Occasional Essay

Lymphangioleiomyomatosis

Calling It What It Is: A Low-Grade, Destructive, Metastasizing Neoplasm

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Lymphangioleiomyomatosis (LAM) is a progressive cystic lung disease primarily affecting women that has historically been classified and clinically managed as a nonneoplastic interstitial lung disease. The purpose of this document is to outline the accumulating data that support reclassification of LAM as a low-grade, destructive, metastasizing neoplasm. This major conceptual shift actually began more than 10 years ago in the pathology community. The 1999 World Health Organization classification of lung tumors regarded LAM as a "tumour-like" lesion, and in the 2004 classification, it was codified as a mesenchymal neoplasm (1, 2). The pulmonary community seems to have been slower to adopt this viewpoint, however, and continues to consider LAM one of the "other" idiopathic interstitial pneumonias.

LAM occurs in patients with tuberous sclerosis complex (TSC) and also as a sporadic illness in patients without heritable disease. In either case, the smooth muscle–like "LAM cells" that diffusely infiltrate the lungs, lymphatics, and angiomyolipomas of patients with LAM have a low proliferative index and little or no evidence of cellular atypia, suggestive of a benign process. However, mounting genetic and cellular evidence has shown that, despite their innocent appearance, LAM cells exhibit the features and behaviors of a neoplasm. The finding of loss of heterozygosity for tuberous sclerosis complex genes in the lung, kidney, and lymphatic lesions of patients with LAM is consistent with clonal origins for these tumors. In the handful of patients who have had multiple tissues available for sequencing, identical TSC mutations found in the angiomyolipomas, lymph nodes, and lungs are indicative of seeding from a common, most likely extrapulmonary source (3). Angiomyolipomas have been proposed as a potential primary tumor, but they are present in a minority of patients with sporadic LAM (4). The expression of smooth muscle markers (5) and steroid hormone (estrogen and progesterone) receptors (6), variation of symptoms with the menstrual cycle (7), and report of LAM lesions in 9 of 10 resected uterine specimens from patients with LAM in a small series (8) are potentially consistent with a uterine primary tumor, at least in some patients. The TSC mutations that occur in LAM result in inappropriate, constitutive signaling through the mammalian target of rapamycin pathway, which senses energy balance and nutrient availability in the cell, controls protein translation, and is activated in most human cancers (9). LAM recurs in transplanted lungs, and the cells that comprise the lesion within the allograft express the TSC mutations of the host (3, 10–13), consistent with a metastatic mechanism for the disease. Additional features that LAM cells have in common with neoplastic cells include inappropriate proliferation and invasion (14), metabolic reprogramming to a "Warburg" glycolytic mode (15), modest angiogenesis and exuberant lymphangiogenesis (16, 17), dissemination via blood and lymph (13, 16, 18, 19), and protease-driven matrix degradation (20–22). In summary, LAM cells have growth-promoting DNA mutations, evidence of clonal origins, invasive and metastatic potential, and metabolic profiles that are entirely consistent with a neoplastic process.

If LAM is a neoplasm, is it benign or malignant? The pathologic appearance and the proliferative capacity are certainly more consistent with the former. The pace of the illness is also a good fit for a benign label. Indeed, the median survival in some LAM cohorts is almost certainly measured in decades (23). Even metastatic potential does not define LAM as malignant, since there are several examples of rare metastasizing pulmonary diseases that are clearly benign from a natural history perspective, such as benign metastasizing leiomyoma (24). However, in our view, the fact that LAM results in remote tissue destruction, progressive respiratory failure, and death or need for lung transplantation is inconsistent with a benign designation. These are more typical behaviors of a malignant process, albeit one with a remarkably long disease course and exquisite target organ restriction. We submit that the descriptive modifiers "low-grade, destructive, metastasizing" are more appropriate than the conventional labels, "benign" or "malignant," and that these elements should be included in the description of LAM to patients.

Should LAM be labeled a cancer? Few biologists or clinicians would draw a sharp distinction between a destructive, metastasizing neoplasm and cancer, regardless of the pace of illness. LAM is unique among TSC-related neoplasms in that it meets the definitions of cancer published by the National Cancer Institute (25) and the World Health Organization (26), which require loss of growth control, and local and remote tissue invasion and destruction. However, the term "cancer" can be interpreted differently by society than by the scientific and medical communities. The word can be frightening to patients, and can connote a tempo and degree of lethality that is not commensurate with the natural history of LAM. In addition, although slow-moving cancers with long survival times are already very familiar to the public, including chronic lymphocytic leukemia, nonmelanoma skin cancer, and low-grade lymphoma, there are movements afoot to remove the word "cancer" from the most indolent of these. For example, some providers in the breast cancer community feel that the word "cancer" applied

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to ductal carcinoma *in situ* has an unwarranted emotional impact and promotes overly aggressive management. A similar debate has arisen in the case of prostate cancer. Because most elderly men with low-volume, low-grade prostate cancer will never suffer adverse consequences from their malignancy, a recent National Institutes of Health panel concluded that it may be a mistake to apply the term "cancer" to them, for the same reasons invoked for ductal carcinoma *in situ*. However, in an editorial titled "Call It Cancer" in *The Oncologist* (27), Drs. Chabner and Smith countered, "Prostate cancer is cancer. It has the potential to kill, and decisions about whether to screen or not to screen, to treat or not to treat, may well affect an individual's survival and quality of life. Patients deserve to know this uncertainty, and to make informed decisions. Ignoring the fact that it is cancer, or renaming it something else, does not help this discussion."

With only one validated therapeutic intervention for LAM (28), the fear of provoking overly aggressive management decisions is perhaps less of an issue in LAM than in breast or prostate cancer. However, the concern that a cancer label may cause anxiety among patients with LAM, family members, and some clinicians is certainly important to address. Through the efforts of The LAM Foundation and their network of LAM Clinics, patients with LAM are generally well versed on this topic. The Foundation has posted a question-and-answer section about "LAM and Cancer" on their website since 2005, and has published many articles by patients and clinicians on the topic in their quarterly newsletter. A "LAM and Cancer" focus group was held in Chicago in 2011 to gauge patient reaction to the concept, and an open forum panel discussion entitled "LAM as Cancer" with 150 patients and investigators in attendance was held at the 2012 annual LAM research meeting. Laura Lentz, a patient with LAM and Chair of the LAM Foundation Board of Directors, summarized her observations of those activities: "It is a rare LAM patient who has not heard of the links between LAM and neoplastic disease. Patients have a right to know the facts as the scientists and clinicians see them. Please 'call it what it is'." We conclude that LAM pathogenesis should be accurately described to the patient. Whether the word "cancer" is introduced into the discussion is up to the clinician, but in our experience, most patients will be left seeking an explanation of the differences and similarities between LAM and the cancers with which they are familiar. We suggest that these questions should be anticipated and proactively addressed.

Viewing LAM from the vantage point of a metastatic, destructive neoplasm rather than as an idiopathic interstitial lung disease does not change what it is to the medical care team, insurance adjuster, researcher, pulmonary transplant committee, or the patient and her family. It will continue to be a slowly progressive lung disease (in most patients) that can lead to exercise intolerance, requirement for supplemental oxygen, lung destruction, respiratory failure, need for pulmonary transplantation, and death. Actuarial tables will not require modification. The National Heart, Lung, and Blood Institute, which has been an unfailing champion for LAM for almost two decades, will continue to be the research home for the disease. Patients with LAM will still be referred to pulmonologists, and the focus of postoperative care for lung transplantation patients with LAM will continue to be chronic rejection rather than recurrence. And patients and families will continue to accept LAM for the way it behaves, rather than how it is labeled.

Why this proposal and why now? What new piece of evidence has pushed this issue beyond the tipping point? After all, we have known that LAM is associated with TSC gene mutations, metastasis, and remote tissue destruction for over a decade. Newer findings that LAM cells exhibit cancer cell metabolism and use lymphangiogenesis as a strategy for metastatic spread and tissue remodeling have certainly strengthened the neoplastic link. The primary motivation, however, for what we believe is an overdue change in perspective is that we believe it will promote new approaches to diagnosis and staging, including the use of predictive histologies and biomarkers to forecast disease severity, progression, and treatment response, and of cancer-based treatment strategies, such as combination therapies capable of promoting apoptosis, modulating autophagy, and defeating immune evasion mechanisms. We believe that accepting the pathological and clinical classification of LAM as low-grade neoplasm will lead to a welcome new clarity in our discussions with patients and fellow clinicians, and may ultimately further enhance synergies between the pulmonary and oncology communities that could improve survival and quality of life for patients with LAM.

Author disclosures are available with the text of this article at www.atsjournals.org.

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