A case of lymphangioleiomyomatosis associated with endometrial cancer and severe systemic lupus erythematosus

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Abstract

Background: Lymphangioleiomyomatosis (LAM) is a rare idiopathic disorder that occurs in women of childbearing age, and consists of a diffuse proliferation of abnormal smooth muscle cells along the thoracic and abdominal lymphogenous route.

Case presentation: We experienced a case of a 47-yo woman with recent history of systemic lupus erythematosus (SLE) diagnosed with endometrial cancer, initially suspected to have metastasized to pelvic and para-aortic lymph nodes based on preoperative diagnostic imaging. Subsequent pathological diagnosis revealed stage IB endometrial cancer without evidence of lymph node involvement. Instead, enlarged pelvic and para-aortic lymph nodes were found to be due to extrapulmonary LAM, from a primary lesion found inside the uterine myometrium. SLE improved after surgery.

Conclusion: This is the first reported case of comorbid endometrial cancer, SLE, and aggressive LAM metastasizing to regional lymph nodes, and strengthens the clinical evidence for a common role of mTOR pathway hyperactivity and estrogen responsiveness in the pathophysiology of metastasizing lesions of the genital tract.
Laboratory results and serologies at the first medical examination

| WBC  | 3.3×10⁹/L | PT % | 90.0 % | RF | 6 IU/mL |
|------|-----------|------|--------|----|---------|
| Hb   | 9.1 g/dL  | PT-INR  | 1.05 | CH50 | 33.7 U/mL |
| Plt  | 2.2×10¹²/μL | APTT  | 62.0 s | SS-A | 240.0 U/mL |
| FDP  | 7.0 μg/mL | C3 | 58 mg/dL |
| Alb  | 3.3 g/dL  | D-dimer  | 4.3 μg/mL | C4 | 11 mg/dL |
| LDH  | 319 IU/L | DS-DNA | 0.9 IU/mL |
| BUN  | 24.1 mg/dL | CEA | 1.8 mg/mL | SS-DNA | 2.2 U/mL |
| Cre  | 0.85 mg/dL | CA19-9 | 27 U/mL | Antinuclear Ab + |
| Na   | 139 mEq/L | CA125 | 176 U/mL | Lupus AC | 267 |
| K    | 4.2 mEq/L | CA15-3 | 12 U/mL | Anti CL-IgG | 79 U/mL |
| Cl   | 105 mEq/L | NSE | 11.0 mg/mL |
| AST  | 19 U/L | SLX | 25.0 U/mL | ESR | 48 |
| ALT  | 23 U/L | SCC | 2.1 mg/mL |
| CRP  | 0.29 mg/dL | CA72-4 | 4.4 U/mL |
gynecological healthcare providers will continue to be important to correctly diagnose LAM and/or cancer-related diseases.

**Discussion**

LAM is an idiopathic and intractable disease predominantly affecting females of childbearing age. Classified into pulmonary and extrapulmonary types, most patients are identified by onset of pulmonary complications, such as respiratory failure after pneumothorax [1]. Sporadic extrapulmonary LAM remains an unusual diagnosis in the clinical setting [5]. No previous publication has reported on its association with both SLE and endometrial cancer, and this unique case suggests a possible common etiology involving dysfunction of cell regulation functions of the mTOR pathway.

As noted above, the loss of function mutations identified in TSC1 and TSC2, have been broadly detected in pulmonary LAM cells, and likely explains the high correlation found between pulmonary LAM and TSC [16]. These TSC1/TSC2 loss of function mutations activate mammalian target of rapamycin (mTOR) protein kinases, which promote both cell proliferation and survival, have been implicated in various types of cancer.

**Fig. 1**

a Axial preoperative T2-weighted contrast magnetic resonance imaging (MRI) shows endometrium thickness in the uterine body. It has been diagnosed as Endometrial cancer of stage IB due to more than 50 % depth of myometrial invasion (red arrowhead). b The positron emission tomographic (PET) with CT scan. c shows pathologically elevated glucose metabolism in enlarged paraaortic lymph nodes (orange arrowhead).

**Fig. 2**

a Intraoperative photo showing the swollen paraaortic lymph nodes left along the aortic vessels (red arrowhead). b The excised maximum lymph node, approximately 7 cm in size, was solid and tender characteristic tumor.
Recently, the mTOR pathway has been found to play a crucial role in the development of endometrial cancer with high frequency of mutations in PTEN and/or PIK3CA [18]; knowledge about genetic alterations involved in this pathway offer potential treatment strategies. Furthermore, constitutive activation of the mTOR pathway has recently been reported in SLE [19]. Taken together, the four diseases (LAM, TSC, SLE, and endometrial cancer) appear to share a robust association with mTOR pathway activation. It is noteworthy that no particular risk factors for endometrial cancer were found in her personal or family history. Therefore, it is a reasonable assumption that our patient’s history of SLE may be causally related to both LAM and endometrial cancer. Though we have not yet performed genetic testing for germline mutations to reveal an association with mTOR pathway deregulation that may cause TSC, the presence of severe SLE, highly suggestive of constitutive hyperactivation of mTOR signaling, may lead to endometrial cancer as well as particularly aggressive LAM cells present in uterine myometrium and lymphogenously invading the retroperitoneal lymph nodes.

**Conclusion**

Clinicians should also be aware of a previous report suggesting that extrapulmonary uterine LAM may precede both TSC and pulmonary LAM by several years [4, 6], a reasonable finding in the setting of ongoing and unremitting mTOR hyperactivity and estrogen responsiveness. As such, we anticipate that this patient will continue to be at risk for pulmonary LAM in the future. In Japan, there have been several reported cases of pulmonary LAM recurrence even after lung transplant. For treatment of LAM, gonadotropin releasing hormone agonists or progesterone therapy has been used for decades, though their effectiveness remains controversial and definitive treatment remains elusive. Recently, sirolimus, an mTOR inhibitor, has been investigated as a potential therapeutic agent [20]. As a previous study has described pulmonary LAM discovered a decade after initial diagnosis of a gynecologic lesion [5], novel therapies may play a role in both treatment as well as prevention. Based on currently available evidence, we feel that sirolimus on gynecologic field should be used with caution, and considered only after thorough assessment and in conjunction with scheduled imaging surveillance for recurrent disease.

As mentioned above, the gold standard for diagnosis of LAM is made by histopathological findings. However, as in this case, decision to pursue and timing of surgical treatment is patient-specific. CT and MRI imaging remain the most accessible modalities for diagnosing lymphadenopathy in the absence of surgical exploration. Nonetheless, this case also highlights the appropriate
controversy that exists regarding the accuracy of identifying lymph node metastasis from endometrial cancer solely by integrated imaging techniques, which more recently also include PET-CT imaging [15, 21]. In diseases which may mimic metastasis associated with gynecologic malignancy, we think PET-CT may offer substantial advantages in distinguishing key pathological feature of lymphadenopathy. However, slightly increased FDG uptake, as seen in this case, may cause difficulty in accurate characterization of the underlying abnormality. A review of more cases, further examining how to best evaluate pelvic and para-aortic lymph node metastasis or LAM in patients with comorbid endometrial cancer, is warranted to clarify the optimal diagnostic modality for early detection of sporadic LAM.

Abbreviations
APSA, anti-phospholipid antibody syndrome; CT, computed tomography; E2, estrogen; ER, estrogen receptor; FICO, federation of gynecology and obstetrics; HMB, human melanin black; ITP, idiopathic thrombocytopenic purpura; LAM, lymphangioleiomyomatosis; mPSL, methylprednisolone; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; PEC, peritumoral epitheloid cells; PET-CT, positron emission tomography/computed tomography; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homolog; SLE, systemic lupus erythematosus; SMA, smooth muscle actin; SUV, standardized uptake value; TSC, tuberous sclerosis complex

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Availability of supporting data
The dataset supporting the conclusions of this article is owned by the University of Tokyo hospital but could be made available on request. Personal information will not be provided to ensure anonymity of the patient.

Authors’ contributions
KS and KN performed literature review and wrote the manuscript. KO, YM, TA, KK, YO, and TF participated in literature review. HA, DM and MF performed pathological diagnosis and prepared images. All authors were involved in the management of the patient. All authors read and approved the final manuscript.

Competing interest
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Ethics and consent to participate
The study was performed under the approval of the ethics committee of the medical faculty at the University of Tokyo and with written informed consent.

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