

[CASE REPORT]

Successful Sirolimus Treatment of Lymphangiomyomatosis in a Hepatitis B Virus Carrier

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Abstract:

A 34-year-old woman experiencing shortness of breath was referred to our hospital. The patient was diagnosed with sporadic lymphangiomyomatosis based on the observation of bilateral diffuse multiple thin-walled cysts on computed tomography of the chest, chylous effusion, elevated serum vascular endothelial growth factor-D levels and transbronchial biopsy findings. This patient was a hepatitis B virus (HBV) carrier. Treatment with 1 mg daily of sirolimus was started after HBV DNA was brought below the cut-off level using entecavir. Sirolimus was effective, as the chylous effusion resolved completely and the dyspnea improved. The sirolimus dosage was increased to 2 mg daily without causing HBV reactivation.

Key words: lymphangiomyomatosis, lymphangiomyomas, hepatitis B virus, sirolimus, entecavir

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Introduction

Lymphangiomyomatosis (LAM) is a rare condition characterized by the presence of pathological smooth muscle-like LAM cells. It can occur sporadically or in association with tuberous sclerosis complex (TSC). The two most common initial symptoms and presenting features of LAM are pneumothorax (43%) and exertional dyspnea (36%) (1). Chylothorax was previously observed in 21 of 173 cases (12%) during the total observation period (1). In the guideline panelists' clinical practices, a clinical diagnosis of LAM is based on a combination of characteristic high-resolution computed tomography (HRCT) features plus one or more of the following: presence of tuberous sclerosis complex (TSC), angiomyolipomas, chylous effusions, lymphangiomyomas (lymphangiomyomas), or elevated serum vascular endothelial growth factor-D (VEGF-D) of ≥ 800 pg/mL (2). The pathological diagnosis relies on characteristic LAM cell morphology and positive immunoreac-

tivity to smooth muscle actin and Human Melanoma Black-45 (HMB-45) antibodies (3, 4).

Sirolimus (also known as rapamycin) is a molecular-targeted drug that inhibits the mammalian target of rapamycin (mTOR). Sirolimus treatment (2 mg daily, sirolimus concentrations were maintained between 5-15 ng/mL) has been shown to improve the lung function [as measured by the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)], functional performance, and quality of life in patients with LAM. It also reduces the volume of angiomyolipomas, lymphangiomyomas, and chylous accumulation (5, 6).

In general, patients respond well to sirolimus treatment, and adverse effects are mild. The most common adverse events are mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash, and swelling in the lower extremities (7). Additional toxicities that are encountered with mTOR inhibitors treatment include the risk of infections due to immunosuppression (5). It is known that reactivation occurs when immunosuppressive therapy or chemotherapy is used

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Table. Laboratory and Pleural Fluid Data on Admission.

Hematology		Creatinine	0.61 mg/dL	Anti-TBGL antibody	1.8 U/mL
White blood cells	8,200 / μ L	Na	139 mEq/L	Anti-mycobacteria antibody	(-)
Neutrophils	64.8 %	K	4.5 mEq/L	β -D glucan	1 pg/mL
Monocytes	2.9 %	Cl	104 mEq/L		
Eosinophils	1.2 %	Ca	9.9 mg/dL	Pleural fluid (right)	
Lymphocytes	30.7 %	Serology		pH	7.2
Red blood cells	562 \times 10 ⁴ / μ L	C-reactive protein	0.04 mg/dL	Cell	2,600 / μ L
Hemoglobin	15.9 g/dL	Anti-nuclear antibody	(-)	Neutrophils	3 %
Hematocrit	47.7 %	Rheumatoid factor	2 IU/mL	Eosinophils	2 %
Platelets	23.1 \times 10 ⁴ / μ L	Anti-SSA antibody	(-)	Lymphocytes	41 %
Biochemistry		Anti-SSB antibody	(-)	Macrophages	54 %
Total protein	8.1 g/dL	IgG	1,797 mg/dL	Adenosine deaminase	28.8 U/L
Albumin	4.8 g/dL	IgA	170 mg/dL	Protein	5.2 g/dL
Total bilirubin	0.46 mg/dL	IgM	149 mg/dL	Glucose	95 mg/dL
AST	17 IU/L	IgE	57 IU/mL	Lactase dehydrogenase	271 IU/L
ALT	12 IU/L	CA125	149.8 U/mL	Triglyceride	2,507 mg/dL
γ -GTP	13 IU/L	ACE	29.1 U/L	Total cholesterol	85 mg/dL
LDH	172 IU/L	VEGF-D	5,280.9 pg/mL	CEA	1.5 ng/mL
CPK	86 IU/L	Infection		CYFRA	7.2 ng/mL
Glucose	91 mg/dL	HB surface antigen	(+)	ProGRP	24.4 pg/mL
Urea nitrogen	18.6 mg/dL	HBV-DNA	<2.1 Log copy/mL	cytology	negative

Anti-SSA antibody: antiSjögren's syndrome A antibody, Anti-SSB antibody: antiSjögren's syndrome B antibody, CA125: cancer antigen 125 (normal, \leq 35.0 U/mL), ACE: angiotensin I converting enzyme (normal, 8.3-21.4 U/L), VEGF: vascular endothelial growth factor (cut off level, 800 pg/mL), HBV: hepatitis B virus, TBGL: tuberculous glycolipids, CEA: carcinoembryonic antigen, CYFRA: cytokeratin fragment, ProGRP: pro-gastrin releasing peptide

in patients who are hepatitis B virus (HBV) carriers (8). According to the hepatitis B guideline: "When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to HbsAg-positive inactive carriers on pretreatment screening tests, nucleoside analogue therapy should be commenced without delay" (9).

However, there are no written reports regarding the efficacy and safety of such treatments in patients with both LAM and HBV. This is the first report of a LAM patient with HBV being successfully and safely treated with sirolimus after HBV DNA was brought under the cut-off level using entecavir.

Case Report

A 34-year-old woman suffered from shortness of breath for 4 years. Findings from HRCT of her chest in response to a bacterial pneumonia infection suggested that she might have LAM. She was referred to our institution for a further evaluation in February 2014. The patient was an ex-smoker who had had a 4-packs/year habit until 24 years of age.

On a physical examination, her blood pressure was 113/80 mmHg, heart rate was 82 beats/min, O₂ saturation was 90% under room air-conditioning, and her breathing sounds were normal. The initial laboratory evaluation revealed elevated serum levels of cancer antigen 125 (CA125) (149.8 U/mL; normal, \leq 35.0 U/mL), angiotensin-converting enzyme (ACE) (29.1 U/L; normal, 8.3-21.4 U/L), and VEGF-D (5,280.9 pg/mL; cut-off value, 800 pg/mL) (Table). Right-sided pleural fluid was observed on chest X-ray (CXR)

(Fig. 1a), and HRCT of the chest showed bilateral diffuse multiple thin-walled cysts (Fig. 1d and e), as well as nodular shadows and consolidations suspected to indicate infectious disease (suspected nontuberculous mycobacterial infection) in the right middle lobe (Fig. 1e). Pleural fluid obtained from the right pleural cavity was salmon pink-colored and proved to be chylous: triglyceride levels in the pleural fluid were elevated to 2,507 mg/dL (normal, <110 mg/dL), cholesterol was within the normal range at 85 mg/dL, and the pleural/plasma cholesterol concentration ratio was <1.0 (10, 11). Fiberoptic bronchoscopy was performed to identify the infectious disease and to obtain a pathological diagnosis. No pathogenic organisms were detected in bronchial lavage recovered from the right middle lobe. Transbronchial lung biopsy (TBLB) specimens showed LAM cells in the form of round, oval, or spindle-shaped cells growing in haphazardly arranged bundles in the thickened pulmonary interstitium (LAM cell nests; Fig. 2a and b). An immunohistochemical examination showed the LAM cells to be positive for SMA (Fig. 2c), ER, PgR, and HMB-45 (Fig. 2d). Abdominal and pelvic magnetic resonance imaging (MRI) revealed huge-sized lymphangioliomyomas in the para-aortic region and the interior of the pelvic cavity (26 \times 19 \times 8 cm), without any indication of the presence of renal angiomyolipoma (AML) (Fig. 3a). The patient was diagnosed with LAM based on these clinical, radiological, and pathological findings in July 2014.

The patient required long-term oxygen therapy (LTOT) in response to dyspnea and hypoxemia arising from the chylorhax and bilateral lung disease. Despite the application of

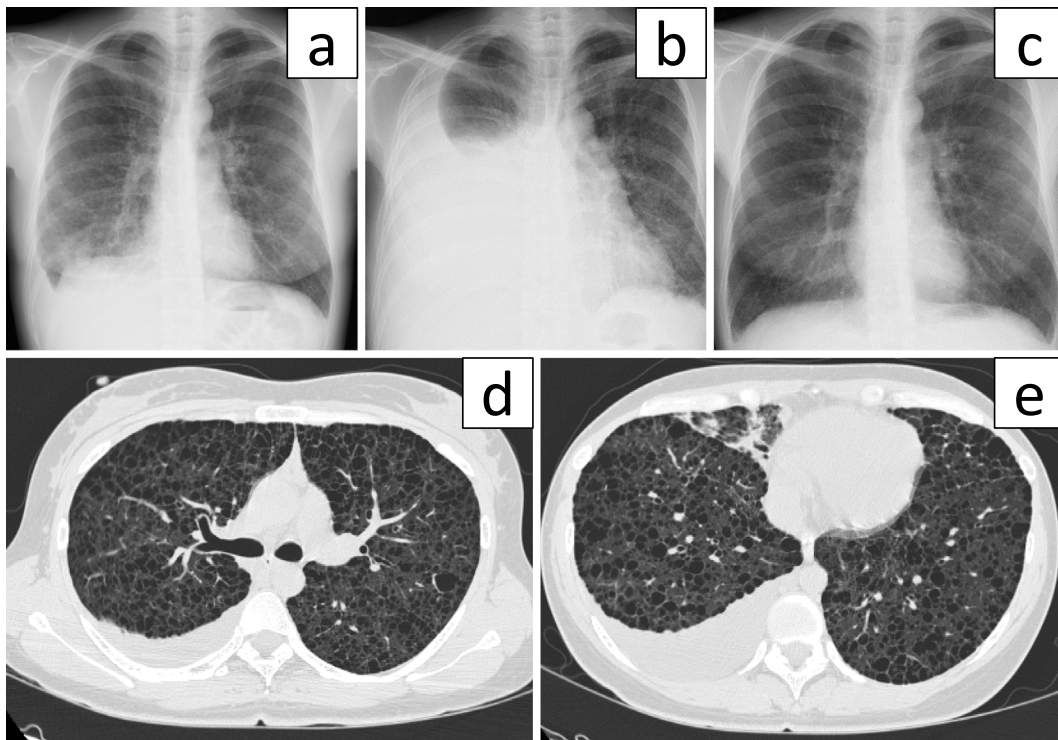


Figure 1. Chest X-ray at the first visit shows a small, right-sided pleural effusion (a). The massive right-sided pleural effusion persisted on chest X-ray obtained before sirolimus treatment (b) but disappeared after six months of sirolimus treatment (c). HRCT of the chest at the first visit shows bilateral, diffuse, multiple, thin-walled cysts with right-sided pleural effusion (d, e) and consolidation in the right middle lobe (e).

low-fat diet therapy and the administration of leuporelin acetate (a luteinizing hormone-releasing hormone analog; 1.88 mg six times every 4 weeks via hypodermic injection), frequent pleural drainage was required to control the right massive chylous effusion (Fig. 1b). Serologies revealed that the patient was hepatitis B surface antigen (HBsAg)-positive, surface antibody (anti-HBs)-negative, core antibody (anti-HBc)-positive, IgM antibody to hepatitis B core antigen (anti-HBc IgM)-negative, envelope antigen (HBeAg)-negative, and envelope antibody (anti-HBe)-positive with a hepatitis B PCR viral load of <2.1 Log copies/mL. She had no transfusion history, family history, or vaccination history. There were no findings suggestive of liver disease on CT or MRI.

Oral sirolimus treatment (1 mg per day) was started from February 2015 after the hepatitis B polymerase chain reaction viral load dropped below 2.1 Log copies/mL due to the oral administration of entecavir (0.5 mg/day) according to the guideline (9). We regularly monitored HBsAg and HBV-DNA out of concern regarding HBV reactivation in response to the sirolimus treatment. The HBs antigen continued to be positive after the start of sirolimus, and HBV-DNA was undetected. In addition, we feared that the pulmonary infections with nodular shadows and consolidations in the right middle lobe (Fig. 4) might worsen, so we monitored the patient for any respiratory symptoms, such as coughing and sputum, as well as checked the white blood cell count and

C-reactive protein value through blood tests, CXR, and sputum examinations. Although the trough sirolimus concentrations was <5 ng/mL (dose of sirolimus 1 mg/day), the chylous fluid of the right pleural cavity resolved completely within 6 months of sirolimus treatment (Fig. 1c), and LTOT was discontinued. The large lymphangioleiomyoma in the para-aortic region and the interior of the pelvis were dramatically reduced in size (Fig. 3b). The sole adverse effect of the sirolimus treatment was mild stomatitis, which did not require any drug treatment.

While this sirolimus treatment at a dosage of 1 mg per day was effective, we increased the dose of sirolimus to 2 mg per day from August 2015, as the trough level in blood during the administration of sirolimus 1 mg daily was 3.4 ng/mL (<5.0 ng/mL), the standard dose of sirolimus was 2 mg daily, and we believed that an even higher dose of sirolimus would be more effective. The stomatitis remained stable and mild. After the dosage of sirolimus was increased, HBV-DNA was not detected, and HBV did not reactivate for 2.5 years.

Discussion

mTOR inhibitors, such as sirolimus and everolimus, block the mTOR-mediated activation of downstream kinases and restore homeostasis in cells with a defective TSC gene function (12). mTOR inhibitors have also been shown to de-

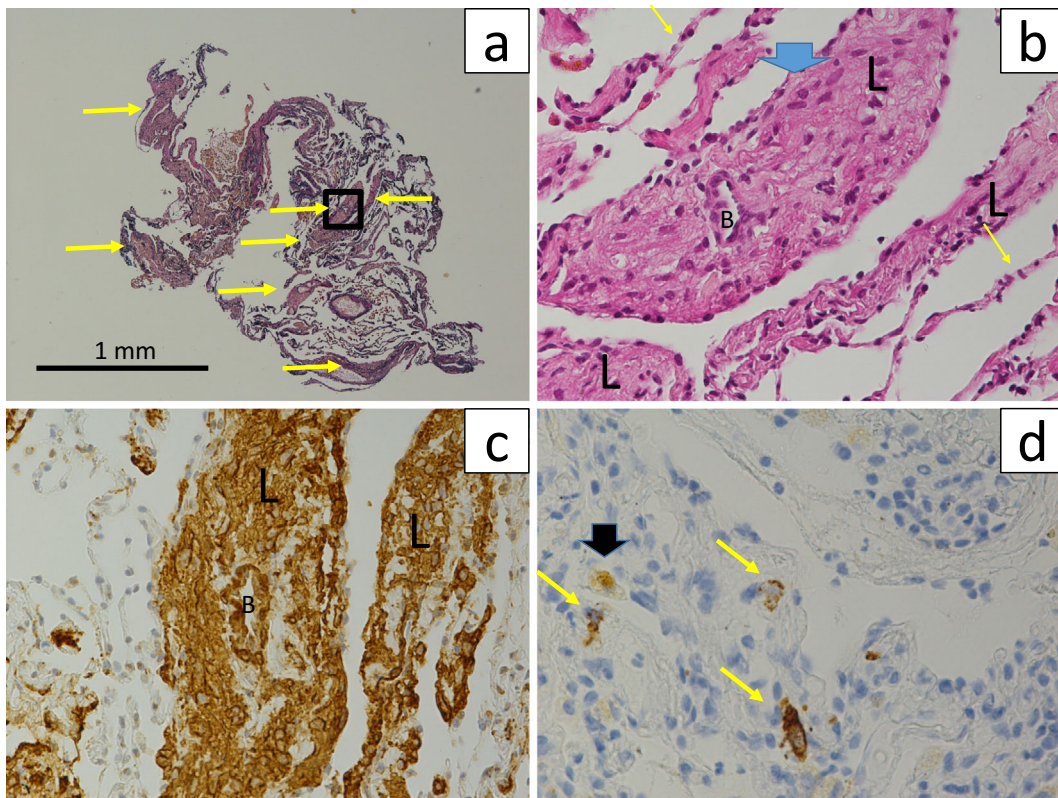


Figure 2. Transbronchial lung biopsy specimens were taken from (1, 2) the right upper lobe (rtB2b, rtB3a) and (3, 4) the right lower lobe (rtB8a). Lung specimens of (2-4) revealed lymphangiomyomatosis (LAM) cell nests in the lung interstitium. (a-d) Histological and immunohistological findings of (4) the right lower lobe (rtB8a). (a) An elastic tissue stain of the lung tissue measuring 2.6×2 mm revealed 7 foci of LAM cell nests in the lung interstitium (arrowhead), including the adventitia of small blood vessels measuring up to 650×100 μ m (left upper corner). The lung specimen revealed LAM cell nests in approximately 10% of the lung tissue, while about 50% of the alveolar walls remained normal with a thickness measuring 1-2.5 μ m in width. (Weigert's elastic van Gieson stain; \times 4; Bar=1 mm). (b) A higher magnification of the rectangular area of (a). Three foci of LAM cell nests (L) were observed in the lung interstitium. One LAM cell nest measuring 310×90 μ m formed around a small blood vessel (B) measuring 30×45 μ m. The LAM cells had nuclei measuring 12×3 μ m, 19×3 μ m, 10×4 μ m, etc. The LAM cells had one or two nucleoli (the LAM cell indicated by an arrow has two nucleoli) and eosinophilic cytoplasm with indistinct cell borders. Normal alveolar walls are indicated with arrows (Meyer's Hematoxylin and Eosin staining; \times 60). (c) Three LAM cell nests were positive for alpha-smooth muscle actin (alpha-smooth muscle actin stain; \times 40). (d) Human Melanoma Black-45 (HMB-45) stain revealed three positive cells in a high-power field of view of the LAM cell nest with positive brown granules in the cytoplasm of LAM cells (thin arrows; HMB-45 stain; \times 60). Estrogen receptor (ER) stain was positive for the nucleus of 2-6 LAM cells in a high-power field of view (\times 40; data not shown). Progesterone receptor (PgR) stain was positive for the nucleus of seven LAM cells in a high-power field of view (\times 40; data not shown). Brown pigmented hemosiderin granules measuring 1-3 μ m in diameter were observed in the cytoplasm of an alveolar macrophage (thick arrow). These hemosiderin granules were stained blue with Prussian blue stain (not shown).

crease the size of AML (13) and stabilize the lung function in patients with LAM (7). The Multicenter International LAM Efficacy of Sirolimus (MILES) trial showed that sirolimus stabilizes the lung function and improves the quality of life in patients with LAM. The trial involved two-stages of sirolimus treatment for 89 patients with LAM who had moderate lung function impairment and a 12-month randomized, double-blind comparison of sirolimus with placebo, followed by a 12-month observation period. The blood

trough sirolimus levels were maintained at 5-15 ng/mL (7), although there was no evidence of the ideal range of sirolimus concentration. The Multicenter Lymphangiomyomatosis Sirolimus Trial for Safety (MLSTS) conducted in Japan showed that long-term sirolimus treatment of Asian patients with LAM was associated with a large number of adverse events, including three episodes of pneumonitis. However, most patients completed the two-year course of medication with good drug compliance and a stable quality

of life and lung function.

HBV reactivation can lead to clinically apparent acute hepatitis, which can be severe and result in acute liver failure and death. The mortality rate associated with fulminant hepatitis was significantly higher among patients with HBV reactivation than among those with acute HBV infection (14). Inhibition of mTOR can also block interleukin (IL)-2 signaling, which induces T cell growth and suppresses the Th1-cell function (15). Teng et al. reported that therapy using mTOR inhibitors for hepatocellular carcinomas may activate HBV replication in patients with chronic HBV infection (16). DeFilippis et al. (17) reported that a patient being treated with octreotide and sirolimus in response to an islet cell tumor developed hepatitis B reactivation, leading to fulminant liver failure and death. Additional reports have described cases in which patients being treated with everolimus in response to renal cell carcinoma developed hepatitis B reactivation with liver failure (18, 19). Lubel et al. stated that the prevention of HBV reactivation must be considered during immunosuppressive therapy or chemotherapy (8). The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines recom-

mend that HBsAg-positive candidates for chemotherapy and immunosuppressive therapy undergo preemptive nucleoside analogue administration during therapy and for 12 months after the cessation of therapy (20). In our case, the patient was an inactive HBV carrier who took entecavir. She started sirolimus after HBV was confirmed to be below the cut-off. HBV reactivation did not occur, and her symptoms improved.

In our case, a low sirolimus dose (1 mg/day) was selected because we were concerned about the possibility of HBV reactivation. After commencing sirolimus treatment, even at a blood trough level of <5 ng/mL, the chylothorax disappeared completely, and the extrapulmonary lymphangiomyoma decreased within six months (Fig. 3). Ohara reported a case in which sirolimus (1 mg/day) treatment improved both persistent chylous pleural and peritoneal effusions in a 32-year-old woman with LAM who underwent living donor lung transplantation (21). Ando et al. reported the results of a careful review of Japanese patients with LAM who were treated with a low dose of sirolimus at a trough level of ≤ 5 ng/mL (22). These studies provide clear evidence of an improved or stabilized pulmonary function (FVC and FEV₁) and decreased chylothorax (22). This supports the notion that even at a blood trough level of <5 ng/mL, sirolimus may be clinically useful and effective from the viewpoints of clinical safety and cost.

The clinical course of this patient provided three important clinical suggestions. First, an HBV carrier with LAM can safely follow a regiment of 1 or 2 mg (regular dose) of sirolimus daily, so long as HBV reactivation is suppressed by the administration of entecavir. Second, low-dose sirolimus (1 mg per day) was effective because her dyspnea improved, the chylous effusions resolved completely, and the large lymphangiomyoma in the para-aortic region and interior of the pelvis shrank in size. Third, possible infectious diseases suggested by CT findings (right middle lobe) should be examined in order to rule out active infection by bronchoscopy prior to sirolimus treatment.

The authors state that they have no Conflict of Interest (COI).

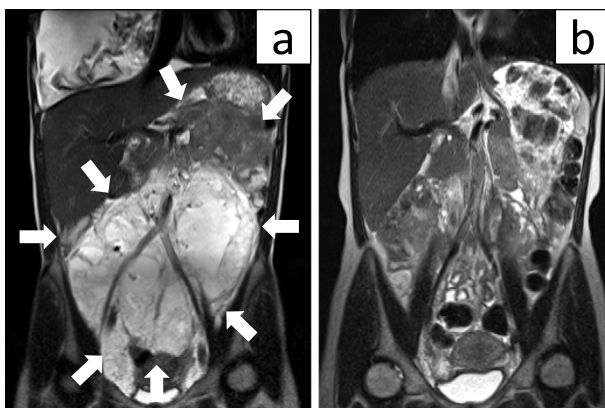


Figure 3. Abdominal and pelvic MRI shows huge lymphangiomyomas in the para-aortic area and interior of the pelvis before sirolimus treatment (a). The large lymphangiomyomas in the para-aortic area and interior of the pelvis were reduced in size after six months of sirolimus treatment (b).

2014 Jan.	Jul.	2015 Jan.	Jul.	2016 Jan.	Jul.	2017 Jan.	Jul.
Long-term oxygen therapy (LTOT)							
Entecavir (0.5 mg/day, oral)							
sirolimus							
every 4 weeks							
Leuprorelin 1.88mg		1mg		2mg			
Sirolimus trough level (ng/mL)			3.4	4.6		5.6	
AST (IU/L)		17	19	13	14	18	15
ALT (IU/L)		12	12	11	11	21	13
VEGF-D (pg/mL)		4,910	3,114	2,740	2,321		4,731
FVC (mL)		1,980	3,020	2,970	3,030		3,140
FEV ₁ (mL)		1,350	2,850	2,680	2,710		2,420

Figure 4. Clinical course of the patient.

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