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Prevalence of Uterine Leiomyomas in Lymphangioleiomyomatosis

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Abstract

Objective—To determine the frequency of uterine leiomyomas and hysterectomy in patients with lymphangioleiomyomatosis (LAM), a disease characterized by proliferation of abnormal-appearing smooth muscle-like cells.

Design—Retrospective study.

Patients—456 patients with sporadic LAM and LAM associated with tuberous sclerosis complex (LAM/TSC).

Setting—Natural history study at the National Institutes of Health.

Intervention(s)—Review of records and pelvic computed axial tomography scans.

Main Outcome Measure(s)—prevalence of uterine leiomyomas and hysterectomy.

Results—A total of 174 women had uterine leiomyomas (38%). One hundred eighteen were diagnosed by CT scan and 56 were diagnosed by hysterectomy. Among 323 patients who did not have hysterectomy, 105 of 270 patients (39%) with sporadic LAM and 13 of 53 (25%) with LAM/TSC had uterine leiomyomas. Hysterectomy was performed in 108 of 378 subjects with sporadic LAM and 25 of 78 with LAM/TSC. Fifty six patients were found to have uterine fibroids at hysterectomy. The most common indications for hysterectomy were uterine leiomyoma, lymphangioleiomyomatosis and endometriosis.

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Conclusions—Uterine leiomyomas are not more common in LAM than in the general population. However, in LAM, the frequency of hysterectomy is higher because of it having been recommended for treatment of LAM.

Keywords

Uterine leiomyomas; hysterectomy; lymphangioleiomyomatosis

Introduction

Lymphangioleiomyomatosis (LAM) is a multi-system disease affecting women, which is caused by proliferation of abnormal neoplastic smooth muscle-like cells (LAM cells), leading to cystic lung destruction, lymphatic abnormalities and renal angiomyolipomas (1–3). Common presenting symptoms are dyspnea, recurrent pneumothoraces, chylous effusions and mediastinal, abdominal, and pelvic lymphatic tumors (lymphangioleiomyomas) (1–3)

Lymphangioleiomyomatosis can occur as an isolated disease (i.e., sporadic LAM) or in association with tuberous sclerosis complex (TSC), an autosomal dominant disorder with variable penetrance caused by genetic mutations in the *TSC1* or *TSC2* genes (4–8). Sporadic LAM occurs in about 2–5 persons per 1 million (1); thirty to 40% of women with TSC are affected with LAM. (4–6).

As in LAM/TSC, the LAM cells of patients with sporadic lymphangioleiomyomatosis exhibit mutations in *TSC* genes (9). These findings are compatible with the conclusion that *TSC1* and *TSC2* are susceptibility genes for lymphangioleiomyomatosis.

Although lymphangioleiomyomatosis affects primarily women and estrogen is believed to contribute to the pathogenesis of disease (1), there is no information regarding gynecologic pathology in lymphangioleiomyomatosis. As in LAM, estrogens are equally considered to be a major promoter of the growth of uterine leiomyomas, the most common benign tumor growths of uterine smooth muscle cells (10). Given the fact that LAM is caused by proliferation of smooth muscle-like cells, we investigated the prevalence of uterine leiomyomas in patients with lymphangioleiomyomatosis.

Materials and methods

Patient population

Four hundred fifty six subjects with LAM (378 with sporadic LAM and 78 with LAM/TSC) evaluated at the National Institutes of Health Clinical Center from 1995 through 2006 are the subject of this study. Subjects were enrolled in protocol 95-H-0186, which was approved by the National Heart, Lung, and Blood Institute Institutional Review Board. All subjects provided written informed consent. The diagnosis of lymphangioleiomyomatosis was established by tissue biopsy in 260 patients. In the remaining 196 subjects, LAM was diagnosed by computed tomography scan findings, which consisted of multiple thin-walled cystic lesions throughout the lung along with renal angiomyolipomas, and abdominal and/or pelvic lymphangioleiomyomas (1,2). Criteria for diagnosis of TSC were those of the TSC Consensus Conference in Annapolis, Maryland (e.g., dermatologic manifestations, cortical tubers, subependymal giant-cell tumor, renal angiomyolipomas, bone cysts) (11).

Review of Medical Records

A certified registered nurse practitioner reviewed the medical charts of all subjects. Data regarding history of and indication for hysterectomy or myomectomy were collected.

Computed Tomography

Axial 5-mm sections were obtained through the pelvis in all patients using multidetector helical scanners following the administration of oral and intravenous contrast. The images were reviewed by one of the authors, a board-certified radiologist, who recorded the following findings: presence or absence of uterus and ovaries, presence or absence of uterine leiomyomas and ovarian cystic or solid masses. Uterine leiomyoma was diagnosed if the uterine mass enhanced differently from uterine tissue or if it contained coarse calcifications.

Results

Subject Characteristics

Subject characteristics are summarized in Table 1. Although percentages of African American and Asian women differed slightly between the two groups, LAM and LAM/TSC, ethnic backgrounds were generally similar in both.

Prevalence of Uterine Leiomyomas and Hysterectomy

One hundred seventy four patients were diagnosed with leiomyomas (38.1%) (see Table 2 and Figure 1). One hundred and eighteen tumors were diagnosed by CT scan and 56 were diagnosed at the time of hysterectomy (Table 2). One hundred and five of 270 patients (38.8%) with sporadic LAM and thirteen of 53 patients with LAM/TSC (24.5%) had uterine leiomyomas (Figure 1). The overall frequency of leiomyomas diagnosed by CT scan was 36.5% (Figure 1).

Fifty six of the 133 patients (42%) who underwent hysterectomy had uterine leiomyomas (Table 2, Figure 1). Forty two of 108 patients with LAM (38.8%) and 14 of 25 patients with LAM/TSC (56%) were found to have uterine fibroids at hysterectomy (Figure 1). There was no difference in body mass index between the patients with fibroids and those without them (25.9 ± 6 versus 26.8 ± 6 kg/m²).

Because lymphangioleiomyomatosis may more frequently affect women of child-bearing age than older women, we analyzed separately subjects who were 40 years of age or younger (Figure 2). The overall prevalence of leiomyomas in 182 patients 40 years of age or younger with sporadic LAM and LAM/TSC was 29.6 %. The frequency of these tumors was higher in sporadic LAM (33.3%) than LAM/TSC (18.1%).

Forty two of 116 subjects with sporadic LAM were diagnosed by CT scan (28.9%) and four of 22, were diagnosed at hysterectomy. Six of 36 subjects with LAM/TSC who were 40 years of age or younger had leiomyomas by CT scan and two of eight patients were found to have uterine leiomyomas at hysterectomy.

In 274 patients above the age of 40 the prevalence of uterine leiomyomas was 33.2 %. In 55 patients the diagnosis was made by CT scan. In the remaining patients leiomyomas were present at hysterectomy.

Indications for Hysterectomy

Sixty eight of the 133 patients who underwent hysterectomy patients had it before the diagnosis of LAM was established; sixty five patients underwent hysterectomy following the diagnosis of LAM. The most common indications for hysterectomy (Table 1, on-line supplemental data Table) were treatment for uterine leiomyoma, lymphangioleiomyomatosis, or endometriosis. Specifically, among 108 subjects with sporadic LAM, the procedure was performed for removal of uterine leiomyoma in 42 (38.8%), for treatment of LAM in 21 (19.4%) and for treatment of endometriosis in 13 (12.0

%). In 14 of 25 subjects with LAM/TSC, hysterectomy was performed for removal of uterine leiomyoma, in five for treatment of endometriosis, and in two for treatment of lymphangioleiomyomatosis. Some subjects underwent hysterectomy for two indications, including dysmenorrhea and menorrhagia, and endometriosis and ovarian cysts. Other less frequent indications for hysterectomy were menorrhagia, ovarian cysts, ovarian mass, cervical dysplasia, dysmenorrhea, infection, undetermined reasons, positive BRCA gene, cervical cancer, endometrial cancer, menorrhagia and endometriosis, uterine prolapse, rectal wall tear, chronic pelvic pain, ruptured uterus, and ovarian cancer.

One hundred fifteen of the 133 patients who had hysterectomy also had bilateral salpingoophorectomy. The most common indication for salpingoophorectomy for 65 patients who had surgery after the diagnosis of LAM was established was because of it being recommended for treatment of LAM.

There was no difference in lung function between patients who had hysterectomy and those who did not have it. This was also true for the 65 patients who underwent hysterectomy only after the diagnosis of LAM was established. The patients who had hysterectomy were significantly older than those who did not have it: 48.9 ± 8.6 versus 40.8 ± 8.8 years. The mean age of the patients in whom hysterectomy was done after the diagnosis of LAM was 44.4 ± 8.1 years.

Discussion

The incidence of uterine leiomyomas and hysterectomy in lymphangioleiomyomatosis, a multi-system disease characterized by proliferation of LAM cells, which have a smooth muscle cell-like phenotype, has not been previously reported. In 456 women with LAM, we found that the prevalence of uterine leiomyomas detected by CT scans was not higher than that in the general population (12,13). The frequency of hysterectomies was higher than in the general population but this finding was due to a higher prevalence of hysterectomy for treatment of lymphangioleiomyomatosis and not to a higher frequency of uterine leiomyomas. Thus, the hypothesis that LAM would be associated with a higher frequency of uterine leiomyomas and consequent hysterectomy than the general population was not confirmed.

Uterine leiomyomas are the most common solid pelvic tumors in women (10). Overall, the reported prevalence of uterine leiomyomas is highly variable depending whether the study involves symptomatic patients and what diagnostic technique is employed (12–16). Baird et al. (12), reported a 51% prevalence of uterine leiomyomas in premenopausal women who had not been previously diagnosed and underwent pelvic ultrasounds. The proportion was higher in black women than white (59 versus 43%). The incidence of these tumors increased with age (12). However, a study performed in 335 asymptomatic 25–40 year old white women using transvaginal sonography detected uterine leiomyomas in only 5.4% (14). In a study undertaken in 2,034 consecutive women presenting with pelvic symptomatology, pelvic sonography revealed uterine leiomyomas in 29.9% (14). Using all available methods including histological assessment, it is estimated that the prevalence of uterine leiomyomas in premenopausal women ranges from 30–70% (16). In our cohort of subjects with LAM or LAM/TSC the overall prevalence of uterine leiomyomas, including those who underwent hysterectomies, was 38 % (174 out of 456 patients).

Several limitations of this study may have resulted in an underestimation of the frequency of uterine leiomyomas in LAM. Computed tomography is less sensitive than ultrasound in detection of uterine leiomyomas (17). Indeed, in 16 of our subjects pelvic CT scans were inconclusive. Computed tomography was used to study this cohort, because it is best for

detection of some manifestations of lymphangioleiomyomatosis, including renal angiomyolipomas, and abdominal/pelvic lymphangioleiomyomas. An enlarged uterus and a deformed uterine contour are the most common CT findings of leiomyoma (18,19,20), but the attenuation values of leiomyomas are similar to those of normal uterus. Accordingly, ultrasonography continues to be the first-line imaging study, with magnetic resonance imaging being the next choice because of greater sensitivity and specificity than CT (17,18). If a more sensitive method than computed tomography scan of the pelvis had been used to identify uterine leiomyomas, the prevalence of tumors detected might have been higher.

The incidence of uterine leiomyomas and hysterectomy is higher in African American women than in Caucasian women, consistent with ethnic background as a risk factor for these tumors (12,21,22). In the current study, however, since 29 (6.3%) of 456 subjects were African American, compared to 12.8% of the general population in the United States (23), the prevalence of uterine fibroids may have been underestimated. Finally, although 56 of 133 (42%) patients who underwent hysterectomy, had uterine leiomyomas as the main indication for surgery, these patients were symptomatic and their data can not be compared to those gathered from a normal asymptomatic random population.

Surgical treatment of uterine leiomyomas is common, and hysterectomy is the second most frequent major surgery performed in women of reproductive age in the United States, where approximately 600,000 hysterectomies are performed annually (10, 24). Women 40 to 44 years of age have a significantly higher rate of hysterectomy, 11.7 per 1,000, than any other age group; the rate was 16.8 for African American women, 10.8 for Caucasian, and 12.4 per 1,000 for women of other ethnic backgrounds. Higher rates of hysterectomy among African American women may reflect a higher incidence of uterine leiomyomas in this ethnic group (12,21,22).

The three most common indications for hysterectomy among women with LAM, were uterine leiomyoma, treatment of lymphangioleiomyomatosis, and endometriosis; whereas the three most common indications for hysterectomy reported in the general population of the United States are uterine leiomyoma, endometriosis, and uterine prolapse (24). Our data suggest that bilateral salpingo-oophorectomy with hysterectomy for treatment of lymphangioleiomyomatosis accounts for the higher incidence of hysterectomy in patients with LAM. Pelvic discomfort secondary to lymphangioleiomyomas or large renal angiomyolipomas, rather than uterine leiomyomas, may also have contributed to the high rate of hysterectomy in patients with LAM. We have no objective data besides physiologic data regarding the potential influence of hysterectomy on the prognosis of LAM. Changes in lung function from enrollment to the last visit were similar in patients who did not have hysterectomy, patients who had hysterectomy and the subgroup of patients who only had hysterectomy after the diagnosis of LAM was established. In women 40 years of age or younger the hysterectomy rate was 14.2 % (26 of 182); 13 % (18 of 138) in sporadic LAM and 18.1% (8 of 48) in LAM-TSC. Only six patients underwent hysterectomy because of uterine leiomyoma-related symptoms. In contrast, 20% of women in the general population of the United States have had a hysterectomy by age 40. Thus, the rates of hysterectomy in women younger than 40 years of age with sporadic LAM or LAM-TSC, are no greater than those in the general population.

In summary, we found that women with sporadic LAM and LAM/TSC do not have an increased prevalence of uterine fibroids. A higher frequency of hysterectomy in LAM than in the general population can be accounted for by the use of hysterectomy and oophorectomy for treatment of LAM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Prevalence of uterine leiomyomas detected by computed tomography and hysterectomy in 456 patients with LAM, of which 378 had sporadic LAM and 78 had LAM/TSC. Two hundred seventy patients with LAM and 53 patients with LAM/TSC had CT scans. One hundred and eight patients with LAM and 25 patients with LAM/TSC had hysterectomy.

Figure 2.

Prevalence of uterine leiomyomas detected by computed tomography and hysterectomy in 182 LAM patients whose age was forty years or less, of which 138 had sporadic LAM and 44 had LAM/TSC. One hundred sixteen patients with LAM and 36 patients with LAM/TSC had CT scans. Twenty two patients with LAM and eight patients with LAM/TSC had hysterectomy.

Table 1Demographic characteristics of 456 patients with lymphangioleiomyomatosis^a

	LAM (n = 378)	LAM/TSC (n= 78)
Age at enrollment	43.5±0.5	38.7±1.1
Female gender	378 (100)	78 (100)
Ethnic background		
Caucasian	324 (85.5)	67 (85.9)
African American	22 (5.8)	7 (9.0)
Asian	23 (6.1)	2 (2.6)
Hispanic	10 (2.6)	2 (2.6)
Diagnosis: histology	236 (62.4)	24 (30.8)
Diagnosis: CT scan	142 (37.5)	54 (69.2)

^a Age (years), mean ± SEM. In parenthesis, percentage of total.

Abbreviations: LAM, lymphangioleiomyomatosis; LAM/TSC, lymphangioleiomyomatosis with tuberous sclerosis complex; CT, computed tomography

Table 2Frequency of uterine leiomyomas in 456 patients with lymphangioleiomyomatosis^a

	LAM (n = 378)	LAM/TSC (n= 78)
Uterine leiomyoma present on CT scan	105/270	13/53
Possible uterine leiomyoma on CT scan	10/270	6/53
No uterine leiomyoma on CT scan	155/270	25/53
Uterine leiomyoma present at hysterectomy	42/108	14/25

^aFor abbreviations see Table 1.