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Effect of Fasting on the Size of Lymphangioleiomyomas in Patients With Lymphangioleiomyomatosis

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BACKGROUND: Lymphangioleiomyomas occur in 38% of patients with sporadic lymphangioleiomyomatosis (LAM) and may cause pain and increased abdominal girth, mimicking the presence of a malignancy. Lymphatic involvement in LAM is closely associated with elevated serum levels of vascular endothelium growth factor-D (VEGF-D). Because lymphangioleiomyomas undergo diurnal variation in volume, we hypothesized that daytime ingestion of food, by increasing chyle formation and lymphatic flow, is the cause of an increase in lymphangioleiomyoma volume.

METHODS: Subjects had abdominopelvic sonograms and blood drawn for measurement of serum VEGF-D levels under nonfasting (day 1) and fasting (day 2) conditions. The size of the lymphangioleiomyomas was determined by a radiologist who was blinded to the subjects' status. The Wilcoxon signed rank test was used to determine whether the nonfasting tumor size was different from the fasting tumor size.

RESULTS: Thirty-five women were studied (aged 45.2 ± 8.5 years; FEV_1, 82% ± 25%; diffusing capacity of the lung for carbon monoxide, 64% ± 25% predicted). Images suitable for volume measurements were obtained in 30 subjects. Fasting decreased the tumor size by 20.7 ± 39.3 cm^3 (24% ± 40%, $P < .001$). Fasting VEGF-D levels (10,650 ± 900 pg/mL) were not significantly different from nonfasting values (12,100 ± 800 pg/mL, $P = .56$).

CONCLUSIONS: Lymphangioleiomyoma volume decreased during the fasting state. Conversely, a combination of food intake and decreased chyle flow through lymphatics partially obstructed by LAM cells may account for increases in lymphangioleiomyoma size. Imaging studies performed under fasting conditions may help in determining whether an abdominal tumor is a result of LAM or malignancy.

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ABBREVIATIONS: IQR = interquartile range; LAM = lymphangioleiomyomatosis; LCC = lymphangioleiomyomatosis cell cluster; NHLBI = National Heart, Lung, and Blood Institute; VEGF = vascular endothelial growth factor

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Lymphangioleiomyomatosis (LAM) is a multisystem disorder affecting primarily women that is characterized by cystic lung destruction, abdominal angiomyolipomas, and lymphatic abnormalities comprising lymphadenopathy, lymphangioleiomyomas, and chylous effusions.[1] LAM occurs sporadically, primarily as a result of mutations in *TSC2*[2,3] in patients with no evidence of genetic disease as well as in patients with tuberous sclerosis complex,[4] an autosomal-dominant syndrome caused by mutations in *TSC1* or *TSC2*.[5]

The lymphatic vasculature has been recognized as playing a major role in the pathophysiology of LAM. Indeed, LAM may present with thoracoabdominal lymphangioleiomyomas,[6,7] chylothorax, and ascites,[6,8] suggesting the presence of a malignancy.[9,10] Lymphangioleiomyomas, which occur in about 38% of patients with sporadic LAM,[11] are usually located along the axial lymphatics in the thorax and abdomen, retroperitoneum around the aorta, renal and superior mesenteric arteries, and pelvic region.[6,7] Macroscopically, lymphangioleiomyomas consist of well-circumscribed masses with prominent cystic formations filled with chylous fluid.[6] The symptoms associated with lymphangioleiomyomas may be disabling, including an increase in abdominal girth, abdominal pain suggesting an acute abdomen, obstipation, urinary frequency, incontinence, Horner syndrome, chyloptysis, malabsorption syndrome, and bladder obstruction.[12-16] Extrapulmonary lymphatic lesions may precede the appearance of pulmonary LAM.[6,17]

The lesions of LAM result from organ infiltration by a neoplastic cell (termed the "LAM cell") that displays characteristics of both smooth muscle cells and melanocytes.[6,18] LAM cells comprise both spindle-shaped and epithelioid smooth muscle-like cells. Both cell types react with antibodies against the smooth muscle antigens α-actin, vimentin, and desmin.[6,18] The epithelioid LAM cells react with human melanin black antibody (HMB-45), a monoclonal antibody that recognizes a premelanosomal protein (gp100) encoded by the *Pmel17* gene.[6,18] In the lungs, LAM cells are arranged either in a haphazard pattern or in follicles, bundles, or papillary formations containing slit-like channels that are lined by lymphatic endothelial cells and may contain lymphocytes and RBCs.[6,18] Aggregates of lymphoid cells may form lymphoid follicles.[6,18] Lymphatic vessels may be dilated as a consequence of compression of the thin-walled lymphatic channels by proliferating LAM cells.[6,18] LAM cell clusters (LCCs) have been noted in chylous effusions and elsewhere.[19] These LCCs consist of LAM cells surrounded by lymphatic endothelial cells.[19,20] LCCs are present in lung lymphatics, lymph nodes, uterus, and chylous fluid.[19,20] LAM cells infiltrate and penetrate the lymphatic channels and pulmonary arterioles, leading to leakage of chyle and blood.[6,18,20] Occlusion or infiltration of pulmonary arterioles by LAM cells may account for the hemoptysis described by patients with LAM.[11] Through the lymphatic channels, LAM cells gain access to the systemic circulation, facilitating the metastatic spread of the disease.[20] In summary, LAM cells appear to invade the wall of the lymphatic vessels, causing damage and leakage of chylous fluid and obstruction of chyle flow and leading to the formation of lymphangioleiomyomas.

LAM cells exhibit positive immunoreactivity for vascular endothelial growth factor (VEGF) receptor-3.[21] VEGF-C and VEGF-D are ligands for VEGF receptor-3, which is also expressed by lymphatic endothelial cells.[20,21] The degree of lymphangioleiogenesis and VEGF-C expression has been reported to correlate with the histologic severity of lung disease.[21] LAM cells also exhibit positive immunoreactivity for VEGF-D, and serum levels of VEGF-D are increased in patients with LAM, especially those with lymphatic involvement.[22,23] High VEGF-D levels are associated with severity of lung disease as measured by the degree of airflow obstruction, impairment of lung diffusion capacity, and cysts on CT scans.[22,23] Measurement of serum VEGF-D has been shown to be useful as a diagnostic tool and in grading the severity of the disease and the potential response to therapy.[24,25]

Lymphangioleiomyomas have a distinctive radiologic appearance, and diurnal variation in size of these tumors has been reported.[7,26,27] In one study, CT scans taken in the evening hours showed a 140% increase in volume from morning values.[24] This finding was also documented by ultrasonography.[27] In the latter study, 21 of 44 patients with LAM showed morning to evening variation, with an increase in the size of the lymphangioleiomyomas ranging from 10% to 484%.[27]

Flow of chyle in lymphatics is determined by food intake, depending predominantly on the fat content of the diet.[28] Studies of chylothorax have demonstrated a reduction in daily fluid drainage and complete resolution of effusions when patients were placed on a low-fat diet and total parenteral nutrition, with the only source of fat being medium-chain triglycerides.[29-32] Conversely, during various surgical procedures, visualization of the