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Case Report

Malignant presentation of uterine lymphangioleiomyomatosis

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ABSTRACT

Objective: The main aim of this case report was to present the method of diagnosis, management, and the 12-year-follow-up of a patient diagnosed with primary uterine lymphangioleiomyomatosis (LAM).
Case Report: A 47-year-old woman was admitted to the Department of Thoracosurgery due to pulmonary lesions suspected to be metastatic. The potential primary site of the neoplasm was not identified by previous imaging studies and specialist counseling. The patient had a history of total abdominal hysterectomy without ovaries due to a uterine tumor recognized as cellular leiomyoma and left salpingo-oophorectomy due to a solid ovarian tumor also recognized as leiomyoma. She had previously undergone the removal of a left kidney angiomyolipoma. After histopathological examination of the pulmonary lesions and repeated evaluation of the ovarian and uterine tumors, the diagnosis of primary uterine LAM with metastases to the ovary and the lungs was established. Although new metastatic lesions occurred, the patient remained in good condition during the 12-year-follow-up.
Conclusion: The history of our patient and review of the literature suggest that although uterine LAM presents malignant features (i.e., metastasis), the disease is long lasting and the patient can be in good condition for a number of years.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease characterized by the proliferation of abnormal smooth muscle cells. The disease usually affects women of reproductive age. LAM may be sporadic or associated with the tuberous sclerosis complex (TSC), which is an autosomal dominant, multisystem condition characterized by the development of hamartomas and neoplasms at various body sites, especially the skin, central nervous system, and kidney. Mental retardation and epilepsy are also frequent in patients with TSC [1].

The exact etiology of LAM is currently unknown, despite recent progress in understanding its pathology [2,3]. LAM occurs mainly in the interstitium of the lungs, however, cases of extrapulmonary LAM have also been reported. LAM has been detected in several body regions, including the retroperitoneum, mesentery, ureter, biliary tract, liver, ovary, adrenal gland, and inguinal or supraclavicular lymph nodes [4–6]. We present a rare case of uterine LAM with malignant course of the disease.

Case Report

A 47-year-old woman was admitted to the Department of Thoracosurgery of Wielkopolska Center of Pulmonology and Thoracosurgery (Poznan, Poland) in January 2010 for a consultation regarding lung lesions resembling distant metastases. The lesions in the lungs were diagnosed in November 2008 during a routine chest X-ray examination. The patient had previously received counseling by a surgeon and internist. Previous imaging studies had failed to recognize the site of origin of the lung metastases. On admission to the Department of Thoracosurgery, the patient was in good condition without any clinical symptoms.

The patient had a history of total abdominal hysterectomy without ovaries because a uterine tumor was recognized as a cellular leiomyoma in 2001. In November 2008, she had left salpingo-oophorectomy due to a solid ovarian tumor. The tumor

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was surprisingly recognized as an ovarian leiomyoma during the first histopathological examination. Immunohistochemical results were positive for desmin, vimentin, and smooth muscle actin, and negative for CD1, inhibin, cytokeratin AE1/AE3, S100 protein, and CD34. The expression of CD31 was weak. The expression of Ki67 was found in 3% of the cell nucleus. Preoperative serum CA125 level was 60.3 IU/mL. In December 2009, she underwent a third laparotomy due to a left renal tumor. She had partial nephrectomy, and the final histopathological examination revealed renal angiomyolipoma.

We performed an X-ray computed tomography (CT) examination of the chest, which revealed metastatic lesions, mainly in the III and VI segments of the right lung and VI and X segments of the left lung, without fluorodeoxyglucose uptake on positron emission tomography. Several emphysematous bullae and enlargement of lymph nodes of the pulmonary hilum were also visualized. We then decided to perform video-assisted thoracoscopy with wedge tumor resection of the right lung. The diagnosis of benign metastasizing leiomyoma was made following histopathological examination with the revision of the uterine and ovarian tissue samples.

Two months later, the patient was admitted to the hospital due to dyspnea with suspected disease progression. An increased diameter of the lesion in the left lung was detected by CT scans. Thoracotomy and left lung laser wedge resection was performed in June 2010. Subsequent histopathological examination with review of the uterine, ovarian, and renal lesions revealed primary uterine LAM with metastases to the ovary and lungs. Final diagnosis was established after immunohistochemical analyses, which revealed the expression of human melanoma black protein 45 (HMB45) in the ovarian tumor and lung lesions. There was no possibility for conducting immunohistochemical analyses on the uterine tumor samples because the samples were utilized after 10 years of storage.

Experimental tamoxifen therapy was initiated due to intolerance of gestagens and disease progression. However, after 5 months of stabilization, new metastatic lesions were found in the right lung. We then stopped tamoxifen therapy, and performed right thoracotomy with wedge laser lung resection and enlarged lymph node excision. After few months of stabilization, a tumor of 68 mm × 44 mm × 52 mm in size in the retropubic area was visualized by CT examination. The tumor was excised in March

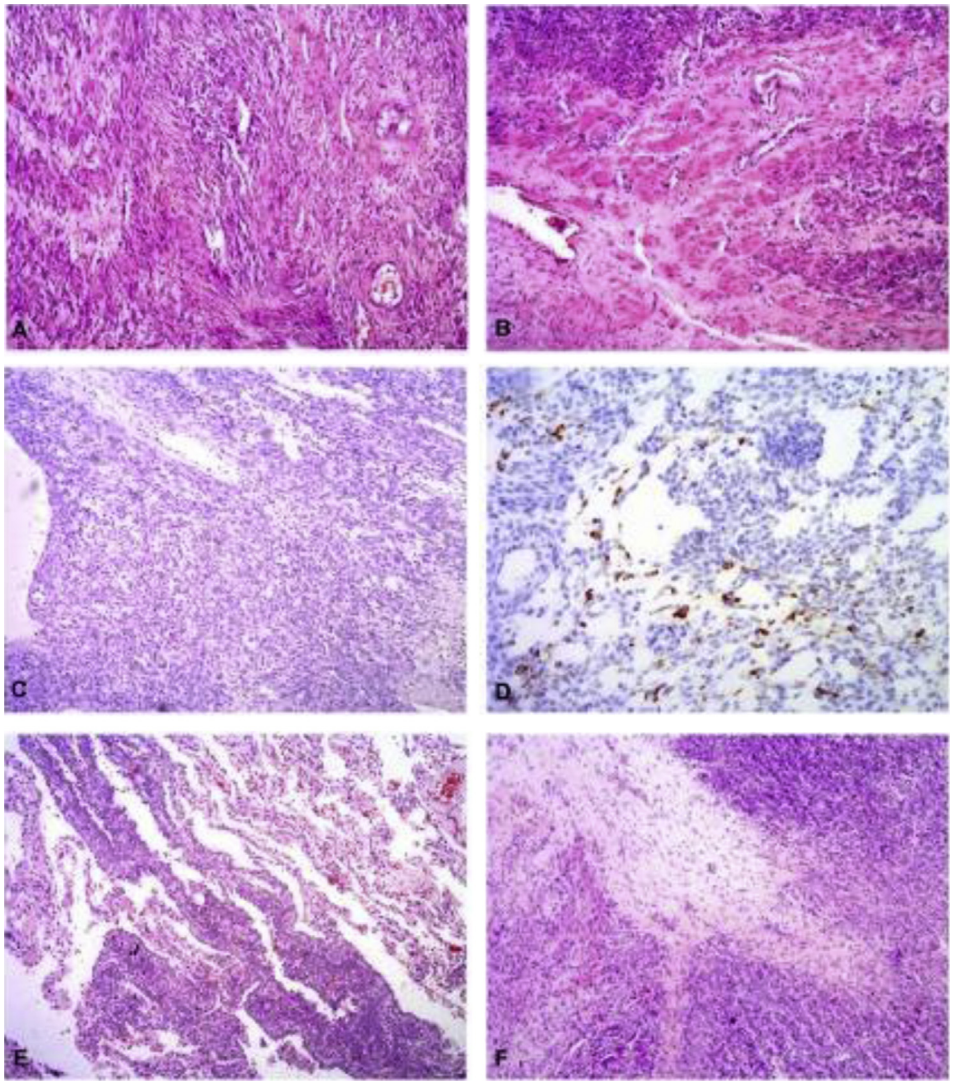

Figure 1. (A) Primary uterine lymphangioleiomyomatosis (LAM). (B) Primary uterine LAM. The photograph shows penetration of LAM cells into the myometrium. (C) LAM metastasis of the ovary. (D) LAM metastasis to the ovary with a positive reaction for human melanoma black protein 45 (HMB45). (E) LAM metastasis of the lungs obtained from the first video-assisted thoracoscopy wedge resection. The photograph presents LAM lesions within lung tissue. (F) LAM metastasis of the lungs from right thoracotomy (third resection of LAM metastasis of lungs). LAM lesions resemble uterine and ovarian tumors. All images, magnification 50×.

Table 1
Clinical characterization, and immunohistochemical and imaging findings in patients diagnosed with uterine lymphangioleiomyomatosis.

Study	Clinical manifestation of uterine involvement	Age (y)	Stigmata of TSC	Histopathology	LAM of the lungs	Evidence of malignant course	Imaging findings	CA125 (IU/mL)
Han et al [10]	Prolonged vaginal bleeding	46	NA	Smooth muscle actin (+), HMB45 (+)	Absent	Metastases to iliac and paraaortic lymph nodes	TVU: hypervascular tumor (5.57 cm × 2.91 cm) between the uterus and right ovary. MRI: tumor (4.0 cm × 5.0 cm × 4.0 cm) situated at right posterior of the uterus, near to and below right ovary. Low signal on T1W1 and intermediate signal on T2W1	26.7
Kim et al [11]	Anemia, abdominal distension, menometrorrhagia, dysmenorrhea	29	Present	Smooth muscle actin (+), HMB45 (+)	Present	Involvement of both adnexa, pelvic side walls, and omentum	CT: multiple, large, lobulated, thick-walled cystic masses involving uterus and entire pelvic cavity. Hemorrhagic component within the cysts, without solid components and calcifications. MRI: huge, irregularly shaped, cystic masses involving uterus and parauterine pelvic cavity. T1: Hyperintense masses, hematoma within uterine cavity. T2: heterogeneously hypointense and hyperintense, intralesional hemorrhage. Contrast-enhanced MRI - no enhancing solid parts	204.01
Torres et al [3]	Abdominal distension, progressive renal insufficiency	33	Present	Proliferating spindle cells. Smooth muscle actin (+), desmin (+), vimentin (+), HMB45 (+), PCNA (+), ER (+), PR (+), epithelial membrane antigen (−), S-100 (−), CD57(−)	Present	At diagnosis: concurrent LAM involvement of the uterus, perinephric lymph node, and perirenal cyst	USG and MRI: renal, peripelvic and perirenal cysts occupying abdomen and pelvis. Hemorrhagic cyst of the left adnexa	NA
Torres et al [3]	Progressive abdominal distension 20 y after hysterectomy due to menometrorrhagia, LAM involvement of the uterus.	38	Present	Proliferating spindle cells. Smooth muscle actin (+), desmin (+), vimentin (+), HMB45 (+), PCNA (+), ER (+), PR (+), epithelial membrane antigen (−), S-100 (−), CD57(+)	Present	LAM of the abdomen 20 y after LAM involvement of the uterus	CT: enlarged kidney by diffuse angiomyolipomatous infiltration	NA
Torres et al [2]	3 y of episodic right pelvic pain	29	Present	Proliferating spindle cells. Smooth muscle actin (+), desmin (+), vimentin (+), HMB45 (+), PCNA (+), ER (+), PR (+), epithelial membrane antigen (−), S-100 (−), CD57 (−)	Present	At time of diagnosis: LAM of the uterus coexisting with cystic LAM lesion in the right pelvic sidewall	USG, CT, MRI: partial cystic mass (5 cm × 3 cm × 4 cm) in the right pelvic sidewall, peritoneal free fluid	NA
Longacre et al [12]	Abdominal pain, menometrorrhagia, anemia	49	Present	Smooth muscle actin (+), desmin (+), HMB45 (+)	Present	LAM involvement of the right fallopian tube, left, and right pelvic lymph nodes	CT: large uterine mass consistent with a fibroid, peritoneal free fluid, suspicion of metastatic implant in the liver	NA
Gyure et al [8]	Incidental finding, signs of primary disease − ovarian carcinoma	29	Present	Microscopic finding. Numerous nodules of LAM. Focal area, sarcomatous transformation of the LAM cells. HMB45 (+), smooth muscle actin (+), desmin (+)	Present	LAM involvement of the pelvic and paraaortic lymph nodes	CT: enlarged retroperitoneal lymph nodes. Microscopic lesions in the uterus	NA
Gyure et al [8]	Incidental finding, without signs	33	Present	Microscopic finding. Multiple, small LAM lesions within myometrium. No areas of necrosis, atypia, or mitotic activity. HMB45 (+), smooth muscle actin (+), desmin (+)	NA	Coexisting retroperitoneal lymphangioma	CT: cystic uterine adnexal mass separated from ovary (retroperitoneal lymphangioma)	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Clinical manifestation of uterine involvement	Age (y)	Stigmata of TSC	Histopathology	LAM of the lungs	Evidence of malignant course	Imaging findings	CA125 (IU/mL)
Lack et al. [7]	Vaginal discharge, abdominal tenderness.	33	Absent	Microscopic foci of LAM within myometrium with intravascular protrusion by irregular nodules of smooth muscle. LAM foci within ovarian stroma. Lack of necrosis and mitotic figures.	Present	Mesenteric lymph nodes involved by LAM. Focuses of LAM cells within liver parenchyma and lymphatic vessels of adrenal gland. Disseminated foci of LAM within myometrium	CT: large, soft tissue mass occupying pelvis, retroperitoneal adenopathy, low density liver metastases	NA

CD57 = Leu7, also known as beta-1,3-glucuronyltransferase 1; CT = computed tomography; ER = estrogen receptor; HMB45 = human melanoma black protein 45; LAM = lymphangioleiomyomatosis; MRI = magnetic resonance imaging; NA = data not available; PCNA = proliferating cell nuclear antigen; PR = progesterone receptor; S-100 = S-100 protein; TSC = tuberous sclerosis complex; TVU = transvaginal ultrasonography; USG = abdominal ultrasonography.

2012 during the fourth laparotomy. The LAM lesions were confirmed by histopathological examination. A right salpingo-oophorectomy was performed during the laparotomy. Currently (i.e., 12 years after the primary diagnosis), the patient is in a stable and good condition. The patient was determined to be disease-free during the last CT examination.

Genetic counseling was performed due to the presence of the renal angiomyolipoma, LAM, and a history of seizures. However, a definite diagnosis of the TSC was not established because of normal brain structure in the magnetic resonance examination. There were no other major or minor signs of the TSC. The patient was also examined by a cardiologist and ophthalmologist, and no signs of TSC were found.

Discussion

To the best of our knowledge, our report is the 10th report of histopathologically confirmed uterine LAM presented in the literature. According to the reviewed cases, uterine LAM mainly affects women of childbearing age (i.e., 29–49 years). The disease is symptomatic in most cases; however, the symptoms are not specified. Frequent abnormal uterine bleeding and abdominal pain are present in uterine LAM patients. Classical stigmata of the TSC were found in all cases, except the case reported by Lack et al [7] and our case.

Although LAM is considered to be histologically benign, this report and previous literature suggest a malignant presentation of LAM. Recent genetic studies have suggested that LAM, especially the lung manifestation, is caused by an unusual mechanism of benign cell metastases [8,9]. Furthermore, we were able to provide evidence of infiltrating growth of LAM lesions, which indicates malignant characterization of the disease (Figure 1).

All but one case of uterine LAM had lung involvement, whether histopathologically confirmed or clinically suspected [10]. In the case of our patient, we did not conduct a radiological examination of the lungs before the first surgery because the uterine tumor was initially recognized as a cellular leiomyoma.

Metastases to regional lymph nodes were identified in the majority of uterine LAM cases. As found in our patient, the uterine adnexa were involved in two previously described LAM cases [11,12]. Kim et al [11] reported about the dissemination of LAM lesions within the pelvic side walls and omentum. In the case reported by Lack et al [7], proliferating LAM cells were found within the liver parenchyma and lymphatic vessels of the adrenal gland. In our case, there was no evidence of lymph node involvement during CT imaging. Moreover, intraoperative examination of a frozen section of the ovarian tumor did not indicate malignant disease. Therefore, the lymph nodes were not resected.

There is a lack of information regarding long-term follow up of patients with uterine LAM. Han et al [10] and Lack et al [7] reported 6 months of follow up after initial surgery without evidence of recurrence, and Gyure et al [8] reported 8 months of follow up. We presented 12 years of patient follow up. We were able to show that although uterine LAM is characterized by multiple recurrences and dissemination within distant parts of the body (i.e., lungs), the disease progresses slowly and is not debilitating, because the patients remain in good condition without evidence of cachexia during the years of follow up. Characterization of all cases of uterine LAM, including imaging findings and CA125 levels, are summarized in Table 1.

The treatment of LAM is a challenge for clinicians due to the lack of a clinically proven therapy. Currently, the efforts for treating LAM are mainly focused on the inhibition of estrogen action using gestagens. However, this therapy is only rarely effective and may even worsen the prognosis in some cases [13]. Although tamoxifen

therapy is not recommended [14], we started the therapy due to a significant intolerance of gestagens by our patient. Unfortunately, the therapy was not successful. Among the new strategies for LAM treatment, the administration of sirolimus seems to be successful [15]. In the case of our patient, hormonal treatment was unsuccessful; however, some benefits were obtained from repeated resections of lung lesions.

To summarize, the history of our patient and review of the literature suggest that primary uterine LAM has a malignant presentation with a tendency for metastasis and recurrence. The disease is frequently associated with LAM involvement of the lungs and regional lymph node metastases. However, despite the lack of an effective treatment, the disease is long lasting and the patient may stay in a good condition for many years.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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