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Title: Highly effective sirolimus therapy for abdominal lymphangioleiomyoma

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Main Text:

Pulmonary lymphangioleiomyomatosis (P-LAM) is a rare interstitial lung disease characterized by cystic lesions in the lung parenchyma. Extrapulmonary lymphangioleiomyomatosis usually affects the kidneys with the formation of angiomyolipomas, but is rarely associated with intra-abdominal lesions such as retroperitoneal lymphangioleiomyoma [1].

We report the case of a 35-year-old woman with a 10-month history of progressive dyspnoea. In 2015, lung CT revealed multiple thin-walled lung cysts evenly distributed throughout the lungs with normal lung parenchyma and enlarged mediastinal lymph nodes (> 1 cm) consistent with P-LAM (**Figure 1**). Abdominal CT visualized a large hypodense retroperitoneal mass consistent with lymphangioleiomyoma (**Figure 1**). Pulmonary function tests demonstrated a severe obstructive pattern and decreased exercise performance with exercise desaturation. Forced expiratory volume in one second (FEV₁) was initially 1.63 L (47% of predicted) with a FEV₁/VC ratio of 51%. Considering the typical chest imaging and abdominal lymphangioleiomyoma, a definitive diagnosis of lymphangioleiomyomatosis was established according to the ERS Guidelines 2010 [1]. The diagnosis was confirmed by elevation of VEGF-D levels to 4000 pg/mL [2]. Following a multidisciplinary staff meeting, sirolimus was initiated at a dose of 2 mg/day and then progressively increased to 5 mg/day. Therapeutic drug monitoring was performed to obtain a therapeutic level between 8 and 12 µg/L. No serious side effects were observed. Pregnancy was contraindicated and oestrogen-free contraception was initiated. Six months after initiating sirolimus therapy, a significant improvement of pulmonary function tests was observed with a 670 mL increase in FEV₁ (2.27 L, 66% of predicted), but exercise desaturation and dyspnoea remained unchanged. After 14 months of sirolimus therapy, no improvement was observed on lung CT, whereas abdominal CT showed a significant reduction of the volume of the retroperitoneal lesion (70%

reduction of the volume of the target lesion) (**Figure 1**). At 30-month follow-up, the improvement of pulmonary function tests remained stable and the abdominal lymphangioleiomyoma had completely disappeared.

Lymphangioleiomyomatosis occurs sporadically or in association with tuberous sclerosis complex, a genetic disease [1]. Tuberous sclerosis complex is caused by germline mutations of either TSC1 or TSC2 gene. Both genes are tumour suppressor genes encoding hamartin (TSC1) and tuberlin (TSC2). Inherited mutations of the TSC-1 or TSC-2 genes have recently been shown to be the cause of tuberous sclerosis complex, while acquired (somatic) mutations of either gene are associated with sporadic lymphangioleiomyomatosis, resulting in constitutive activation of the kinase mammalian target of rapamycin (mTOR). As in our case report, lymphangioleiomyomatosis usually affects women of childbearing potential and oestrogens likely play a fundamental role in disease progression. Some reports have suggested that oestrogen administration or pregnancy may accelerate disease progression [3].

Pulmonary manifestations of lymphangioleiomyomatosis usually consist of thin-walled lung cysts distributed throughout the lungs, mediastinal lymphadenopathy and/or chylous pleural effusion. Pulmonary function tests frequently show an “obstructive” or “mixed” pattern [3].

As observed in the present case, 24% to 77% of cases of lymphangioleiomyomatosis present abdominal abnormalities including renal angiomyolipomas, abdominal lymphadenopathy, lymphangioleiomyomas and/or chylous ascites [4]. Abdominal manifestations mimicking retroperitoneal tumours may precede the diagnosis of pulmonary lymphangioleiomyomatosis, leading to delayed diagnosis [4,5]. Abdominal lymphangioleiomyoma is a rare manifestation of lymphangioleiomyomatosis, usually occurring in the upper retroperitoneal area close to the abdominal aorta and/or pelvic cavity according to the anatomical distribution of lymphatic vessels [5].

Sirolimus is now recommended as treatment for patients with lymphangioleiomyomatosis with abnormal/declining lung function or symptomatic chylous fluid accumulations [2,6–8]. Taveira-DaSilva *et al.* enrolled patients with chylous pleural effusions and other lymphatic manifestations of lymphangioleiomyomatosis in an open-label, uncontrolled trial [9]. Twelve patients with chylous fluid accumulations were treated with sirolimus. All patients obtained complete or near-complete resolution of their chylous fluid accumulations and presented improvement or stabilization of lung function. We observed a similar benefit of sirolimus on lymphangioleiomyoma with a dramatic reduction in size, which was maintained in our patient with complete disappearance of the abdominal lymphangioleiomyoma after 30 months of sirolimus therapy. Compared to previous studies, we observed an unusual marked improvement of lung function. As shown by Argula *et al.*, this improvement may be partly explained by the effect of sirolimus on proliferating smooth muscle cells in small airways [10]. By reducing cell infiltration in the small airways, sirolimus may relieve airflow obstruction and reduce gas trapping, leading to increased lung compliance.

In the present case report, sirolimus appeared to be highly effective for both pulmonary lymphangioleiomyomatosis and abdominal lymphangioleiomyoma. In the latest guidelines, sirolimus is now recommended for patients with lymphangioleiomyomatosis with abnormal/declining lung function [2]. Sirolimus therapy has also been proposed in patients with symptomatic chylous fluid accumulations prior to invasive management. However, this recommendation is based on very low-quality evidence and additional prospective clinical trials of mTOR-based treatment in patients with lymphangioleiomyomatosis are warranted.

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Figure legends:

Figure 1: Chest CT (a, b) and abdominopelvic CT (c, d) before sirolimus therapy showing multiple thin-walled lung cysts and a large abdominal lymphangioleiomyoma (86.5mm in longest diameter on the axial view). Chest CT (e,f) and abdominopelvic CT (g,h) after 14 months of sirolimus therapy showing significant reduction of the volume of the retroperitoneal lesion (25mm in longest diameter on the axial view).