Case Report

Successful Everolimus Treatment of Renal Angiomyolipoma and Lymphangioleiomyomatosis: A Case Report

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ABSTRACT: A 42-year-old woman with renal angiomyolipoma and lymphangioleiomyomatosis associated with tuberous sclerosis complex was treated with the mammalian target of rapamycin (mTOR) inhibitor everolimus. After 6 months of treatment, the maximum size of the renal angiomyolipoma decreased from 58×41 to 37×32 mm on abdominal contrast-enhanced computed tomography (CT). Pulmonary nodules also decreased in size on chest CT. Forced expiratory volume in 1 second (FEV_1) decreased from 1740 to 1680 ml, but $\dot{V}50/\dot{V}25$ ratio improved from 4.38 to 3.58 on pulmonary function testing. Although stomatitis is a known major adverse effect of everolimus treatment, it was mild in severity in the present patient.

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Tuberous sclerosis complex (TSC) is caused by a mutation in *TSC1* or *TSC2*, which control expression of hamartin and tuberin, respectively. TSC is characterized by development of hamartoma in some organs and lymphangioleiomyomatosis (LAM). Hamartoma may result in organ system dysfunction.

LAM is a progressive cystic lung disease and is associated with inappropriate activation of mammalian target of rapamycin (mTOR) signaling, which regulates cell growth and angiogenesis. Sirolimus (rapamycin) inhibits mTOR and has shown promise in phase 3 trials of patients with LAM. The mTOR inhibitor everolimus is a derivative of and functions similarly to sirolimus.

In this report, we describe the first case of successful use of everolimus for treatment of renal angiomyolipoma (AML) in a patient with AML and LAM associated with TSC.

Case Report

A 42-year-old woman was referred to our hospital for evaluation of LAM, in February 2012. Approximately 6 years earlier she had developed bilateral pneumothorax and underwent bilateral partial thoracoscopic lung resection. The diagnosis of LAM was based on pathological analysis of surgical specimens of the lungs. She was started on progesterone therapy but pneumothorax later recurred. She had a smoking history of 6.5 pack-years but had stopped smoking approximately 17 years earlier. She had no known allergies or dust exposure. Her family history was noncontributory.

Oxygen saturation was 97% in ambient air. She had white leaf-shaped macules on the right and rear of her

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torso. Arterial blood gas analysis in ambient air showed a pH of 7.39, $PaCO_2$ of 36.0 mmHg, PaO_2 of 93.8 mmHg, and HCO_3^- of 22.5 mmHg. The results of analysis of peripheral blood were within normal ranges. The chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) score was 18. A chest radiograph showed diffuse reticular opacities bilaterally and increased lung volumes (Fig. 1A). Computed tomography (CT) images of the chest showed bilateral diffuse cystic opacification (Fig. 1B). A contrast-enhanced CT scan of the abdomen showed enhanced, dense, soft-tissue masses associated with fat density in the kidney and liver. These imaging findings were consistent with a diagnosis of AML. The maximum size of renal AML in the left kidney was 58×41 mm (Fig. 1G). Brain magnetic resonance imaging (MRI) revealed a brain cortical tuber and subependymal nodule. A pulmonary function test (PFT) in February 2012 revealed no obstructive impairment: forced expiratory volume in 1 second (FEV_1) (% predicted) was 1,740 ml (72.2%), diffusing capacity of the lungs for carbon monoxide (D_{LCO}) (% predicted) was decreased, at 11.62 ml/min/mmHg (59%), and peripheral respiratory tract resistance was increased, with a $\dot{V}50/\dot{V}25$ ratio of 4.38. Histopathological examination of a surgical bullectomy specimen obtained from the right upper lobe in 2006 showed proliferating spindle-shaped cells (LAM cells) (Fig. 2A). Smooth muscle actin (SMA), human melanin black (HMB) 45 (HMB45), and estrogen receptor (ER) were positive for LAM cells on immunohistochemical studies (Fig. 2 B, C, D). These findings satisfy the criteria for LAM. The diagnosis of TSC was based on the presence of renal and liver AML, LAM, brain cortical tuber, subependymal nodule, and confetti skin lesions.[1]

Because of the risk of AML rupture, the patient was started on oral everolimus 2.5 mg/day in June 2013. Six months later, she was admitted for evaluation of everolimus effectiveness. The maximum size of AML decreased from 58×41 mm to 37×32 mm on abdominal contrast-enhanced CT (Fig. 1G, H). Pulmonary nodules also decreased in size on chest CT (Fig. 1C, D, E, F). FEV_1 decreased from 1740 to 1680 ml, but $\dot{V}50/\dot{V}25$ ratio improved from 4.38 to 3.58. CAT score improved from 18 to 10. Stomatitis and nausea are known major adverse events but were of mild severity (grade 1) in our patient. These adverse events disappeared within 2 months of beginning oral care.

Discussion

The Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial showed that sirolimus treatment slowed the decline in lung function and improved quality of life (QOL).[2] In our patient, FEV_1 declined from 1740 to 1680 ml after 24 months. The FEV_1 slope from baseline was −2.5 ml per month, which was slower than that of the placebo group in the MILES trial (−12±2 ml per month). $\dot{V}50/\dot{V}25$ ratio improved from 4.38 to 3.58 in our patient. We hypothesize that everolimus reduced LAM cell nodules in the peripheral respiratory tract wall, which improved peripheral respiratory tract resistance. CAT score is an indicator of respiratory symptoms and QOL in our patient and improved after everolimus treatment. We speculate that this improvement had a role in improving $\dot{V}50/\dot{V}25$ ratio and reducing lung nodules.

Although a previous study found no change in nodule size or number during follow-up CT imaging of in 22 TSC patients with multiple pulmonary nodules who did not undergo pathological examination (duration of follow-up, 2.0 ±1.1 years; range, 0.9-4.9 years),[3] everolimus treatment reduced the size and number pulmonary nodules in our patient. Since pathological examination was not performed, we could not determine whether these nodules were LAM lesions or multifocal micronodular pneumocyte hyperplasia (MMPH). Since many of the nodules in our patient were solid nodules rather than the ground-glass attenuation typically seen in high-resolution chest CT images of patients with MMPH, and because no previous study reported that MMPH decreased in size in response to mTOR inhibitor treatment, we believe that these lung nodules were LAM lesions.

The EXamining everolimus In a Study of TSC 2 (EXIST-2) trial reported that everolimus was more effective than placebo for AML and LAM.[4] Rupture of AML is a major cause of death in TSC. As AML lesions grow, they can develop micro- and macroaneurysms, which increase the risk of spontaneous bleeding.[5] Renal AML larger than 4 cm or AML of any size in a patient with symptoms are candidates for treatments such as arterial embolization, tumor enucleation, partial nephrectomy, and mTOR inhibitor therapy. Many patients with TSC-associated renal AML have multiple or bilateral lesions, and recurrence after surgery is a concern. mTOR inhibitors are minimally invasive and can preserve renal function. However, the

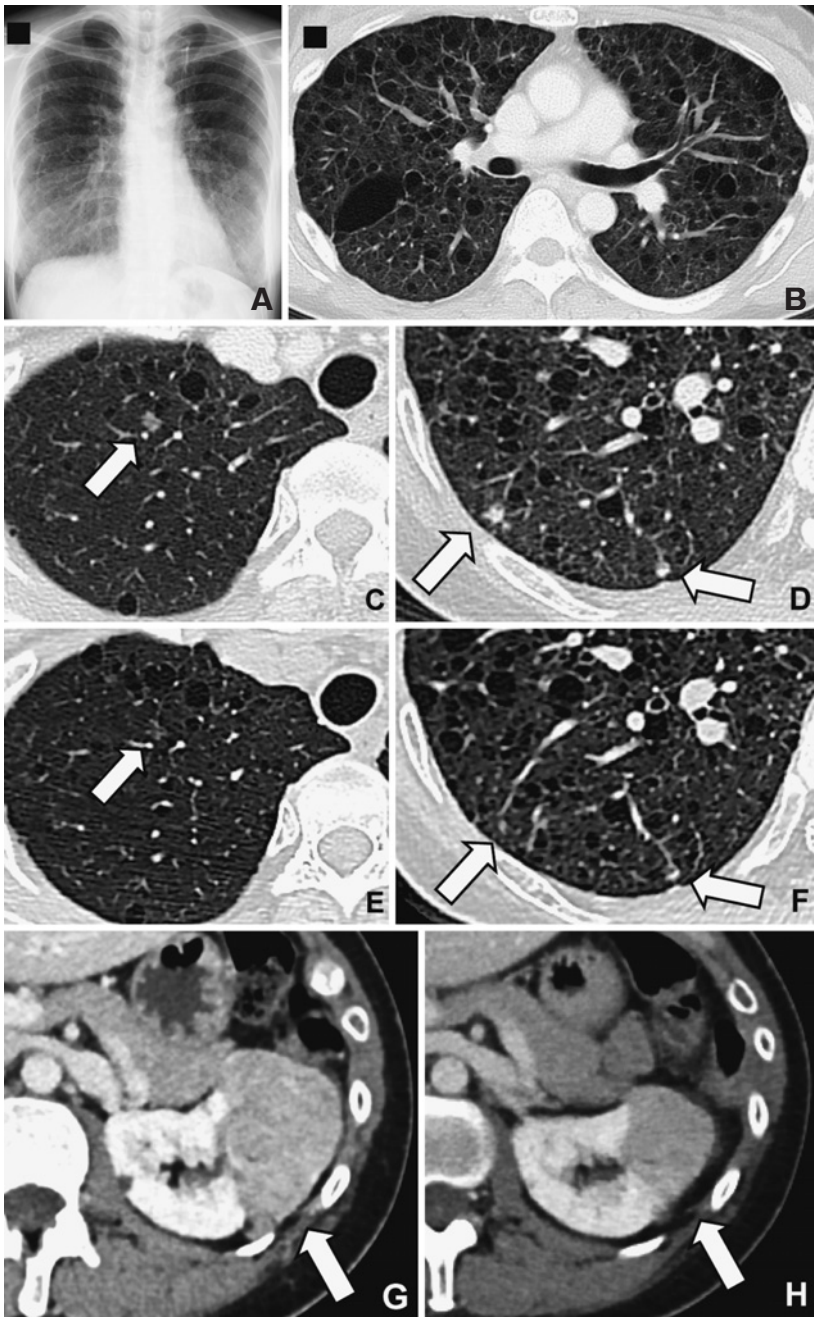

Fig. 1

A: Chest radiograph obtained on presentation shows diffuse interstitial infiltrate with overinflation in both lung fields.

B: Chest computed tomographic (CT) image obtained on presentation shows diffuse cystic lesions throughout the lobes of both lungs.

C, D: Chest CT images obtained on presentation show pulmonary nodules (arrows).

E, F: Chest CT images obtained 6 months after the start of everolimus treatment show improvement in pulmonary nodules (arrows).

G: Abdominal contrast-enhanced CT image obtained on presentation to our hospital shows a maximally enhanced, dense, soft-tissue mass (58×41 mm) associated with fat density in the left kidney (arrows).

H: Abdominal contrast-enhanced CT image obtained 6 months after the start of everolimus treatment shows shrinkage of the mass in the left kidney (maximum size of mass, 37×32 mm) (arrows).

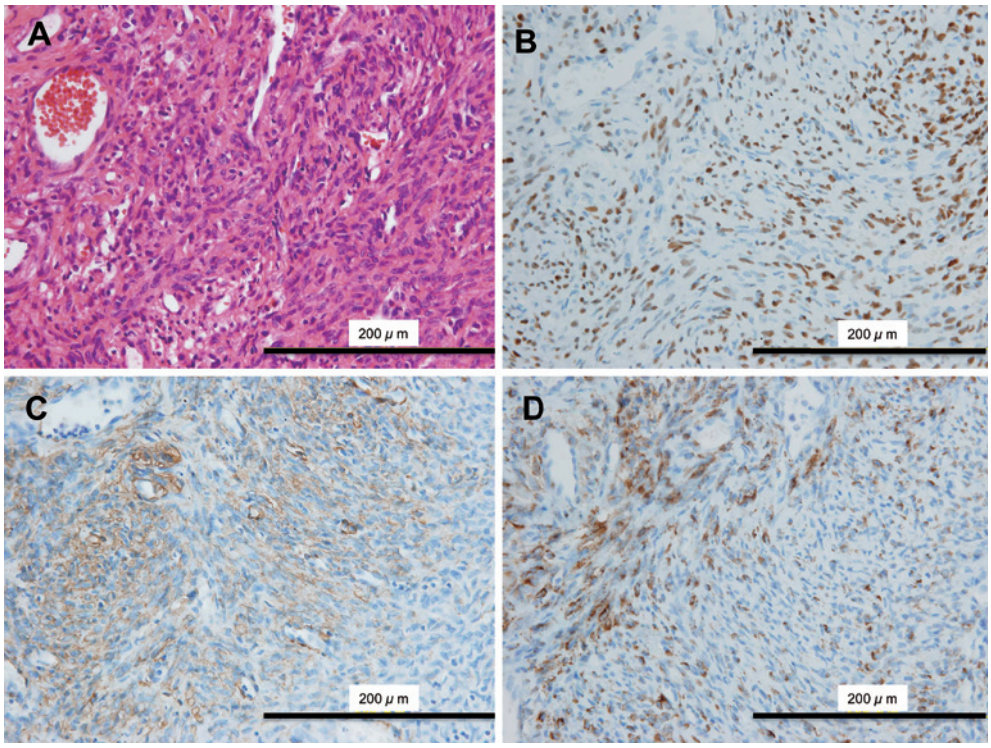

Fig. 2

A: Lung biopsy specimen from the right upper lobe shows proliferating lymphangioleiomyomatosis cells stained with hematoxylin and eosin (A: ×400).

B, C, D: Histopathological examination shows many cells positive for SMA, HMB45, and ER (B: SMA×400, C: HMB45×400, D: ER×400).

SMA: smooth muscle actin, HMB45: **human melanin black45, ER: estrogen receptor**

risk–benefit ratio for mTOR inhibitors has not been compared with that of other established treatments for AML.

Because of concerns regarding pulmonary toxicity, our patient was given a lower everolimus dosage than that in the EXIST-2 trial. The incidence of pneumonitis, which is occasionally fatal, was 13.5–37.5% in patients with advanced renal cell carcinoma receiving everolimus.[6] Thus, patients receiving an mTOR inhibitor for TSC-LAM should be carefully monitored for pneumonitis.

In conclusion, the mTOR inhibitor everolimus decreased the volume of renal AML and pulmonary nodules and improved QOL, without serious adverse events, in a patient with TSC-LAM.

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