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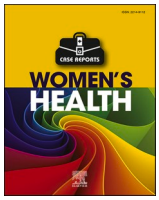

Uterine lymphangioleiomyomatosis in a premenopausal woman with tuberous sclerosis: A case report

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ABSTRACT

Lymphangioleiomyomatosis is a rare disease characterized by abnormal smooth muscle cell growth. It primarily occurs in the lungs but can also rarely occur in other organs, in which case it is classified as extrapulmonary lymphangioleiomyomatosis. It often accompanies tuberous sclerosis complex. This report concerns a case of uterine lymphangioleiomyomatosis with spontaneous uterine rupture in a young woman with tuberous sclerosis complex. A 27-year-old nulligravida patient presented to the emergency room with vaginal bleeding. She had a history of clinical diagnosis of tuberous sclerosis complex and pulmonary lymphangioleiomyomatosis. Initially, abdominopelvic computed tomography and magnetic resonance imaging suggested a hemorrhagic necrosis and rupture of degenerated uterine myoma. She underwent emergency exploratory laparotomy. The right side of her normal-sized uterus were ruptured without any specific mass. Active bleeding and hematoma from the ruptured uterus and partially ruptured right ovary were noted. The procedure included total hysterectomy and right salpingo-oophorectomy. Pathological analysis confirmed lymphangioleiomyomatosis in the uterine serosa and myometrium. Lymphangioleiomyomatosis mainly occurs in women of reproductive age and worsens with estrogen. Early diagnosis and careful follow-up are necessary due to the risk of worsening gynecological symptoms or even uterine rupture during pregnancy. This case enhances our understanding of extrapulmonary lymphangioleiomyomatosis and highlights the importance of comprehensive evaluation in complex clinical scenarios.

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease characterized by abnormal smooth muscle cell growth, occurring mainly in women of reproductive age [1]. It is now considered a part of the family of perivascular epitheloid cell tumors (PEComa), which often infiltrate the smooth muscle of the blood vessels [2]. While most PEComas are benign, malignant forms can metastasize or recur. LAM primarily affects the lung parenchyma, leading to cystic destruction and respiratory failure [1]. However, it can also occur at extrapulmonary sites (EPLAM) along the axial lymphatic pathway in the abdominopelvic cavity, such as lymph nodes, retroperitoneum, and reproductive organs [3]. The clinical features of EPLAM vary based on organ involvement, from asymptomatic cases to abdominal pain or genital bleeding [3–5]. To date, fewer than 30 cases of uterine LAM have been reported worldwide [5].

LAM occurs sporadically in 1 in 400,000 adult women but is found in up to 40 % of women with tuberous sclerosis complex (TSC) [3]. TSC is a disease-causing tumor in various organs due to mutation in the TSC genes [6]. Uterine LAM is a rare manifestation of TSC. This report concerns a case of uterine LAM with spontaneous rupture in a young woman with TSC.

2. Case Presentation

A 27-year-old nulligravida woman presented to the emergency room with dizziness and vaginal bleeding. She had a history of clinical diagnosis of TSC, neurosurgical treatment for subependymal giant cell astrocytoma, LAM and multifocal micronodular pneumocyte hyperplasia

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(MMPH) in lung, multiple bilateral renal angiomyolipomas (AMLs), hypomelanotic macule, and angiofibromas. No mutation was detected in the TSC2 gene. However, she had not visited the hospital for 3 years and was receiving no ongoing diagnostic evaluation or treatment.

Her vital signs were stable, and she reported vague abdominal pain. However, her initial hemoglobin level was 6.0 g/dL, requiring transfusion of five packs of red blood cells. Abdominopelvic computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a hemorrhagic necrosis and rupture of degenerated uterine myoma into the endometrial and extrauterine cavity with massive hemoperitoneum (Fig. 1). Additionally, multiple AMLs up to 4 cm were noted in both kidneys. Compared to 3 years ago, no acute intracranial lesions, nor changes in pulmonary LAM and MMPH in brain CT and chest CT were observed, respectively.

Surgery was performed in light of the stable vital signs and the findings on imaging. The patient had no sexual experience and had no wish to become pregnant. However, because she was a young woman of reproductive age, the possibility of hysterectomy was fully explained to her and her guardian before the surgery, and informed consent was obtained. She underwent an exploratory laparotomy under general anesthesia. More than 2 L of coagulated blood was removed. The right side of normal-sized uterus were ruptured without any specific mass. Bleeding and hematoma from the ruptured uterus and partially ruptured right ovary were noted. Small friable nodules were observed on the surface of the uterus and ovaries. The mass presumed to be a myoma rupture on imaging was actually a large hematoma with irregular margins and heterogenous echogenicity at the rupture site. A total hysterectomy and right salpingo-oophorectomy were performed. Upon cutting the uterus lengthwise, it was found to be full of hematoma inside.

The pathological findings were as follows. The uterus measured 9 × 6 × 4 cm with hemorrhage and rupture of the myometrium in the right lateral wall of the uterine body. No diagnostic abnormalities in the right ovary and fallopian tube were noted. A 4.6 × 3.5 × 3 cm poorly demarcated infiltrative mass-like lesion was found in the uterine serosa, myometrium, and round ligament with mild cytologic atypia. Necrosis was not identified, and mitotic activity was <1/50 high-power fields (HPFs). Immunohistochemical (IHC) staining showed that the lesions were diffusely positive for human melanoma black-45 (HMB-45), a highly specific marker for LAM. An additional marker, smooth muscle α-actin (SMA), and estrogen receptor (ER) were also positive (Fig. 2).

The patient's postoperative recovery was uneventful, and no unusual findings were noted during an outpatient visit 3 months after discharge. However, the patient strongly indicated that she did not want further diagnostic evaluation, treatment, or follow-up at the tertiary hospital due to the distance and cost, so no outpatient visits were done thereafter. The patient did, though, report no abnormalities in medical examinations and no unusual findings in a more recent gynecological examination at a local clinic.

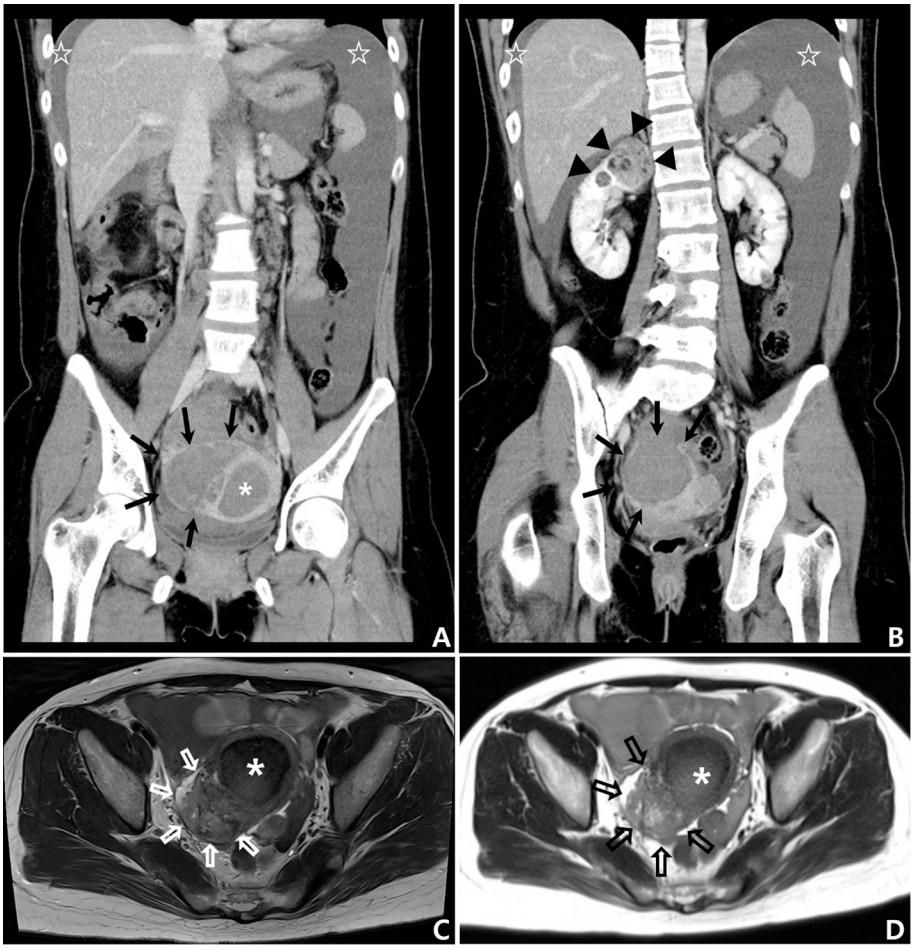

Fig. 1. Coronal contrast-enhanced abdominopelvic computed tomography images (A, B) revealed a lobulated, thick-walled mass like lesion (arrows) communicating with a dilated endometrial cavity filled with hematometra (asterisk) and massive hemoperitoneum up to diaphragm (open asterisk). Multiple angiomyolipomas up to 4 cm are present in the right kidney (triangle). Axial T1-weighted image (C) and axial T2-weighted image (D) show mixed low and high signal intensity of a lobulated mass suggestive of hematoma (open arrows) in right pelvic cavity, with a focal uterine wall rupture on the right side of the uterus. The uterine cavity (asterisk) is dilated and filled with hematoma.

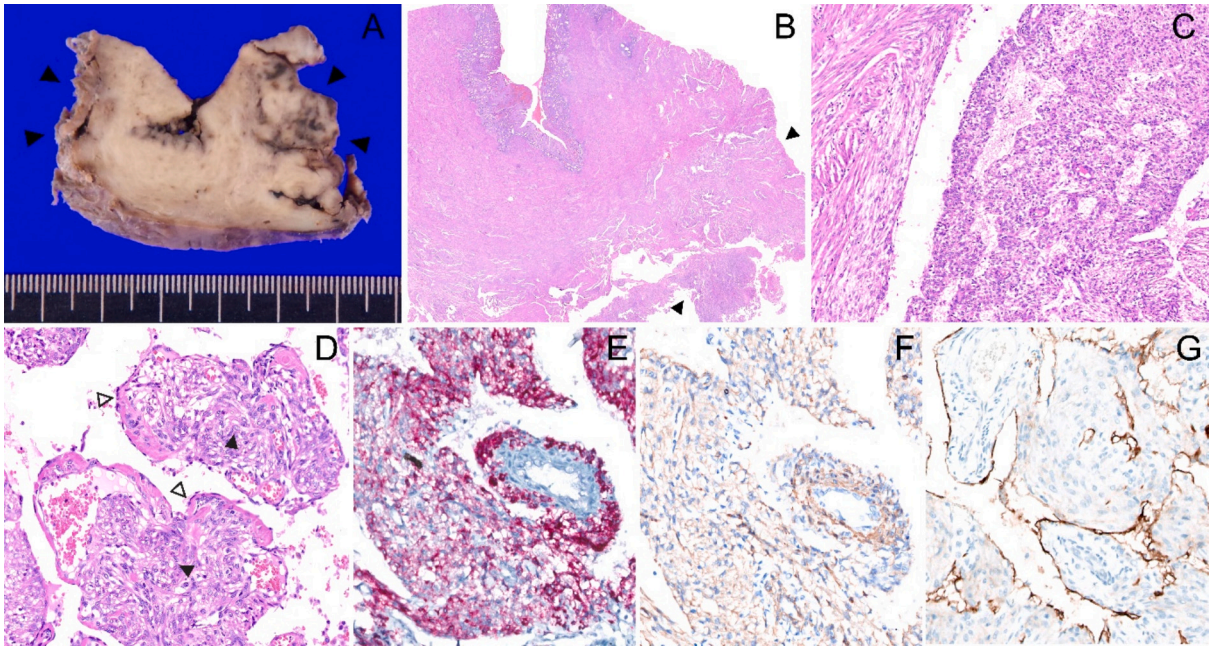

Fig. 2. Macroscopic and microscopic features of uterine lymphangioleiomyomatosis (LAM). (A) Grossly, tumor is located at the uterine serosa-myometrium with a trabeculated appearance (closed arrowheads). (B) Microscopically, diffuse infiltration of tumor is seen (closed arrowheads), showing numerous slit-like spaces with bundles of fascicles. (C) Adjacent normal myometrium (left) differs from LAM (right), which is composed of lymphatic channels and spindled-epithelioid cells. (D) High-power magnification of LAM shows spindled-epithelioid cells (closed arrowheads) within delicate lymphatic vessels (open arrowheads). LAM cells are positive for (E) HMB-45 and (F) SMA, and (G) D2–40 is immunopositive for lymphatic vessels surrounding LAM.

3. Discussion

Although the uterus is a common site of LAM involvement, uterine LAM is a very rare, with fewer than 30 histopathologically confirmed cases reported globally [5]. A previous literature review indicates that 40 % of uterine LAM are associated with TSC [7]. Therefore, uterine LAM should be considered in patients with a history of TSC presenting with vague gynecological symptoms.

The clinical manifestations of uterine LAM can vary from being asymptomatic to causing symptoms such as dysmenorrhea, heavy menstrual bleeding, abnormal uterine bleeding or pelvic pain [7–9]. The definitive imaging features of uterine LAM remain elusive. Ultrasound reveals a heterogeneous echogenic mass within the uterus; however, it may also appear as a solid mass with high vascularity [10]. Even CT and MRI scans may present only nonspecific images: a diffuse, indistinct lesion lacking clear demarcation [5]. Similar to this case, Kim et al. described the radiological imaging findings of uterine LAM: multiple large, lobulated cystic uterine masses and a dilated endometrial cavity filled with fluid on contrast-enhanced CT [11]. On MRI, irregularly shaped uterine masses with high signal intensity were observed on the fat-suppressed T1-weighted images suggesting a hemorrhagic component. Due to its rarity and nonspecific symptoms and imaging studies, uterine LAM is often misdiagnosed as hemorrhagic or degenerative uterine leiomyomas, uterine malignancies, or adenomyosis [8,11]. In this case, too, it was initially misdiagnosed as a ruptured degenerated myoma. However, in similar future cases, uterine LAM should be considered when multiple cystic uterine masses are present in patients with TSC or pulmonary LAM.

The diagnosis of uterine LAM can be confirmed through characteristic pathologic features and specific immunohistochemical stains. In particular, HMB-45 and SMA are recommended for accurate diagnosis, while the ER and progesterone receptor can aid in diagnosis [3]. Additionally, other markers such as vimentin and desmin can help differentiate LAM from other diseases [10]. LAM is considered one of the PEComa family: mesenchymal tumors with distinct IHC features, positive for both smooth muscle and melanocytic markers [2]. The cells of these tumors aggregate and infiltrate vascular muscles at multiple sites. PEComas range from benign to malignant, though the latter are rare. Malignant PEComa can be suspected when two or more of the following seven parameters are met: size >5 cm, high cellularity, high-grade nuclear atypia, mitotic activity >1/50 HPFs, necrosis, infiltrative margin, and vascular invasion [12]. This case met only the infiltrative margin criterion, suggesting a benign character.

The etiology of LAM is related to genetic mutations in the tumor suppressor genes TSC1 and TSC2; these mutations are associated with pulmonary LAM and renal AML [2,13], but mutations in TSC genes can nevertheless often be found in cases of sporadic LAM [8]. TSC mutations cause overexpression of the mammalian target of rapamycin (mTOR) complex, forming benign tumors in various organs [13–15]. This patient underwent only TSC2 testing due to cost concerns, as TSC2 mutations are more common (70 %) than TSC1 mutations (20 %) and are associated with more severe phenotypes [16,17]. Although this patient did not have a mutation in the TSC2 gene, this does not rule out a diagnosis of TSC; this is because gene mutations are not found in up to 15 % of patients with TSC [13].

Recently, estrogen has been considered another possible cause of LAM [3]. LAM mainly occurs in women of reproductive age, worsens with estrogen, and ER is confirmed in about half of cases. Therefore, hormonal changes during pregnancy may cause uterine LAM to enlarge and exacerbate symptoms. According to reported cases of PEComas during pregnancy, even previously small and asymptomatic uterine PEComas can grow rapidly, leading to uterine rupture by 30 weeks of gestation [18]. Another case report describes spontaneous hemoperitoneum resulting from a ruptured PEComa of the round ligaments at 34 weeks of gestation [19]. However, not all PEComas cause rupture during pregnancy, as some are disguised as retained placenta after a delivery [20]. Fertility preservation and management in patients with uterine LAM are important due to the risk of worsening gynecological symptoms or even uterine rupture during pregnancy. However, there is no established standard treatment for LAM or EPLAM. Medical treatments such as mTOR inhibitors or antiestrogen strategies are available; however, there is no firm data on their efficacy against the diseases [3]. Therefore,

early diagnosis and careful follow-up are necessary.

4. Conclusion

In conclusion, uterine LAM is a rare but important disease. It is generally considered a benign tumor that does not require further treatment [8,12]. However, as in this case, it can suddenly rupture in young women, with serious consequences, and occasionally present a malignant condition such as metastasis or sarcomatous transformation [9]. Therefore, when a patient with a history of TSC presents with abnormal uterine bleeding or abdominal pain, uterine LAM should be suspected and investigated. With few reported cases, this case enhances our understanding of uterine LAM and also highlights the need for further research due to its diverse presentation and diagnostic difficulties.

Contributors

Eun Min Lee contributed to acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Ju Hee Kim contributed to patient care, conception of the case report, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Uiree Jo contributed to acquiring and interpreting the data, and drafting the manuscript.

Yoon Jung Cho contributed to patient care, conception of the case report and acquiring and interpreting the data.

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Patient consent

The patient consented to the publication of the report and accompanying images.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

References

[1] S.R. Johnson, A.E. Tattersfield, Clinical experience of lymphangioleiomyomatosis in the UK, Thorax 55 (12) (2000) 1052–1057.
[2] K. Thway, C. Fisher, PEComa: morphology and genetics of a complex tumor family, Ann. Diagn. Pathol. 19 (5) (2015) 359–368.
[3] S.R. Johnson, J.F. Cordier, R. Lazor, V. Cottin, U. Costabel, S. Harari, et al., European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis, Eur. Respir. J. 35 (1) (2010) 14–26.
[4] A.M. O'Mahony, E. Lynn, D.J. Murphy, A. Fabre, C. McCarthy, Lymphangioleiomyomatosis: a clinical review, Breathe (Sheff.) 16 (2) (2020) 200007.
[5] K. Yamada, Y. Yamanishi, J. Aratake, N. Sasagasako, Y. Inayama, R. Gou, et al., A case of uterine Lymphangioleiomyomatosis complicated by tuberous sclerosis complex, Case Rep. Obstet. Gynecol. 2022 (2022) 2893975.
[6] E.P. Henske, S. Jozwiak, J.C. Kingswood, J.R. Sampson, E.A. Thiele, Tuberous sclerosis complex, Nat. Rev. Dis. Primers 2 (2016) 16035.
[7] T. Pongsuvareeyakul, S. Maleki, B.D. DeNardo, D.S. Dizon, C. Phornphutkul, K. Singh, Sporadic uterine Lymphangioleiomyomatosis (LAM): report of a unique case arising in the lower uterine segment with short review, Gynecol. Oncol. Rep. 37 (2021) 100812.
[8] L. Grant, S. Chipwete, S. Soo Hoo, A. Bhatnagar, Extrapulmonary uterine lymphangioleiomyomatosis (LAM) and dysfunctional uterine bleeding: the first presentation of LAM in a tuberous sclerosis complex patient, BMJ Case Rep. 12 (2) (2019).
[9] D. Szpurek, S. Szubert, P. Zielinski, A. Frankowski, S. Sajdak, R. Moszynski, Malignant presentation of uterine lymphangioleiomyomatosis, Taiwan. J. Obstet. Gynecol. 54 (5) (2015) 603–607.
[10] J.M. Han, K.H. Lee, S.J. Kim, C.C. Rhim, Y.H. Park, J.B. Kang, et al., A case of lymphangioleiomyomatosis originated in the pelvic cavity, J. Gynecol. Oncol. 19 (3) (2008) 195–198.
[11] Y.S. Kim, S.E. Rha, J.Y. Byun, A. Lee, J.S. Park, CT and MR imaging findings of lymphangioleiomyomatosis involving the uterus and pelvic cavity, Korean J. Radiol. 12 (2) (2011) 261–265.
[12] A.M. Acosta, B.P. Adley, Predicting the behavior of perivascular epithelioid cell tumors of the uterine Corpus, Arch. Pathol. Lab Med. 141 (3) (2017) 463–469.
[13] H. Northrup, M.E. Aronow, E.M. Bebin, J. Bissler, T.N. Darling, P.J. de Vries, et al., Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations, Pediatr. Neurol. 123 (2021) 50–66.
[14] P. Curatolo, N. Specchio, E. Aronica, Advances in the genetics and neuropathology of tuberous sclerosis complex: edging closer to targeted therapy, Lancet Neurol. 21 (9) (2022) 843–856.
[15] M.E. Tyburczy, K.A. Dies, J. Glass, S. Camposano, Y. Chekaluk, A.R. Thorner, et al., Mosaic and Intronic mutations in TSC1/TSC2 explain the majority of TSC patients with no mutation identified by conventional testing, PLoS Genet. 11 (11) (2015) e1005637.
[16] J. Ni, F. Yan, W. Qin, L. Yu, G. Zhang, F. Liu, et al., Mutational analysis of renal angiomyolipoma associated with tuberous sclerosis complex and the outcome of short-term everolimus therapy, Sci. Rep. 9 (1) (2019) 14337.
[17] S.L. Dabora, S. Jozwiak, D.N. Franz, P.S. Roberts, A. Nieto, J. Chung, et al., Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs, Am. J. Hum. Genet. 68 (1) (2001) 64–80.
[18] E. Babayev, K.E. Fay, J.M. Horowitz, J.A. Goldstein, A.L. Alexander, A.E. Strohl, et al., Perivascular epithelioid cell tumors (PEComa) in pregnancy with uterine rupture and ongoing abdominal gestation: a case report, Case Rep. Womens Health 25 (2020) e00172.
[19] K. Nitahara, M. Sasaki, S. Ichikawa, K. Tsuji, Y. Yoshida, Rupture of perivascular epithelioid cell neoplasm at 34 weeks' gestation: a nonendometriosis case of spontaneous hemoperitoneum in pregnancy, J. Obstet. Gynaecol. Res. 45 (3) (2019) 709–713.
[20] M. Tilstra, J. Maksem, A. Bakhru, S.J. Carlan, J. Wilson, Perivascular epithelioid cell tumor masquerading as retained placenta, J. Ultrasound Med. 34 (8) (2015) 1515–1517.