomyosarcoma was the sole neoplasm in the uterus. The location of the leiomyosarcoma in the uterine wall was noted in all patients. Four were intramural, 2 subserosal, and 1 submucosal (table 1). A mitotic count of 10 or more per 10 HPF and cellular

Table 3. Uterine leiomyosarcoma outcome

atypia were found in 3 specimens; 4 specimens had a mitotic count of 5-9 per 10 HPF (table 2). Three of the seven patients had adjuvant chemotherapy (table 3). One patient whose tumor had 62 mitoses per 10 HPF recurred and died 3 months after surgery. Of the remaining 6 patients, 1 is alive with disease and 5 are alive without evidence of disease 9-86 months after surgery (table 3).

In 13 of the 91 patients with uterine myoma, degeneration was identified within the tumor by ultrasonography. The 95 % confidence limits of LDH and ALP levels for the patients with leiomyoma were 140-245 and 32-105 IU/1, respectively (table 2). LDH levels were elevated preopera-tively in 3 of the 7 patients with leiomyosarcoma compared to those with leiomyoma (table 3). The 3 patients with increased LDH levels had tumors with 10 or more mitoses per 10 HPF. Furthermore, in these patients degenerative changes were identified within the tumors by ultrasonography. LDH levels fell to within normal limits after surgery in all of them. However, the LDH level increased again to 414IU/1 just before death in the patient who died 3 months after sugery. ALP levels were not elevated preoperatively in any of the 7 patients with leiomyosarcoma compared to those with leiomyoma (table 2).

Discussion

The incidence of leiomyosarcoma in patients first seen with symptoms and signs that warranted hysterectomy for uterine myomas in this study (0.37%) is in general agreement with the results of other reported studies. Coscarden and Singh [7] reported 32 patients with leiomyosarcoma

among 15,000 clinically diagnosed cases of fibromata (0.21 %). Nineteen of the 32 women died of leiomyosarcoma, a 59% mortality rate. Montague et al. [8] reported 38 patients with leiomyosarcoma occurring among 13,000 examined myomata (0.29%). Eighteen of the 38 women with leiomyosarcoma died of the disease, a 47% mortality rate. Boutselis and Ullery [9] reported 14 women with leiomyosarcoma among 2,361 gynecologic admissions for myomata, a 0.6% incidence. Twelve of these 14 women died of leiomyosarcoma, an 86% mortality rate. Lcibsohn et al. [10] reported 10 patients with leiomyosarcoma among 1,429 women first seen with symptoms and signs that warranted hysterectomy for uterine leiomyomas (0.7%), and 5 of the 10 women died (50%). The crude mortality rate of 14.2% (1 in 7) in this study is low compared to the previous studies. However, only 3 of the 7 patients have been followed for more than 5 years after surgery. Therefore, the low mortality rate may in part be ascribed to the short period of follow-up.

The preoperative diagnosis of uterine leiomyosarcoma is most difficult. Preoperative diagnosis of leiomyosarcoma was not made in any of the 7 patients in this study. Vardi and Tovell [11] established the preoperative diagnosis of leiomyosarcoma in 5 of the 24 patients (20.8%) by curettage, and Gallup and Corday [12] in 2 of 8 patients (25 %). Leibsohn et al. [10] established the preoperative diagnosis in 3 of 8 patients (37.8 %) by curettage or endometrial biopsy. In 2 of the 3 patients in whom the preoperative diagnosis was made, the tumors were large polypoid masses in the uterine cavity attached to the uterine wall by narrow stalks. In the remaining 1 , the tumor was submucosal. Thus, the location of the tumor in the uterine wall appears to be critical for the diagnosis of leiomyosarcoma by curettage, and endometrial biopsy or curettage is not likely to be highly reliable. Furthermore, the experience in this study suggests as others noted [10] that cervical cytology is not helpful for the diagnosis of this tumor. It has been reported that ultrasonography of the pelvis is not helpful for the diagnosis of this tumor

[10]. Although a preoperative diagnosis of leiomyosar-coma was not made in any of the 7 patients by ultraso-nography in this study, degenerative changes were identified by ultrasonography in the tumors of 5 of them. In contrast, the incidence of degeneration was 14.3% (13 in 91) in patients with uterine leiomyoma. Thus, a degenerative change was a frequent finding in uterine leiomyosar-coma.

Biochemical evaluations may aid in the diagnosis of leiomyosarcoma of the uterus. Bodon and Mijangos [13] reported the case of a woman with uterine leiomyosarcoma who had a preoperatively elevated ALP, which decreased to within normal limits after surgery. However, ALP levels were within normal limits preoperatively in all patients with leiomyosarcoma in the present study. Therefore, serum ALP is not invariably elevated in patients with uterine leiomyosarcoma. Serum LDH levels were increased preoperatively in 3 of the 7 patients with uterine leiomyosarcoma compared to those with leiomyoma. The 3 patients with increased LDH levels had tumors with 10 or more mitoses per 10 HPF. The LDH level fell within normal limits after surgery in these patients. And therefore, measurement of serum LDH may be useful for detecting leiomyosarcoma with an increased mitotic count.

In 1 of the 5 premenopausal patients, suspicion of leiomyosarcoma arose intraoperatively, and TAH/BSO was performed. The other 4 patients underwent TAH only. If the diagnosis of leiomyosarcoma had been made preoperatively, it could have altered the plan for adnexal conservation in these women. Subclinical metastases to the uterine adnexae can occur in leiomyosarcoma clinically confined to the uterus.

Most investigators agree that the number of mitoses in 10 HPF serves as a useful prognostic index. Montague et al. [8] noted that, when 2-5 mitoses per 10 HPF were present, 100% of patients survived 1 year and 77% survived 5 years. In patients whose tumors had 5-10 mitoses per 10 HPF, the survival rate dropped to 35% at 5 years, and none survived 5 years when more than 10 mitoses per 10 HPF were present. According to Kempson and Bari [14], tumors with less than 5 mitoses per 10 HPF are benign. Those with higher mitotic counts are malignant. The prognosis for leiomyosarcomas with greater than 10 mitoses per 10 HPF is poor and metastases are frequent. The behavior of tumors with mitotic counts between 4 and 9 per 10 HPF is less certain, but some tumors with this level of mitotic activity will metastasize. Four of the four premenopausal patients who underwent TAH only in the present study had tumors with less than 10 mitoses
per 10 HPF. None of them underwent surgery again for staging or adnexetomy, but all of them are alive with no evidence of disease at 11-72 months after surgery (tables 2 and 3, patients 4-7).
The movement toward conservative treatment of uterine leiomyoma has gained momentum with the recent clinical introduction of a new therapeutic modality, GnRH-a. GnRH-a can control symptoms and decrease the size of leiomyomas. These modalities seem most applicable to women close to menopause. If these tumors can be controlled until menopause, one may be able to avoid major surgery. However, this is one of the clinical situations in which delay and incorrect management of leiomyosarcoma can occur. Clinically, the response to GnRH-a therapy appears to offer minimal assistance in differentiating benign and sarcomatous tumor growth [15]. Therefore, conservative medical management and delayed intervention should be approached cautiously in a perimenopausal woman with uterine enlargement presumably resulting from myomatous disease.
Degenerative change was a frequent finding in uterine leiomyosarcomas. Serum LDH levels were elevated in 3 of the 3 patients with leiomyosarcomas with 10 or more than 10 mitoses per 10 HPF. It has yet to be determined whether serum LDH levels are invariably elevated in patients with leiomyosarcomas with increased mitotic rates. However, a degenerative change within the uterine mass and an increased LDH level, when present, should suggest consideration of the diagnosis of leiomyosarcoma. Furthermore, the prognosis for the leiomyosarcomas with increased mitotic counts is poor. And therefore a woman with presumed leiomyoma with degenerative change within the uterine mass and an increased LDH level is not likely to be a candidate for conservative treatment.
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