CASE REPORT

Recovery of chylous pulmonary congestion in tuberous sclerosis complex-associated lymphangioleiomyomatosis

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SUMMARY

Chyloptysis and chylous pulmonary congestion are extremely rare complications of lymphangioleiomyomatosis (LAM). We report a case of a 50-year-old woman with tuberous sclerosis complex-associated LAM, who presented with expectorating milky-white bronchial casts. She was diagnosed with chyloptysis and chylous pulmonary congestion by sputum analysis. Her symptoms and lung infiltration were improved by oral sirolimus therapy; moreover, serum Krebs von den Lungen-6 (KL-6) levels paralleled the symptoms and lung infiltration of these complications. We suggest that serum KL-6 may be a useful monitoring biomarker of chyloptysis and chylous pulmonary congestion in LAM.

BACKGROUND

Lymphangioleiomyomatosis (LAM) is a multisystem disorder characterised by the unregulated growth of smooth muscle cells through an abnormal mammalian target of rapamycin signalling pathway.¹ Clinical manifestations of LAM include cystic lung destruction, pneumothorax, chylothorax, renal angiomyolipomas, lymphadenopathy and abdominal lymphangiomyomas.¹ Chyloptysis and chylous pulmonary congestion are extremely rare complications of LAM.² We report a case of chyloptysis and chylous pulmonary congestion in tuberous sclerosis complex-associated LAM successfully treated with sirolimus.

CASE PRESENTATION

A 50-year-old non-smoking woman with tuberous sclerosis complex-associated LAM was referred to our institution for expectorating milky-white bronchial casts (figure 1). Eighteen months before initiating sirolimus therapy, she had presented with multiple parenchymal cysts and left chylothorax

(figure 2A). She underwent a surgical lung biopsy, and LAM was confirmed pathologically (figure 3A, B). Moreover, we established the diagnosis of tuberous sclerosis complex-associated LAM based on the presence of cortical tubers and non-renal hamartoma (2 cm in right hepatic lobe, 3 cm in left hepatic lobe, and 3.5 cm in pancreas head). Chylothorax was then treated with chemical pleurodesis. Six months before initiating sirolimus therapy, chest CT revealed multiple parenchymal cysts, ground-glass opacity and interlobular septal thickening (figure 2B). Sputum chemical analysis (induced using 0.9% saline for 15 min) revealed high triglyceride (540 mg/dL), cholesterol (94 mg/dL), vascular endothelial growth factor-D (VEGF-D; 4435 pg/mL) and Krebs von den Lungen-6 (KL-6; 4937 U/mL) levels. Microscopically, her sputum contained Sudan III positive materials (figure 4). Therefore, she was diagnosed with chyloptysis and chylous pulmonary congestion.

OUTCOME AND FOLLOW-UP

Five months before initiating sirolimus therapy, her clinical course improved slightly with only a low-fat diet (figure 2C) but deteriorated again 5 months later (figure 2D). Therefore, oral sirolimus therapy (1 mg/day) was initiated, and her symptoms of cough and sputum disappeared within a month. Three months after initiating sirolimus therapy, chest CT revealed complete resolution of her lung infiltration (figure 2E) and size reduction of non-renal hamartoma, but the number and size of multiple parenchymal lung cysts remained unchanged.

We measured serum levels of KL-6 and VEGF-D at the time of diagnosis of chyloptysis and chylous pulmonary congestion; KL-6 and VEGF-D levels were elevated as follows: 6216 U/mL (normal range <500) and 4211 pg/mL, respectively. Therefore, we measured serum levels of these biomarkers over time. VEGF-D levels, a disease severity biomarker of LAM, decreased after the onset of sirolimus therapy. Meanwhile, KL-6 levels paralleled the symptoms and lung infiltration of chylous pulmonary congestion (figure 5).

DISCUSSION

Chyloptysis is expectoration of milky-white sputum rich in chyle (high triglyceride and chylomicron content).² Chyloptysis and chylous pulmonary congestion in LAM are speculated to occur infrequently if the thoracic duct is obstructed by

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Figure 1 Milky-white bronchial casts.

Figure 2 Chest radiography and CT acquired at (A) 18 months before initiating sirolimus therapy reveals left pleural effusion; (B) 6 months before initiating sirolimus therapy reveals diffuse ground-grass opacity and interlobular septal thickening; (C) 5 months before initiating sirolimus therapy reveals slight resolution of lung infiltration; (D) the time of initiating sirolimus therapy reveals lung infiltration relapse and (E) 3 months after initiating sirolimus therapy reveals nearly complete resolution of lung infiltration.

abnormal proliferated smooth muscle cell.² When the peribronchial lymphatics are subjected to a circulatory overload, chyle plus lymph fluid from the lungs may herniate through the bronchial mucosa and may rupture into the bronchial lumen producing chyloptysis.² Sirolimus, an inhibitor of mammalian target of rapamycin, has been reported to stabilise lung function and decrease the volume of angiomyolipomas in LAM.^{3–4} With regard to chyloptysis and chylous pulmonary congestion in LAM, efficacy of sirolimus therapy remains unclear because only a limited number of cases have been reported.^{5–8} However, sirolimus therapy is reported to be associated with a decrease in the

size of chylous effusions, a complication that may occur by a similar mechanism.⁵ Therefore, sirolimus therapy may be quite effective for chyloptysis and chylous pulmonary congestion in LAM.

KL-6, a high molecular weight glycoprotein classified in the category of human MUC1 mucin, is expressed on alveolar type II pneumocytes and bronchiolar epithelial cells in human lungs.⁹ Serum KL-6 levels are known to reflect the severity of lung injury in various types of respiratory failure.⁹ In lung injury, serum KL-6 levels increase because of the overexpression by proliferating and regenerating type II pneumocytes and

Figure 3 (A) Nests of smooth muscle cells were found in the interstitium (H&E; original magnification, $\times 40$). (B) Proliferation of short spindle-shaped smooth muscle cells was found in an alveolar septum (H&E; original magnification, $\times 200$).

Figure 4 Sudan III positive materials in sputum.

increased alveolar–capillary permeability.^{9 10} To the best of our knowledge, this is the first case where serum KL-6 levels paralleled the symptoms and lung infiltration of chylous pulmonary congestion in LAM. In patients with LAM or multifocal micronodular pneumocyte hyperplasia, serum KL-6 levels were reported to be within reference values.¹¹ Therefore, we suggest that elevated serum KL-6 levels depend on the development of chyloptysis and chylous pulmonary congestion.

If elevated serum KL-6 levels depend on the development of chyloptysis and chylous pulmonary congestion, how do they elevate? Ohtsuki *et al*¹² reported that lymphatic vessels played very important roles for transportation of intra-alveolar KL-6 to the bloodstream. In the present case, the sputum KL-6 level (4937 U/mL) was much higher than the previously reported levels in the sputum of healthy volunteers (mean±SEM, 68±20 U/mL).¹³ Therefore, we suggest that the obstruction of

lymphatic vessels inhibits the drainage of intra-alveolar KL-6 to the bloodstream and contributes to the intra-alveolar accumulation of KL-6. KL-6 in epithelial lining fluid can also migrate according to an alveolar–vascular concentration gradient.¹⁰ Therefore, elevated serum KL-6 levels may reflect the intra-alveolar accumulation of KL-6 caused by the obstruction of lymphatic vessels. We suggest that serum KL-6 may be a useful monitoring biomarker of chyloptysis and chylous pulmonary congestion in LAM. Further accumulation of cases will be needed to clarify this hypothesis.

Learning points

- ▶ Chyloptysis and chylous pulmonary congestion are extremely rare complications of lymphangioleiomyomatosis.
- ▶ Sirolimus therapy may be quite effective for chyloptysis and chylous pulmonary congestion in lymphangioleiomyomatosis.
- ▶ Serum Krebs von den Lungen-6 can be a useful monitoring biomarker of chyloptysis and chylous pulmonary congestion in lymphangioleiomyomatosis.

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Competing interests None.

Patient consent Obtained.

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Figure 5 Serum VEGF-D levels decreased after the onset of sirolimus therapy. Meanwhile, serum KL-6 levels paralleled the symptoms and lung infiltration of chylous pulmonary congestion. Number of figures corresponds to the numbers in figure 2. KL-6, Krebs von den Lungen-6 antigen; VEGF-D, vascular endothelial growth factor-D.

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