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Sporadic uterine Lymphangioleiomyomatosis (LAM): Report of a unique case arising in the lower uterine segment with short review

Tip Pongsuvareeyakul [a], Sara Maleki [b], Bradley D. DeNardo [c], Don S. Dizon [d], Chanika Phornphutkul [c], Kamaljeet Singh [a,*]

[a] Department of Pathology and Laboratory Medicine, Women & Infants Hospital of Rhode Island, Brown University, Providence, RI, United States
[b] Department of Pathology and Laboratory Medicine, Warren Alpert Medical School of Brown University, Providence, RI, United States
[c] Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI, United States
[d] Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI, United States

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1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare neoplasm of perivascular epithelioid cell tumor (PEComa) family that predominantly affects lungs (Hayashi et al., 2011). LAM can occur sporadically or in association with tuberous sclerosis complex (TSC) (Grant et al., 2019). Usually, LAM shows benign-appearing morphology, and it is regarded as a low-grade lesion, but recurrence or metastasis may occur (Grant et al., 2019; Szpurek et al., 2015). Extrapulmonary LAM involving gynecological organs is rare (Suzuki et al., 2016). To our knowledge, there have been only four reported cases of uterine LAM that appeared as a microscopic focus (Hayashi et al., 2011; Clay et al., 2011; Ando et al., 2020).

Herein we present a unique case of sporadic-LAM in the lower uterine segment. This focal finding can be potentially overlooked in routine tissue examination. We also review and discuss published literature on uterine LAM and its association with TSC.

2. Case report

A 35-year-old female, gravida 4 para 4, presented with heavy and prolonged menstrual periods. The transvaginal ultrasound showed an unremarkable uterus and both adnexa. No symptoms suggestive of tuberous sclerosis complex or pulmonary disease were noted on clinical examination. Her family histories were unremarkable. The patient underwent a total laparoscopic hysterectomy with bilateral salpingectomy.

2.1. Pathologic examination:

The uterus and bilateral fallopian tubes were grossly unremarkable. Microscopically, there was an incidental 0.7 cm LAM located in the junctional area between the lower uterine segment and upper endocervix (Fig. 1A). The tumor showed spindle-shaped cells with mild to moderate atypia and clear or faintly eosinophilic cytoplasm. There were numerous slit-like lymphatic spaces with free-floating LAM cell clusters (Fig. 1B–D). The uterine corpus and cervix were entirely submitted for histologic evaluation and showed only a single focus of LAM. Uterine corpus revealed secretory endometrium. Cervix and bilateral fallopian tubes were unremarkable.

By immunohistochemistry, LAM cells exhibited strong and diffuse cytoplasmic positivity for desmin (D33, Dako) (Fig. 2A), caldesmon (h-CD, Dako), smooth muscle actin (1A4, Dako), and showed diffuse weak to moderate cytoplasmic reactivity for cathepsin K and rare reactivity for HMB-45 (HMB-45, Dako) (Fig. 2B, C). Melan-A (A103, Dako) was negative. The lymphatic endothelial cells enveloping LAM clusters and lining lymphatic spaces were highlighted by D2-40 (D2-40, Dako) (Fig. 2D). TFE-3 was negative.

The patient's postoperative course was uneventful. There was no recurrence four months after surgery. A whole-body computed

* Corresponding author at: Department of Pathology, Women & Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI, United States.
E-mail address: 410jeeta@gmail.com (K. Singh).

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tomography scan showed no systemic manifestations of LAM or TSC. The germline testing for TSC1 and TSC2 was negative. The final diagnosis was sporadic-LAM of the uterus.

3. Discussion

Extrapulmonary LAM has been described in three major locations: posterior mediastinum, retroperitoneal space, and pelvic cavity (Matsui et al., 2000). In the gynecological tract, LAM is more commonly found in the uterus (Suzuki et al., 2016). The clinical features of uterine LAM can vary from asymptomatic presentation to abnormal uterine bleeding, pelvic pain, or mass lesions (Grant et al., 2019; Szpurek et al., 2015). The review of previously reported cases (including our case) is shown in Table 1. The age range is 25 to 83 years (mean age 43 years). Uterine LAM shows a variable size ranging from microscopic focus to grossly apparent mass and occurs as multiple foci involving corpus in approximately 61% of cases.

The diagnosis of LAM in our case was based on the presence of typical morphologic features with confirmatory immunohistochemical stains. The immunophenotype of LAM is different from the other tumors in the PEComa family (Bennett and Oliva, 2021). HMB-45 is usually negative or only weak/patchy staining in LAM cells (Rabban et al., 2015). Moreover, melan-A has relatively low sensitivity and shows negative staining in most cases (Rabban et al., 2015). Diffuse positivity for cathepsin K has been described to have more sensitivity for LAM cells, and it can be used as an alternative marker to melan-A (Bennett and Oliva, 2021; Lombard, 2020). With unusual IHC, recognition of characteristic morphologic features is the key in LAM diagnosis (Rabban et al., 2015). In TSC-associated LAM the lymphatic channels can be inconspicuous (Hayashi et al., 2011).

Most molecular studies in LAM have focused on pulmonary lesions and found the mutation in tumor suppressor gene TSC1/TSC2 in both sporadic and TSC-associated tumors (Grant et al., 2019). To date, genetic alteration of extrapulmonary LAM has not been described, and the relationship between extrapulmonary and pulmonary disease remains unclear. Several studies have suggested that LAM may originate from the uterus and can spread to other sites through the lymphatic system since the tumor occurs almost exclusively in women with a predominant location in the uterus and pelvic lymph nodes, together with the nature of abnormal smooth muscle-like cells that express hormonal receptors (Hayashi et al., 2011; Szpurek et al., 2015; Clay et al., 2011; Ando et al., 2020). However, this hypothesis remains controversial (Hayashi et al., 2011; Ando et al., 2020). Although pulmonary and uterine LAM lesional cells exhibit a similar immunophenotype, the characteristic histomorphologic features of each lesion are different (Matsui et al., 2000). Some studies have proposed that sporadic pulmonary LAM may result from abnormal proliferation of vascular smooth muscle cells (Finlay, 2004). Due to the rarity of disease with a limited number of studies, further studies are needed to clarify the pathogenesis of LAM.

The presence of microscopic uterine LAM without lesion in other sites may represent the earliest manifestation of the disease (Clay et al., 2011). There have been only four reported cases of uterine LAM appearing as a single microscopic focus (see Table 1). Our case adds to the existing evidence that supports a possibility of uterine origin for LAM. Another important finding in our case is the tumor location. To our knowledge, the preferential location of LAM in the uterus has not been described yet. In the study of Hayashi et al., uterine LAM was found at the lower segment in only 1 of 9 cases (Hayashi et al., 2011). Single microscopic LAM in the junctional area between the lower segment and upper endocervix can be potentially unsampled and easily overlooked in routine tissue examination. This may result in delayed or missed clinical screening for TSC.

A review of previously reported cases reveals that uterine LAM occurs in approximately 40% of TSC patients. Most cases are present as

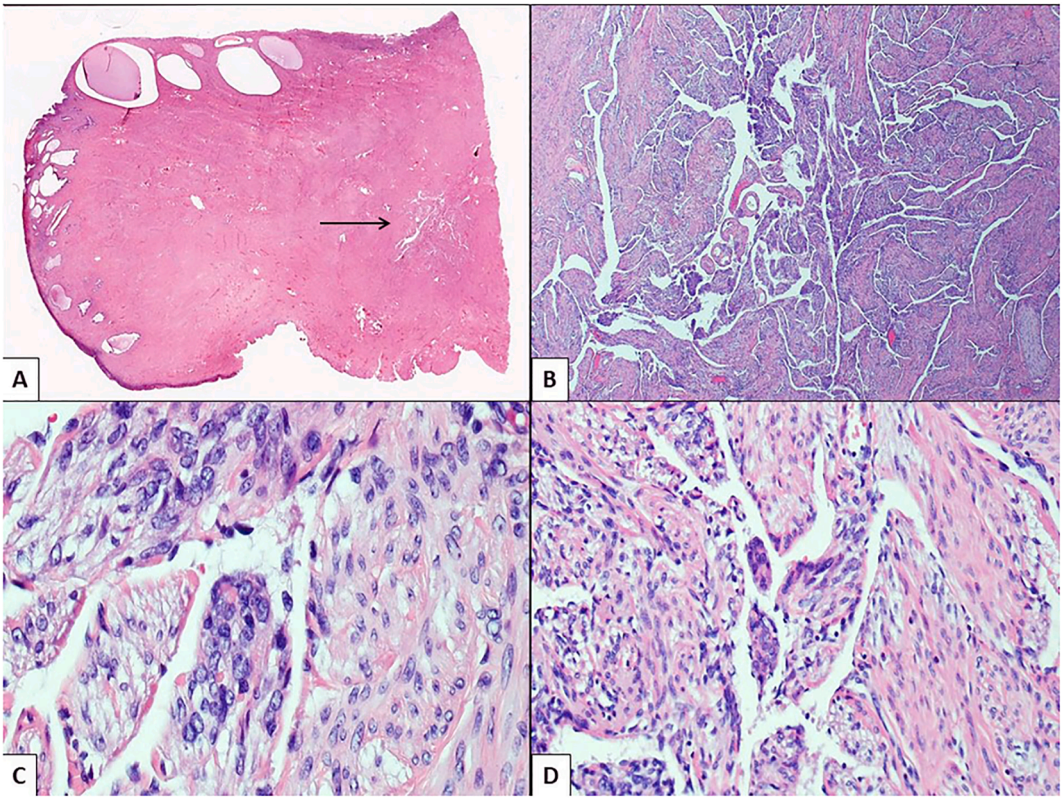

Fig. 1. Lymphangioleiomyomatosis (LAM) (A) Tumor located in the junctional area between upper endocervix and lower uterine segment (H&E, 1.25×). (B) Tumor composed of numerous ramifying networks of delicate lymphatic channels (H&E, 4×). (C) LAM cells with mild nuclear atypia and clear to pale eosinophilic cytoplasm arranged in fascicles around lymphatic spaces (H&E, 40×). (D) Small LAM clusters floating within lymphatic spaces (H&E, 20×).

multifocal lesions in the uterus with multiple distributions in other sites (see Table 1). TSC-associated LAM may contain a greater extent of the lesion compared to sporadic LAM (Hayashi et al., 2011; Lombard, 2020). Nodal involvement by LAM is found in nearly 60% of uterine LAMs, and approximately 25% of these cases have synchronous gynecological tract cancer (see Table 1). Interestingly, lymphadenopathy secondary to LAM, occurring in cancer cases, can mislead to overstaging and overtreatment (Suzuki et al., 2016). Therefore, the clinical assessment should be performed with caution, particularly in TSC patients.

The exact spreading mechanism of LAM has not been completely clarified. In the study of Kumasaka et al., the authors proposed that LAM-associated lymphangiogenesis may be responsible for the shedding of tumor into lymphatic circulation (Kumasaka et al., 2005). Nonetheless, the previously reported cases of uterine LAM showed a favorable outcome (see Table 1), even in cases with multiple site involvement or tumor with malignant behavior (Szpurek et al., 2015). This may indicate slow disease progression (Szpurek et al., 2015); however, most cases had a relatively short follow-up with a mean and median duration of 22 and 6 months, respectively. Interestingly, a case of uterine LAM with sarcomatous transformation has also been reported, but with an isolated report, the clinical significance of this phenomenon is unclear (Gyure et al., 1995). Further investigation is required to elucidate clinical behavior, including the key mechanism driving metastatic potential.

Currently, there is no standard treatment of extrapulmonary LAM (Grant et al., 2019; Wahid et al., 2017; Freitas et al., 2015). Radical resection provides local disease control (Grant et al., 2019). Although the tumor proliferation and progression is linked with estrogen, the anti-estrogenic drugs are rarely effective and may worsen the prognosis (Grant et al., 2019; Wahid et al., 2017). The previous studies have suggested that mutation in TSC1/TSC2 gene leads to activation of mTOR signaling pathway, resulting in uncontrolled cell growth and proliferation; therefore, mTOR inhibitors (sirolimus and everolimus) have been shown to be useful in the treatment of LAM (Grant et al., 2019; Wahid et al., 2017). Although most studies have focused mainly on the pulmonary LAM, the mTOR inhibitors have also been reported to be beneficial in extrapulmonary tumor (Wahid et al., 2017; Freitas et al., 2015). To date, the role of mTOR inhibitors is currently under investigation and more studies of drug efficacy with monitoring the long-term beneficial effect are required.

In conclusion, we report a case of sporadic extrapulmonary LAM that presented as a microscopic focus in the lower uterine segment. Although the literature is extremely scant on the relationship of uterine LAM and TSC, there are reports of uterine LAM in a setting of TSC. Therefore, we recommend clinical evaluation to identify TSC related clinical lesions and consultation with genetic counsellor in a setting of uterine LAM. Awareness and recognition of uterine LAM are essential to provide patients an opportunity to be clinically evaluated for further tuberous sclerosis germline testing.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Contribution statement

TP and KS performed the pathologic evaluation and wrote the main manuscript. SM was responsible for reviewing pathologic findings. BD, DD, and CP were involved in patient treatment. All authors have approved the final manuscript.

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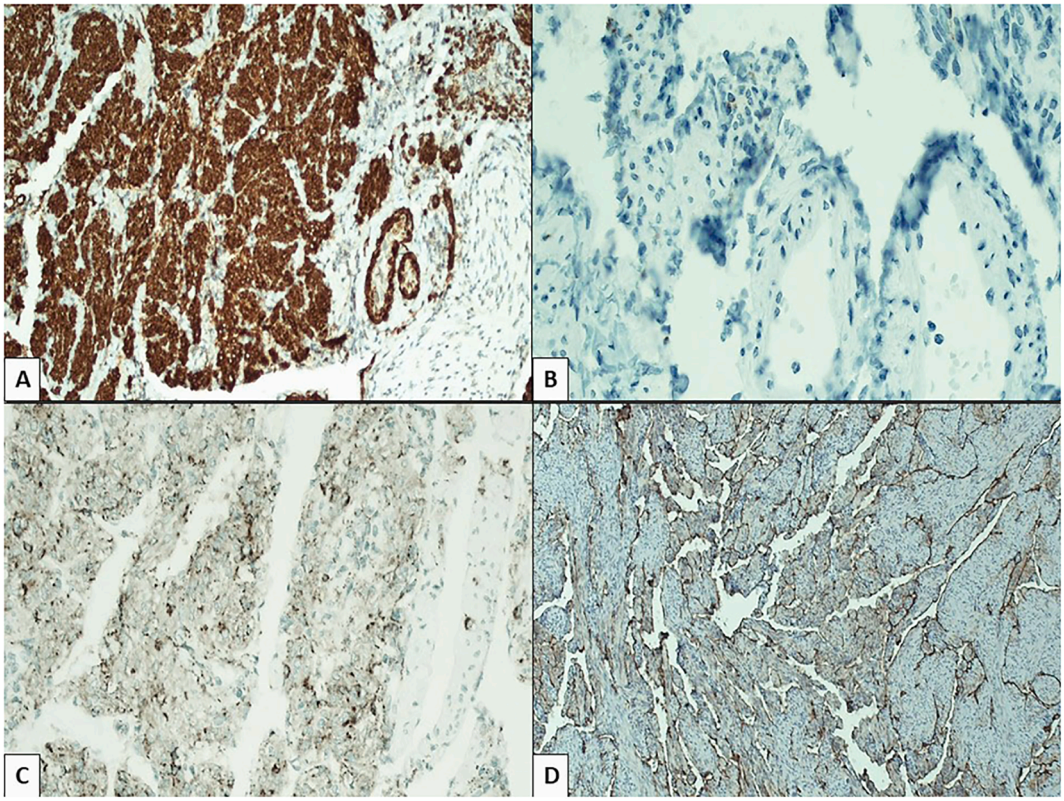

Fig. 2. Immunohistochemical stains of LAM (A) Strong and diffuse cytoplasmic positivity for desmin (20×). (B) Rare cytoplasmic staining for HMB-45 (20×). (C) Diffuse, weak to moderate cytoplasmic positivity for cathepsin K (20×). (D) Lymphatic endothelial cells lining lymphatic spaces highlighted by D2-40 (4×).

Table 1
Reports of Uterine Lymphangioleiomyomatosis.

Author (year)	Age (years)	Distribution of LAM	Maximal size of LAM (cm)	LAM in other sites				TSC	Associated lesions		Outcome (follow-up duration)	Autopsy
				Genital tract	Lymph nodes	Lung	Other sites		TSC-related	Non-TSC lesions		
Lack et al. (1986)	33	Multifocal	Microscopic (not specified)	Ovary	Mesenteric	+	Periadrenal vessels, retroperitoneum, liver	–	–	Leiomyoma, angiomyolipoma of kidney	NED (6 mo)	–
Gyure et al. (1995)	29	Multifocal	N/A	–	Pelvic, paraaortic	–	–	+	+	Mixed high-grade carcinoma of ovary	DOC (N/A)	No
	33	Multifocal	Microscopic (not specified)	–	–	–	Retroperitoneum	+	+	–	NED (8 mo)	–
Torres et al. (1995)	33	N/A	N/A	–	Perinephric	–	Perirenal area	+	+	–	NED (8 mo)	–
	38	N/A	N/A	–	–	–	Abdominal wall	+	+	–	N/A	N/A
	29	N/A	N/A	–	–	+	Pelvic side wall	+	+	–	AWD (N/A)	–
Longacre et al. (1996)	49	Multifocal	5	–	Pelvic	–	–	+	+	–	NED (N/A)	–
Han et al. (2008)	46	Unifocal	5	Ovary, periadnexal tissue	Pelvic, paraaortic	–	–	–	–	Uterine leiomyoma	NED (6 mo)	–
Clay et al. (2011)	46	Unifocal	0.2	–	–	–	–	–	–	–	N/A	N/A
Hayashi et al. (2011)	29	Multifocal	0.3	Broad ligament	Pelvic/ paraaortic	+	N/A	–	–	Endometrial cancer	N/A	No
	33	Multifocal	0.3	Broad ligament	Pelvic/ paraaortic	+	N/A	–	–	–	DUN	+
	37	Multifocal	N/A	Broad ligament, ovary	Pelvic/ paraaortic	+	N/A	–	–	–	DUN	+
	45	Multifocal	N/A	–	Pelvic/ paraaortic	+	N/A	–	–	Uterine leiomyoma, ovarian serous borderline tumor	N/A	No
	48	Multifocal	N/A	–	N/A	+	N/A	–	–	Uterine leiomyoma, cervical epithelial dysplasia	N/A	No
	83	Multifocal	N/A	Broad ligament, ovary	Pelvic/ paraaortic	+	N/A	–	–	Cervical cancer	DUN	+
	25	Unifocal	Microscopic (not specified)	–	Pelvic/ paraaortic	+	N/A	+	–	Uterine leiomyoma, adenomyosis	DUN	+
	41	Multifocal	Microscopic (not specified)	Broad ligament, ovary	Pelvic/ paraaortic	+	N/A	+	+	Uterine angiosarcoma	DUN	+
	50	Multifocal	Microscopic (not specified)	–	N/A	+	N/A	+	+	Uterine leiomyoma, adenomyosis	N/A	No
Kim et al. (2011)	29	Multifocal	3	Ovary, tube	–	+	Pelvic cavity, pelvic side wall, omentum	+	+	–	AWD (N/A)	–
Szpurek et al. (2015)	47	N/A	N/A	Ovary	–	+	Retropubic area	–	–	Angiomyolipoma of kidney	NED (12 yr)	–
Vatansever et al. (2015)	36	Multifocal	9	–	Pelvic	–	–	–	–	–	NED (6 mo)	–
Suzuki et al. (2016)	47	N/A	N/A	–	Pelvic, paraaortic	–	–	–	–	Endometrial cancer	NED (N/A)	–
Grant et al. (2019)	42	Multifocal	2.2	–	–	+	–	+	+	Uterine polyp, leiomyoma	AWD (N/A)	–
Lombard (2020)	47	Multifocal	0.075	–	Pelvic	–	–	–	–	Endometrial cancer, uterine leiomyoma	N/A	N/A
Ando et al. (2020)	47	Unifocal	0.9	–	Pelvic	–	–	–	–	Endometrial cancer	NED (10 mo)	–
	49	Unifocal	5	–	–	–	–	–	–	Uterine leiomyoma	NED (18 mo)	–
	44	Unifocal	0.5	–	–	–	–	–	–	–	NED (4 mo)	–
Our case	35	Unifocal	0.7	–	–	–	–	–	–	–	NED (4 mo)	–

N/A, not available; NED, no evidence of disease; DOC, dead of other causes; AWD, alive with disease; DUN, dead of unknown cause.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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