Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8645-16
Intern Med 56: 3327-3331, 2017
http://internmed.jp

【 CASE REPORT 】

Additional Octreotide Therapy to Sirolimus Achieved a Decrease in Sirolimus-refractory Chylous Effusion Complicated with Lymphangioleiomyomatosis

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Abstract:
Recently, sirolimus, an inhibitor of mammalian target of rapamycin, was reported to decrease chylous effusion in patients with lymphangioleimyomatosis (LAM). We herein report a case of a 34-year-old woman with LAM who developed refractory chylothorax and chylous ascites during sirolimus therapy. In this case, to reduce chylous effusion, we administered octreotide, which is often used to control postoperative chylous effusion, in addition to the sirolimus therapy. This combination therapy reduced the chylothorax and chylous ascites. For patients with LAM, octreotide therapy in addition to sirolimus may be effective for treating sirolimus-refractory chylous effusion.

Key words: lymphangioleiomyomatosis, chylothorax, chylous ascites, octreotide, sirolimus

(Intern Med 56: 3327-3331, 2017)
(DOI: 10.2169/internalmedicine.8645-16)

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease that occurs exclusively in premenopausal women. It is characterized by the proliferation of abnormal atypical smooth muscle-like cells (LAM cells) in the lungs and axial lymphatic system. This proliferation of smooth muscle-like cells is reported to be due to the activation of mammalian target of rapamycin (mTOR) caused by mutations in the *tuberous sclerosis complex 1* (*TSC1*) or *TSC2* genes (1). LAM patients present with polycystic lung destruction, renal angiomyolipomas and abdominal lymphangioleiomyomas. In addition, chylothorax and chylous ascites occur in approximately 12% and 7% of LAM patients, respectively (2). Such chylous effusion is often refractory to medical and surgical management (3).

Recently, the mTOR inhibitor sirolimus, which has been shown to stabilize the lung function in LAM patients (4), was reported to be effective in decreasing chylous effusion (3, 5-7). However, there are a few LAM patients whose chylous effusion is refractory to sirolimus therapy. An appropriate therapeutic strategy has yet to be established for such cases.

We herein report a LAM patient with sirolimus-refractory chylous effusion in whom the effusion was ameliorated by adding octreotide to the sirolimus therapy.

Case Report

A 34-year-old woman presented with left femur edema at a local hospital. Computed tomography (CT) showed multiple thin-walled cysts scattered throughout both lung fields, a left retroperitoneal tumor and periaortic lymphadenopathy in April 2012 (Fig. 1A). A CT-guided needle biopsy of the retroperitoneal tumor revealed the proliferation of LAM cells. Based on these observations, the patient was diagnosed with LAM. Her retroperitoneal tumor and lymphade-

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Received: December 2, 2016; Accepted: April 17, 2017; Advance Publication by J-STAGE: October 11, 2017
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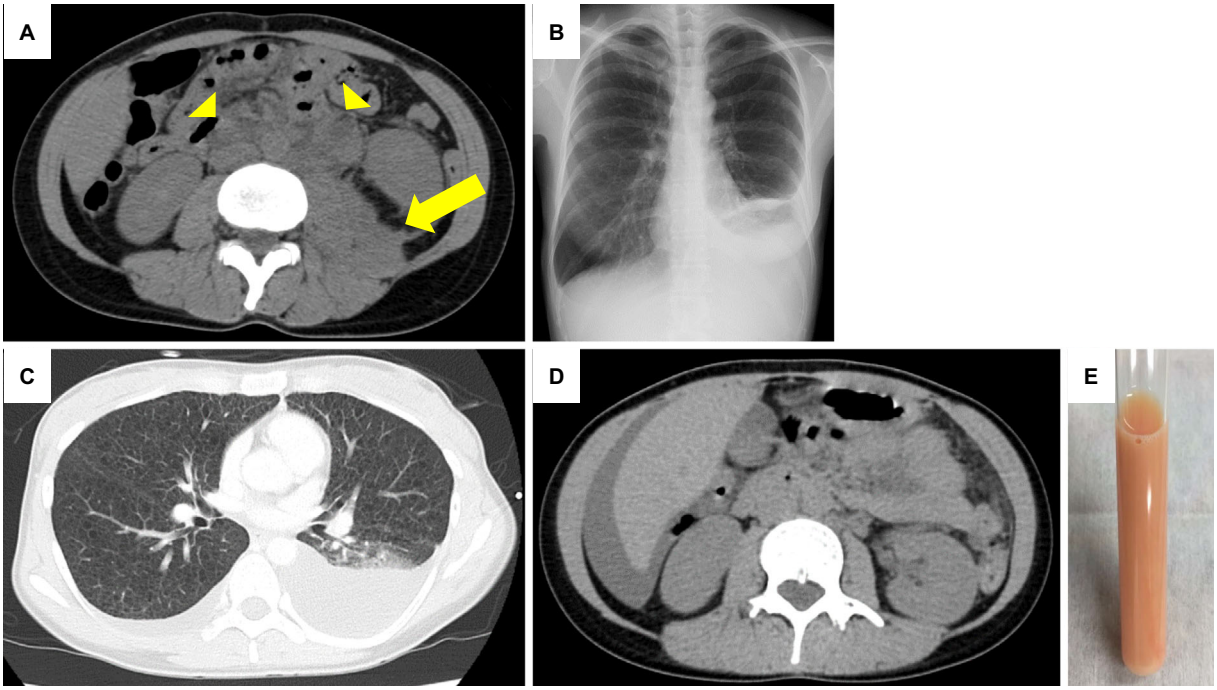

Figure 1. **Radiologic findings of the abdomen (A and D) and chest (B and C). (A) Computed tomography (CT) of the abdomen in April 2012 showed left retroperitoneal solid tumor (arrow) and periaortic lymphadenopathy (arrow head). (B) Chest radiography in January 2015 demonstrated left-sided pleural effusion, and (C) Chest CT showed multiple thin-walled cysts in the both lung fields and bilateral asymmetry pleural effusion, superior to left side. (D) Abdominal CT in January 2015 showed regression of retroperitoneal tumor and lymphadenopathy, whereas ascites emerged. (E) Appearance of the pleural effusion was pale yellow-brown, cloudy.**

nopathy spontaneously decreased in 2 years, and the femur edema also subsided. From July 2013, slight ascites was observed on CT, but the patient did not receive any treatment due to a lack of symptoms.

In January 2015, the patient was admitted to our hospital complaining of dyspnea due to left chylothorax. The oxygen saturation of her peripheral artery was 90% (room air), and a chest examination revealed decreased breath sounds on the left side. A lung function evaluation showed a forced expiratory volume in 1 second (FEV_1) of 0.86 L (31.3% predicted), forced vital capacity (FVC) of 2.03 L (64.4% predicted) and a diffusing capacity of the lung for carbon monoxide (DLCO) of 4.55 mL/min/mmHg (19.6% predicted). Chest radiography demonstrated left-sided pleural effusion (Fig. 1B), and chest CT showed multiple thin-walled cysts in both lung fields, with bilateral asymmetry pleural effusion superior to the left side (Fig. 1C). Abdominal CT revealed ascites (Fig. 1D). Thoracentesis yielded a pale, yellow-brown, cloudy chylous effusion with a triglyceride level of 1,168 mg/dL (Fig. 1E). To ameliorate the chylous effusion, treatment with 2 mg of sirolimus daily and a fat-restricted diet was started. The dose of sirolimus was increased to 3 mg to achieve serum levels between 5 and 15 ng/mL. On day 16 after admission, she was discharged because her dyspnea had improved. Chest radiography showed that the volume of chylothorax had decreased on day 25 after the initiation of sirolimus therapy. However, one month later, she complained of abdominal distension due to chylous ascites. We performed abdominal paracentesis once a month to ameliorate her abdominal distension. Pleural effusion began to accumulate again in January 2016 (Fig. 2A).

She was admitted to our hospital again in February 2016. A physical examination revealed that her body weight was 48.5 kg (43.3 kg in January 2015), and her waist circumference was 85 cm. The multiple cystic lesions in her lungs had not worsened, as shown on a chest CT. However, abdominal CT revealed massive ascites with no tumor or lymphadenopathy (Fig. 2B).

After admission, she was subcutaneously injected with 100 μg of octreotide daily in addition to the sirolimus therapy. Since there were no adverse effects, the dose and administration route were changed to an intramuscular injection of 40 mg every 4 weeks. Chest radiograph showed decreased chylothorax on day 7, and the patient was discharged on day 12 after admission. On day 62, the chylothorax and chylous ascites showed marked amelioration (Fig. 3). Her body weight and waist circumference had also decreased to 45.5 kg and 76 cm, respectively. Improvement in the lung function was observed based on the FEV_1 (1.38 L), FVC (2.52 L) and DLCO (6.59 mL/min/mmHg) values. The patient has continued the sirolimus and octreotide treatments with no increase in chylous effusions and no adverse effects for six months.

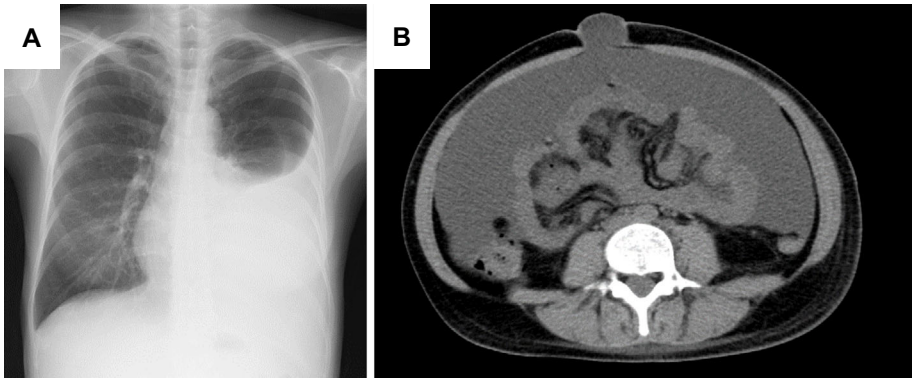

Figure 2. **(A) Chest radiograph in February 2016 showed massive left-sided pleural effusion, and (B) abdominal CT showed massive ascites and the protruding navel.**

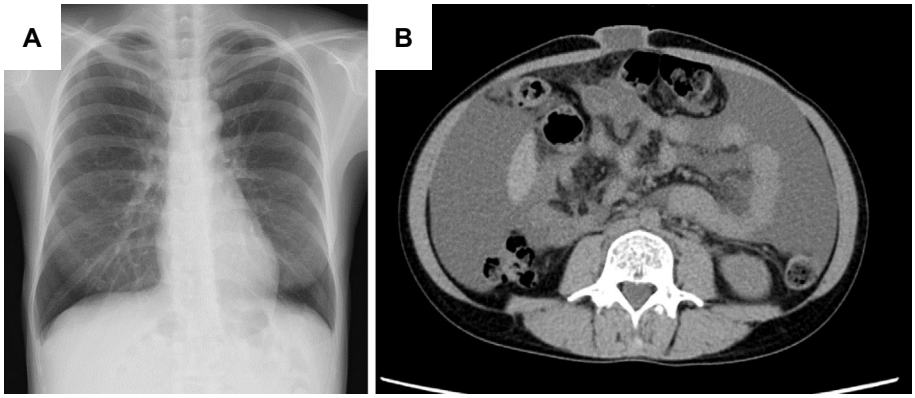

Figure 3. **(A) Chest radiograph in April 2016 showed the disappearance of pleural effusion, and (B) abdominal CT showed ascites decreased and protruding navel improved.**

Discussion

Sirolimus was recently reported to reduce refractory chylothorax and chylous ascites in patients with LAM (3, 5-7). However, in our case, chylous effusion developed during sirolimus therapy. This effusion was ameliorated by the administration of octreotide, a somatostatin analog peptide, in addition to sirolimus.

Chylous effusion in patients with LAM is believed to occur due to lymph duct obstruction and destruction by proliferating LAM cells (8). Since sirolimus inhibits the proliferation of LAM cells (9), it is also expected to reduce chylous effusion. Indeed, some reports have shown that chylous effusion was ameliorated by sirolimus (3, 5-7). In the present case, the patient's lung function was improved a year after the start of sirolimus administration compared with that before the treatment, and multiple thin-walled cysts in both lung fields had not worsened on CT. However, we were able to control the chylous effusion by treatment with sirolimus for only two months. We reasoned that lymph flow might have been improved by a reduction in the size of the LAM lesions by sirolimus, but that sirolimus could not control the leakage of the effusion from the lymph duct fistula formed by the pre-existing LAM lesions.

An appropriate therapeutic strategy has yet to be established for sirolimus-refractory chylous effusion in patients with LAM. At present, two approaches to treating such effusion have been reported. One is non-invasive and involves a fat-restricted diet, hormone therapy and octreotide. The other is invasive and involves pleural/peritoneal drainage, pleurodesis, ligation of the thoracic duct, peritoneovenous shunting (10, 11) and cell-free concentrated ascites reinfusion therapy (CART) (12, 13). It is generally thought that we should initially employ a non-invasive approach, especially a fat-restricted diet. In the present case, a fat-restricted diet was started, but the patient was unable to adhere to the diet because she could not inhibit her appetite. Therefore, hormone therapy was considered. However, similar to sirolimus treatment, the purpose of this therapy is to suppress the proliferation of LAM cells, not to resolve chylous effusion. We therefore did not select this therapy. We ultimately selected a combination of octreotide and sirolimus therapy in our attempts to ameliorate the chylous effusion.

Octreotide is a somatostatin analog peptide that activates somatostatin receptors and suppresses the release of gastrointestinal hormones and exocrine secretions of the stomach, pancreas and liver. Through this effect, octreotide suppresses fat absorption from the gastrointestinal tract and decreases the lymph flow. In addition, octreotide affects the smooth

muscle constriction of vascular and lymph ducts, thereby reducing the leakage of lymph fluid to the thoracic and abdominal cavities (14). Indeed, several reports have shown that octreotide ameliorated postoperative chylous effusion (15-17). In one patient with LAM, octreotide was reported to exert a temporary effect on ameliorating chylothorax (13). However, other reports have found that octreotide monotherapy was not effective in ameliorating chylous effusion (3, 7, 11, 18). In the present case, combination therapy of octreotide, which decreases the lymph flow, and sirolimus, which inhibits the proliferation of LAM cells, may have ameliorated the chylous effusion. These observations suggest that octreotide should be used to treat sirolimus-refractory chylous effusion in combination with sirolimus administration.

However, the long-term safety of octreotide therapy for LAM has not been assessed. This therapy's long-term safety in patients with acromegaly has been reported (19), but whether or not a similar safety profile would be observed for patients with LAM is unclear. Common adverse events of octreotide include diarrhea, abdominal pain, gallstone formation, and local reaction. Gallstone formation and cholecystitis have been reported as side effects of the long-term use of octreotide (20). We should therefore be alert for these adverse events when we administer octreotide to patients with LAM.

LAM is a progressive disease, although the pace of progression varies considerably among patients. However, several reports have shown that the progression of LAM was limited after menopause (21, 22), because hormonal influence to this disease. In the present case, the retroperitoneal tumor and periaortic lymphadenopathy spontaneously diminished without menopause. Although spontaneous remission has been reported as a rare phenomenon in various types of cancer and lymphoma (23, 24), there have been no reports of the spontaneous resolution of a LAM lesion in a premenopausal patient. Because we pathologically diagnosed the retroperitoneal tumor as LAM by a needle biopsy, we cannot deny the possibility that the periaortic lymphadenopathy might have been influenced by different etiologies, e. g. reactive lymphadenopathy, cancer and lymphoma rather than the progression of LAM. The mechanism underlying this spontaneous remission is unclear, so further study is necessary to reach a definitive conclusion.

In conclusion, we herein showed that octreotide therapy, in addition to sirolimus administration, ameliorated sirolimus-refractory chylous effusion. This observation suggests that combination therapy of octreotide and sirolimus may be an effective non-invasive approach to treating refractory chylous effusion in patients with LAM.

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

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