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CHYLOPERITONEUM, CHYLOTHORAX AND LOWER EXTREMITY LYMPHEDEMA IN WOMAN WITH SPORADIC LYMPHANGIOLEIOMYOMATOSIS SUCCESSFULLY TREATED WITH SIROLIMUS: A CASE REPORT

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare disease characterized by diffuse thin-walled cysts throughout the lungs on computed tomography and diffuse proliferation of abnormal smooth muscle-like cells (LAM cells) on lung biopsy. LAM affects women almost exclusively, predominantly in their reproductive age. The most typical presenting symptoms include dyspnea, spontaneous pneumothorax, cough and chylothorax. Abdominal findings represent less common initial manifestations of the disease and may pose diagnostic difficulties. The treatment of LAM has not been fully established. Recent studies report effectiveness of sirolimus in LAM patients.

We report the case of a 45-year-old woman with sporadic LAM, successfully treated with sirolimus, in whom the first manifestation of the disease was chyloperitoneum and after three and nine years, respectively, lymphedema of the left lower extremity and right sided chylothorax occurred.

Keywords: lymphangioleiomyomatosis, sirolimus, chyloperitoneum, chylothorax, lymphedema, lung cysts, LAM cells, lymphscintigraphy

Lymphangioleiomyomatosis (LAM) is characterized by the proliferation of abnormal smooth muscle-like cells (LAM cells) and LAM-associated lymphangiogenesis in the lungs, axial lymph nodes and various abdominal organs (1,2). It is classified as a malignant neoplastic disease belonging to the family of neoplasms with perivascular epithelioid cell differentiation (3). LAM affects women almost exclusively, predominantly in their childbearing and occasionally at postmenopausal age. LAM occurs sporadically, with a prevalence of about 1 per million, and also in 40% of patients with tuberous sclerosis complex (TSC) (1).

Clinical course of sporadic LAM is dominated by pulmonary manifestations. Dyspnea, spontaneous pneumothorax, cough, chest pain and chylothorax are the most common symptoms (4,5). The destructive lung process is progressive and leads to respiratory failure and death unless lung transplantation is performed (1). Abdominal findings, such as renal angiomyolipomas, enlarged abdominal lymph nodes, lymphangioleiomyomas or chylous ascites occur in the course of disease in the majority of patients (4,6). However, if these are the first manifestations of the disease, they may pose diagnostic difficulties.

Treatment of LAM has not been fully established. Although progesterone has been the most commonly used treatment, its efficacy has not been sufficiently demonstrated (7). Etiology of LAM is linked to acquired mutation of the TSC (tuberous sclerosis complex) genes, typically TSC2 gene (8). Deficiency of the TSC2 tumor suppressor gene leads to inappropriate activation of mammalian target of the rapamycin (mTOR) signaling causing uncontrolled proliferation of LAM cells. This observation has led to the use of sirolimus, which specifically blocks the mTOR pathway. Recent studies have provided evidence of the ability of sirolimus to reduce angiomyolipoma volume and improve lung function in LAM patients (9-11).

Here we describe the case of a 45-year-old woman with sporadic LAM, successfully treated with sirolimus, in whom the first manifestation of the disease was chyloperitoneum and after three and nine years, respectively, lymphedema of left lower extremity and right side chylothorax occurred.

CASE HISTORY

A 45-year-old woman was admitted to our hospital for diagnosis and treatment of recurrent chyloperitoneum and chylothorax. She had a history of progressive dyspnea and frequent cough for one month, chyloperitoneum for ten years, slight swelling of left lower extremity for seven years and trace right pleural effusion for one year. The patient had an exploratory laparotomy performed twice, with no abnormalities found other than chylous ascites ten years ago and right ovarian follicular cyst excision two years ago. Paracentesis perfomed ten years ago proved that abdominal fluid was chylous. The patient was still menstruating and had been a lifelong nonsmoker. Her family history was negative for TSC, pneumothorax or pleural effusion.

Physical examination on admission revealed dullness to percussion and decreased respiratory sounds over the lower right lung

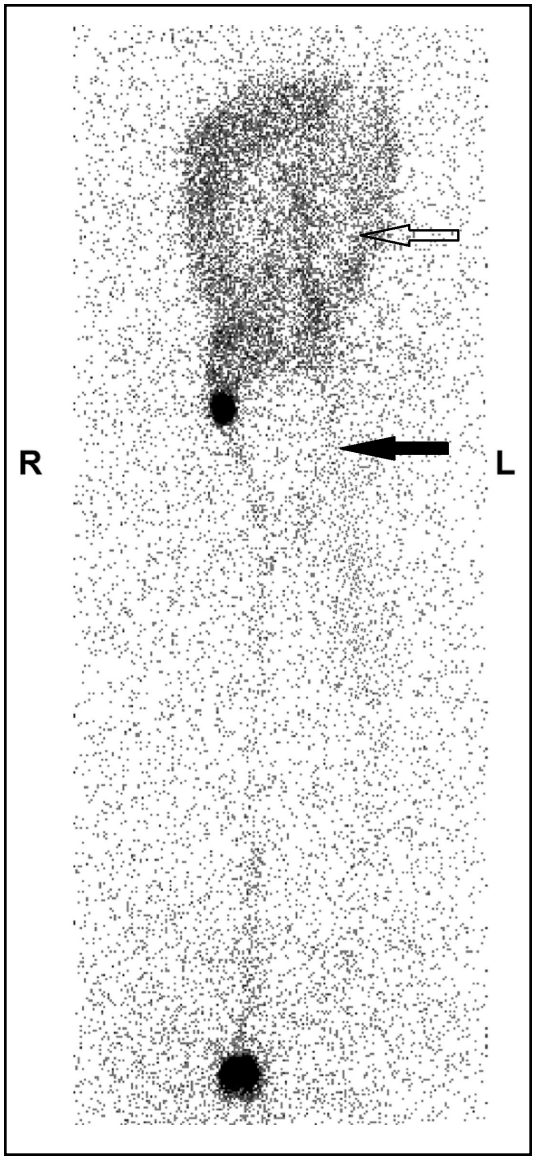

Fig.1. Right lower extremity lymphoscintigram revealing peritoneal effusion and reflux of the radiotracer into the left lower extremity.

to the 6th rib and slight edema of the lower left limb.

Routine laboratory tests revealed only elevated D-dimer level (4250 ng/ml). Chest X-ray revealed right pleural effusion up to the level of the 6th rib. Chest computed tomography (CT) demonstrated bilateral

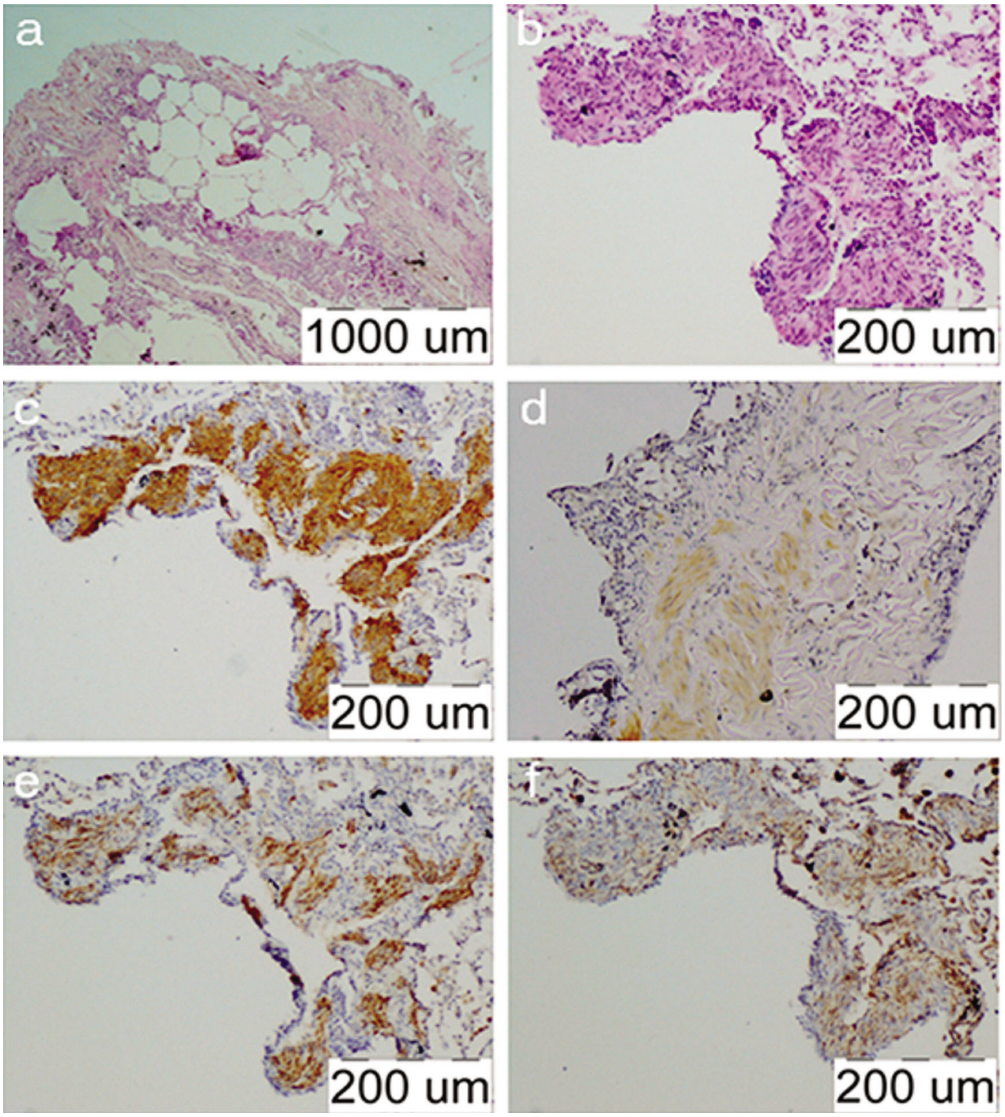

Fig. 2. Histopathological findings in the LAM lesions in the lung. a, b: hematoxylin and eosin staining showing emphysematous changes (a) and interstitial infiltration of cells resembling smooth muscle cells arranged in bundles (b); c-f: positive immunohistochemical staining of LAM cells for SMA (c), HMB45 (d), desmin (e) and vimentin (f).

diffuse multiple cystic lesions in the lung fields with a maximal diameter of 18 mm (central emphysema). Thoracentesis revealed chylous fluid (1600 ml), and spirometry performed after thoracentesis showed restrictive pulmonary function: forced vital capacity (FVC) 66% of predicted, forced expiratory volume in 1 second (FEV1) 54% of predicted and FEV1/FVC ratio 89% of predicted. Echocardiography showed slightly increased amount of pericardial fluid over physiological limit. Abdominal and pelvic CT did not reveal any other abdominal abnormalities than ascites. 99mTc-Nanocoll lymphoscintigraphy of the lower limbs demonstrated diffuse shadowing within the abdominal cavity reflecting the presence of chyloperitoneum and slight tracer backflow

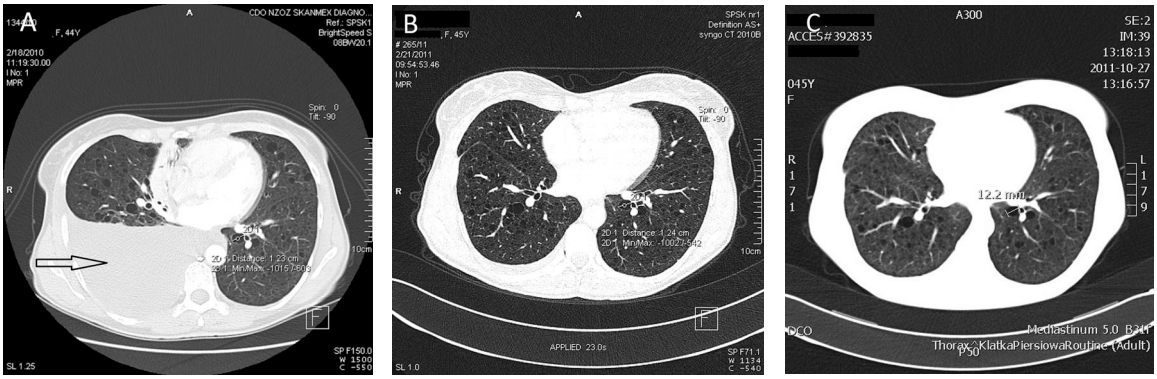

Fig. 3. Chest CT before treatment (A), 12 months (B) and 20 months (C) after treatment with sirolimus. The number and diameter of emphysematous blebs is not changed. Pleural effusion visible in panel A (arrow) disappeared during the treatment.

to the left lower extremity (*Fig. 1*). CT of the brain ruled out tuberous sclerosis changes.

Histopathologic study of the lung specimen taken during the right open lung biopsy demonstrated features of emphysema, numerous hemosiderin-laden macrophages and interstitial infiltration of cells resembling smooth muscle cells arranged in bundles. Immunohistochemical staining revealed that interstitial cells were positive for smooth muscle actin (SMA), HMB45, desmin, and vimentin (*Fig. 2*). This finding was consistent with the diagnosis of pulmonary LAM.

Based on previous reports (10,11), sirolimus was administered to the patient. The patient received 1-2 mg of sirolimus daily under control of the sirolimus blood level (between 6-12 ng/ml). Treatment was well tolerated, and no adverse reactions were observed. After a year of sirolimus therapy, the physical examination revealed only slight lymphedema around the left ankle joint. Chest CT did not reveal pleural effusion or progression of cystic lesions, spirometry showed normal pulmonary function, and abdominal ultrasound demonstrated a significantly smaller amount of abdominal fluid (*Fig. 3*).

DISCUSSION

The first manifestation of LAM in our patient was chylous ascites, which is exceptional. To our knowledge, chylous ascites as a first sign of LAM has been reported only by Yamashita et al and by Ryu et al (12,13). Simultaneous occurrence of chylothorax and chyloperitoneum is also quite rare and occurs in 1.8-8.6% of patients with LAM (4,6,14).

Chylous acites in the course of LAM has been estimated in recent reports as approximately 10% incidence (4,6), chylothorax – approximately 25% (4,15) and pericardial effusion – 6% (4). The pericardial effusion typically does not cause cardiac tamponade and is detected only by special imaging (4). There has been no previous report of lymphedema of the extremities in any LAM patient.

The mechanism of chylous effusions in LAM is thought to be chyle leak secondary to proximal lymphatic vascular occlusion due to proliferating LAM cells, rupture of distended collateral lymphatic vessels, and/or oozing from pleural lymphatics and collateral lymphatics (13). In some cases, chylothorax may be the consequence of transdiaphragmatic flow of chylous ascites (13,14). Lymphedema of the lower extremity in our patient was the result of retrograde chylous reflux into the leg.

Recognizing insufficient proof of efficacy, the European Respiratory Society in 2010 has recommended prudent prescription of sirolimus in LAM patients, such as after rapid decline in lung function or increasing

symptoms (7). After careful evaluation of risk/benefit ratio, we administered sirolimus in our patient, with a very good effect after 20 months of therapy and without any adverse reactions. Our observations are in agreement with the results of the first randomized placebo-controlled trial of sirolimus administration in LAM published recently. The study showed that in LAM patients with moderate lung impairment, sirolimus stabilizes lung function, is associated with a reduction in symptoms and improvement in quality of life, and is not associated with an increase in serious adverse events (9).

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