Case Report

Low-dose sirolimus in retroperitoneal lymphangioleiomyomas

Kamonpun Ussavarungsi, Archana T Laroia[1], Charles D Burger[2]

Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Iowa, Iowa City, IA, [1]Division of Cardiovascular and Pulmonary Imaging, Department of Radiology, University of Iowa, Iowa City, IA, [2]Division of Pulmonary and Critical Care, Department of Internal Medicine, Mayo Clinic, Jacksonville, FL, USA

ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare disease associated with cystic lung destruction and abdominal tumors, including lymphangioleiomyomas, which frequently occur in the retroperitoneal region. Sirolimus therapy is currently recommended for LAM patients with abnormal or declining lung function with an adjusted dose to maintain a serum trough level of 5–15 ng/mL. We describe a significant reduction of retroperitoneal lymphangioleiomyomas after treatment with low-dose sirolimus therapy (serum trough level <5 ng/mL) in a patient with sporadic LAM.

KEY WORDS: Low-dose sirolimus, lymphangioleimyomas, lymphangioleiomyomatosis

Address for correspondence: Dr. Kamonpun Ussavarungsi, Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Iowa, 200 Hawkins Drive, C33 GH Iowa City, IA 52242, USA. E-mail: kamonpun-ussavarungsi@uiowa.edu

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a multisystem disorder that primarily affects women and is characterized by proliferation of abnormal smooth muscle-like cells with associated cystic lung destruction and abdominal tumors, such as renal angiomyolipoma and lymphangioleiomyomas.[1,2]

The double-blind, randomized Multicenter International LAM Efficacy of Sirolimus (MILES) trial demonstrated that sirolimus stabilized lung function and improved quality of life and functional performance.[2] Sirolimus is now recommended for LAM patients with abnormal forced expiratory volume in 1 s (FEV1 <70%) predicted or declining lung function.[3] Sirolimus therapy was also reported to be associated with improvement or reduction in size of chylous effusions and lymphangioleiomyomas.[4] Optimal dose and duration are unsettled. Nonetheless, the sirolimus dose was adjusted during the MILES trial to maintain a serum trough between 5 and 15 ng/mL.[2] Conversely, Ando *et al.* reported the effectiveness of low-dose sirolimus (serum trough <5 ng/mL) for stabilizing lung function in 15 patients with sporadic LAM, but the effect of low-dose therapy on extrapulmonary LAM has not been explored.[5]

Clinical experience is important to report in rare disease states, particularly favorable outcomes with low-dose therapy. We describe a significant reduction of retroperitoneal lymphangioleiomyomas with low-dose sirolimus therapy (serum trough level <5 ng/mL) in a patient with sporadic LAM.

CASE REPORT

A 26-year-old woman with sporadic LAM was diagnosed when she presented with dyspnea on exertion and

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nonmassive hemoptysis with characteristic diffuse thin-walled cysts on chest computed tomography (CT) and elevated vascular endothelial growth factor-D (VEGF-D) level (4458 pg/mL). Abdominal and pelvic CT showed a large lobulated cystic and solid mass in the retroperitoneal region compatible with lymphangioleiomyoma [Figure 1]. The large multicystic lesion involving a large portion of retroperitoneum abutted the kidneys and encased both the descending aorta and inferior vena cava. No intra-abdominal adenopathy, ascites, or intrarenal lesion was identified. Pulmonary function test showed preserved FEV1/forced vital capacity (FVC) ratio with FEV1 4.11 L (112%) and FVC 5.04 (116%) but a reduced diffusing capacity of the lungs for carbon monoxide (DLCO) (59% predicted). Sirolimus was offered as a treatment option due to exertional dyspnea and hypoxemia in association with the reduced DLCO and the large, intra-abdominal disease burden. The patient tolerated sirolimus at 1 mg daily and remained on the same dose with the mean serum trough level at 2.98 ± 1.39 ng/mL. Her respiratory symptoms improved with stabilized FEV1 4.18 L (116%) and DLCO 56% after 14 months of sirolimus treatment. Repeat CT of chest, abdomen, and pelvis revealed stable pulmonary cystic lesions and nearly complete resolution of the retroperitoneal mass [Figure 1].

DISCUSSION

Lymphangioleiomyomas occur most often in the retroperitoneal region and have been observed more frequently in patients with sporadic LAM (29%) than in tuberous sclerosis complex patients with LAM (9%).[6] Extrapulmonary LAM cells form fascicles and papillary patterns that are commonly found in lymph nodes along

Table 1: Published cases of lymphangioleiomyomatosis with abdominal lymphangioleiomyomas treated with sirolimus

Report	Number of patients	Extrapulmonary LAM	Mass size	Sirolimus Dose (mg/day)	Trough (ng/mL)	Treatment duration and outcome
Radzikowska *et al*., 2016[10]	14	All cases retroperitoneal mass 7 cases chylous ascites	Mean 1603.85±2437.56 cm^3	1-5	5-15	10 months, mean volume decreased to 198.01±315.43 cm^3
Harari *et al*., 2016[11]	1	Multiple retroperitoneal, retrorenal, retropancreatic masses Chylous ascites	Not reported	2	5-15	3 months, smaller abdominal mass on MRI, no ascites
Ito *et al*., 2016[12]	1	Retroperitoneal mass, left pelvic cavity Left femoral lymphedema	6.2 cm	1-2	5-15	Day 259 post-LT, near-complete resolution of mass on CT scan
Cabeza *et al*., 2016[13]	1	Multiple retroperitoneal, left para-aortic, pelvic masses	6.8 cm×3.9 cm×5.1 cm	2	Not reported	1 year, complete resolution of abdominal mass
Freitas *et al*., 2015[14]	4	2 abdominal LAM Retroperitoneal mass, abdominal lymph node enlargement Retroperitoneal mass	Not reported 18 cm	2 2	Not reported Not reported	12 months, significant regression of mass 6 months, significant regression of mass
Hecimovic *et al*., 2015[15]	3	3 retroperitoneal mass Retroperitoneal mass Retroperitoneal mass Retroperitoneal mass, chylous ascites	7 cm 10 cm 8 cm	2-3 1 2	5.8-7.7 2.9-3.2 3.7-4.4	10 months, smaller mass on CT scan, 1.9 cm×1.2 cm 9 months, smaller mass on CT scan, 2 cm 3 months, reduction in ascites; mass extirpated before sirolimus
Numata *et al*., 2015[16]	1	Retroperitoneal mass and para-aortic lymph node enlargement Tumor in myometrium of uterus	7.0 cm×6.0 cm×3.5 cm 4.5 cm×4.5 cm×2.5 cm	1	Not reported	Mass resected, TAH and BSO; uterine and retroperitoneal LAM lesion confirmed 10 months, no recurrence of tumor and lymph node enlargement
Rozenberg *et al*., 2013[17]	1	Retroperitoneal mass	16.5 cm×6.8 cm×8.7 cm	Not reported	Not reported	3 months, smaller mass on CT scan, 10.5 cm×4.1 cm×4.4 cm
Taveira-DaSilva *et al*., 2011[4]	19	11 cases abdominal LAM	Mean volume 114±50 mL	1-5	5-15	2.6±1.2 (0.7-5.4) years 9 cases complete resolution 2 cases volume decreased from 44±22 mL to 17±13 mL
Chen *et al*., 2009[18]	1	Abdominopelvic mass	Not reported	1	5-8	3 years, significant regression of mass
Morton *et al*., 2008[19]	1	Retroperitoneal mass, left para-aortic region below renal vessels	5.5 cm×3.0 cm×10 cm	Not reported	3-4	7 months, near-complete resolution of mass, 1.8 cm×0.7 cm×1.8 cm

TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, LT: Lung transplantation, MRI: Magnetic resonance imaging, LAM: Lymphangioleiomyomatosis, CT: Computed tomography

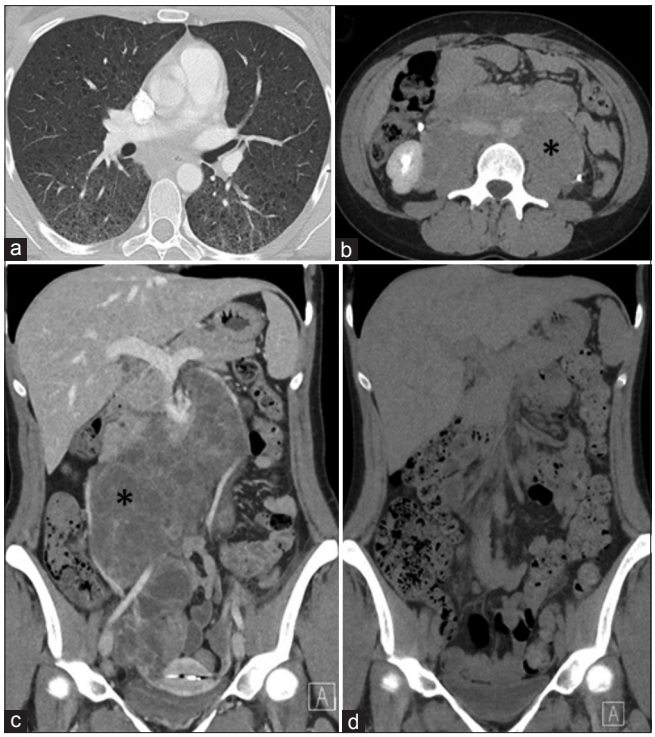

Figure 1: (a) Computed tomography chest demonstrating multiple small cystic lesions throughout the lungs. (b and c) Large multicystic retroperitoneal mass, measuring 26 cm × 14 cm × 8 cm, extending from the level of the superior mesenteric artery and renal arteries, encasing the aorta and inferior vena cava to bifurcation and further extending into the pelvis along the right external and internal iliac arteries. (d) Nearly complete resolution of retroperitoneal lymphangioleiomyomas after 14 months of sirolimus

lymphatic vessels.[7] Lymphangioleiomyoma-LAM cells have infiltrated the fatty capsule surrounding the mass.[8] In addition, chyle-filled cystic lesions resulted from the obstruction of lymphatic vasculature by proliferation of smooth muscle cells.[7,8] Large lesions such as those seen in this case can encase and compress adjacent organs. Our patient also had a markedly high VEGF-D level, which has been shown to reflect lymphatic involvement and negatively correlate with pulmonary function in patients with LAM.[9] Historically, lymphangioleiomyomas were primarily managed with surgical resection but may recur after surgical removal. More recently, medical treatment with sirolimus has surfaced as beneficial due to its favorable effect on lymphangioleiomyoma size.[4,10-19]

Nonetheless, the optimal sirolimus dose and serum level remain undetermined. A review of published case reports and series of LAM patients with abdominal lymphangioleiomyomas who received sirolimus therapy is summarized in Table 1. Most had dramatic reduction of mass with sirolimus trough level >5 ng/mL. In contrast, the effect of sirolimus also remained significant in several cases with serum trough level <5 ng/mL as was the case in our patient.[11,12]

Loss of beneficial effect occurred in the MILES trial; therefore, long-term treatment is generally required. Low-dose sirolimus has the potential to reduce adverse effects and may enhance the safety of long-term therapy. Multicenter Interventional LAM Early Disease (MILED) trial to determine the efficacy of low-dose sirolimus (fixed dose at 1 mg daily) for preventing progression of disease in patients with well-preserved lung function is underway (NCT03150914). Nonetheless, abdominal tumor size is not a primary outcome in MILED trail. Our report reinforces the role of medical therapy for lymphangioleiomyomas that can avoid unnecessary surgery. In addition, favorable responses of extrapulmonary LAM to low-dose sirolimus therapy that is well tolerated are important to report to contribute to the available literature on treatment of this rare disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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