

rate of recurrence, particularly distant recurrence, by approximately 50 percent”¹ and “The addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide reduced the rates of recurrence by half among women with HER2-positive breast cancer.”² Dr. Nash’s letter calls attention to the importance of understanding the difference between absolute and relative risks in analyzing the results of clinical trials.

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Diagnostic Potential of Serum VEGF-D for Lymphangioleiomyomatosis

TO THE EDITOR: Lymphangioleiomyomatosis is a rare, progressive, frequently fatal cystic lung disease that affects women almost exclusively.^{1,2} It occurs in up to 40% of women with the tuberous

sclerosis complex, a tumor-suppressor syndrome associated with seizures, cognitive impairment, and hamartomas in multiple organs, and can also occur in a nonheritable sporadic form that in-

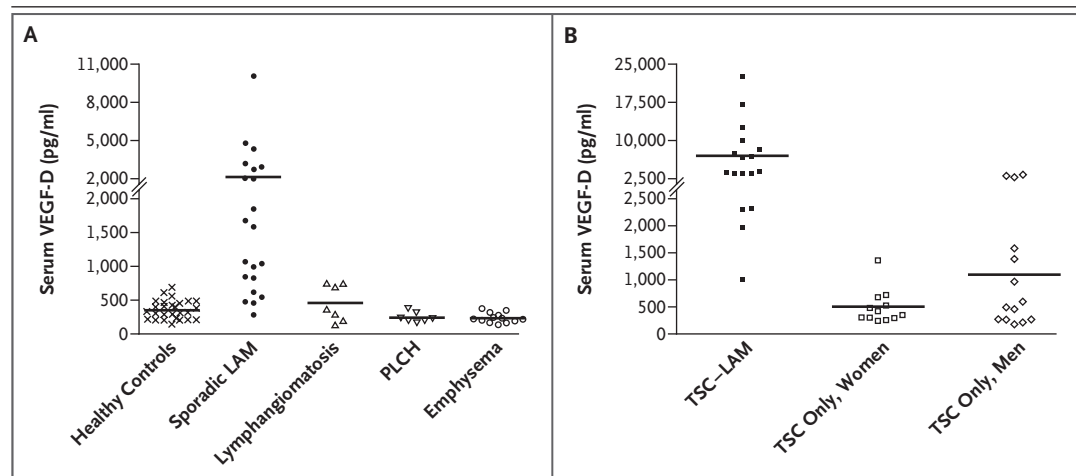


Figure 1. Serum VEGF-D Levels in Patients with Lymphangioleiomyomatosis (LAM) as Compared with Healthy Controls and Patients with Other Diseases, and VEGF-D Levels in Women with the Tuberous Sclerosis Complex (TSC) and LAM as Compared with Women and Men with TSC Only.

After receiving institutional-review-board approval, we obtained serum samples from 38 patients with LAM and 29 healthy controls (86% of whom were women) and evaluated them by means of an enzyme-linked immunosorbent assay (R&D Systems). Panel A shows VEGF-D levels in patients with LAM as compared with healthy controls and patients with other diseases. The group of patients with LAM consisted of 15 patients with biopsy-proven LAM and 23 with clinically definite LAM (17 had TSC, and 6 had cystic lung disease with angiomyolipomata, chylous manifestations, or both). The patients with LAM had a broad spectrum of disease severity, with 40% having mild disease, 31% moderate disease, and 29% severe obstruction on the basis of the forced expiratory volume in 1 second. Patients with other diseases included 7 patients with pulmonary Langerhans'-cell histiocytosis (PLCH) (43% were women), 7 with lymphangiomas (all were women), and 13 with emphysema (31% were women, and 38% had severe obstructive lung disease). Panel B shows serum VEGF-D levels in the 17 patients with TSC and LAM (all of whom were women) as compared with 12 women who had TSC only (with normal chest CT scans), and 14 men who had TSC only. In both panels, different intervals are shown above and below the hatch marks on the y axis; the horizontal lines indicate mean values.

volves only the lung, lymphatics, and kidney.³ The presence of the tuberous sclerosis complex or fat-containing renal hamartomas called angiomyolipomas in a woman with characteristic cystic changes on a high-resolution computed tomographic (CT) scan of the chest is considered to be diagnostic of lymphangioleiomyomatosis. However, half of patients with sporadic lymphangioleiomyomatosis do not have angiomyolipomas, and the accuracy of high-resolution CT is estimated at only 80%,⁴ so thoracoscopic biopsy is frequently required for definitive diagnosis. Lymphangioleiomyomatosis, pulmonary Langerhans'-cell histiocytosis, and emphysema are commonly considered in the differential diagnosis of lymphangioleiomyomatosis.

Vascular endothelial growth factor (VEGF) is a major angiogenic growth factor produced by malignant cells. VEGF-D, a ligand for the lymphatic growth-factor receptor VEGFR-3/Flt-4, induces formation of lymphatics and promotes the spread of tumor cells to lymph nodes. Seyama et al. reported that levels of VEGF-D, but not VEGF-A or VEGF-C, are elevated in patients with sporadic lymphangioleiomyomatosis as compared with healthy controls.⁵

We conducted a study to determine the diagnostic usefulness of VEGF-D levels in distinguishing lymphangioleiomyomatosis from other, clinically overlapping disorders. We found that serum VEGF-D levels were elevated by a factor of up to 30 in patients with lymphangioleiomyomatosis but were normal in patients with lymphangioleiomyomatosis, those with pulmonary Langerhans'-cell histiocytosis, and those with emphysema (Fig. 1A). The area under the receiver-operating-characteristic curve was 0.951 for sporadic lymphangioleiomyomatosis. With a cutoff value for VEGF-D of 574 pg per milliliter, the test sensitivity for sporadic lymphangioleiomyomatosis was 86%, the specificity was 91%, and the positive likelihood

ratio was 9.6; with a cutoff value of 750 pg per milliliter, the sensitivity, specificity, and positive likelihood ratio were 76%, 98%, and 41.7, respectively. Furthermore, VEGF-D levels were much higher in women with the tuberous sclerosis complex and lymphangioleiomyomatosis than in women with the tuberous sclerosis complex and normal high-resolution CT scans: mean value, 6804 pg per milliliter (95% confidence interval [CI], 3826 to 9781) versus 491 pg per milliliter (95% CI, 291 to 691; $P < 0.001$). In contrast, some men with the tuberous sclerosis complex alone had elevated VEGF-D levels (Fig. 1B).

Serum VEGF-D may be a clinically useful diagnostic test that can distinguish sporadic lymphangioleiomyomatosis from other cystic and chylous lung diseases, potentially decreasing the need for lung biopsy; but validation in a longitudinal study with a larger patient population is necessary.

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Sirolimus Therapy in Tuberous Sclerosis or Sporadic Lymphangioleiomyomatosis

TO THE EDITOR: Tuberous sclerosis is an autosomal dominant disorder characterized by hamartomatous growths in many organs and caused by inherited mutations of the *TSC1* or *TSC2* gene.

Acquired (somatic) mutations of either gene occur within pathologic cells in patients with sporadic lymphangioleiomyomatosis. Renal angiomyolipomas occur in both disorders, resulting in