

LETTER TO THE EDITOR

LYMPHANGIOLEIOMYOMATOSIS (LAM) - QUESTIONS

Keywords: lymphangioleiomyomatosis (LAM), sporadic LAM, tuberous sclerosis LAM, vascular endothelial growth factors (VEGF), angiomyolipoma (AML), sirolimus (Rapamycin)

Recently *Lymphology* published an article concerning the lymphatic manifestations of lymphangioleiomyomatosis (LAM) by Gupta and colleagues (1) which brings up more unanswered questions for me. Sporadic LAM is currently classified as a neoplastic disease and it may present as pulmonary LAM, angiomyolipoma (AML), or both. Treatment with mTOR inhibitors (sirolimus, everolimus) has been shown to stop progression of both pulmonary LAM (2) and angiomyolipoma (3). However, questions remain as to who should be treated and when therapy should begin.

Angiomyolipoma usually presents as a small tumor localized usually within kidney or liver. AML is slowly progressive and in some patients, especially those diagnosed with tuberous sclerosis, the course is more aggressive with multiple tumors, quickly growing and recurrent after surgical removal (4). In these patients, mTOR inhibitors have been shown to cause regression of AML (3).

In pulmonary sLAM, treatment with sirolimus was shown to stop progression of the disease in a double-blind randomized study. All the patients in this study suffered from respiratory insufficiency due to pulmonary sLAM (2).

Due to increased availability of CT, chest CT is done more frequently and the diagnosis of asymptomatic sLAM has been found to be

more common in younger women without any symptoms of respiratory insufficiency.

There are many questions to consider:

- Since we know that the course of pulmonary LAM may significantly differ between patients and not all of the patients will progress to respiratory insufficiency (5), should we start therapy immediately in patients diagnosed with pulmonary LAM? If not, how long should we wait?
- When should we start with mTOR inhibitors in patients with angiomyolipomas?
- Should we screen all women with angiomyolipoma for pulmonary LAM?
- In which patients should we perform genetic testing for TSC1/2 mutation?

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RESPONSE

We thank Dr. Szuba for his insightful comments and interesting questions. To enroll in the MILES trial, patients had to have an FEV1 of less than 70% predicted. By extrapolation, many physicians wait until FEV1 becomes abnormal before initiating mTOR inhibitor therapy in patients with LAM (1). However, at our institution, we also consider treating patients with low normal lung function who are declining rapidly, as well as patients with problematic chylous effusions and lymphangiomyomas (2). Treatment approaches to post menopausal women also vary. Since the progression of LAM slows considerably after menopause, it is often prudent to follow patients for a period of time and base treatment decisions on their individual rate of lung function decline. The recommendations for initiation of mTOR treatment in patients with angiomyolipomas are outlined in the Tuberous Sclerosis Association Guidelines (3). About 11% of women with angiomyolipomas discovered incidentally have cystic changes on CT, about

half of whom have four or more total cysts (4). Based on the finding that 1/20 women with angiomyolipomas will have LAM, and that an effective therapy is available, we recommend screening women with sporadic AMLs for LAM, especially those with large or bilateral tumors. Genetic testing is not recommended in patients with pulmonary LAM. Most LAM patients seen in the pulmonary clinic have sporadic LAM and do not have germline mutations. Conventional genotyping of buccal or peripheral blood cells will not identify mutations in those cases; only genotyping of the lesional tissue from the lung, kidney, chylous fluid, lymph node or other source will be informative. There are still no clinically useful genotype/phenotype correlations that would compel a clinician to genotype a TSC-LAM patient.

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