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LYMPHSPIRATION / EDITORIAL

LYMPHANGIOLEIOMYOMATOSIS AND GORHAM-STOUT DISEASE: PRIMARY OR SECONDARY DISORDERS OF THE LYMPHATIC SYSTEM?

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ABSTRACT

Lymphangioleimyomatosis and Gorham-Stout disease, rare disorders which share features of proliferating lymphatic vessels, predominantly in the lung in the former and bone in the latter, commonly manifest as progressive lung disease often associated with life-threatening complications of chylous reflux from central lymphatic obstruction/ leakage. This Lymphspiration-Editorial proposes that, rather than a secondary complication, lymphatic obstruction/ dysfunction is a much earlier or even the primary event in the pathogenesis of both disorders and that lymphostasis drives the cellular proliferative response in both lung and bone and even distant sites.

Keywords: Lymphangioleiomyomatosis (LAM), Gorham-Stout disease (GSD), generalized lymphangiomatosis (GLA), benign metastasis, lymphangioma, lymphatics, lymphostasis, pathogenesis, imaging, treatment

In this, previous, and forthcoming issues of *Lymphology*, lingering and fresh insights raise intriguing questions about the primacy of the lymphatic system and the very nature of two rare and often fatal disorders. Lymphangioleimyomatosis (LAM) is a diffuse pulmonary disease typically featuring hyperplastic smooth muscle-invested intrapulmonary and extrapulmonary lymphatics and associated with a variety of extrapulmonary benign vascular tumors. Gorham-Stout disease (GSD) or "disappearing bone" is usually (but not always) associated with single or multifocal lymphangiomas [overlapping the spectrum of generalized lymphangiomatosis (GLA) with bone involvement] and often associated with progressive lung disease. The clinical and pathologic features and their progression implicate the lymphatic system and specifically lymphatic obstruction as a common component of both disorders contributing to substantial morbidity and mortality (1,2). They also raise the conundrum of "benign metastases," a seeming contradiction of terms.

The key question, and one with important clinical implications, hinges on the exact sequence of events in the pathogenetic process: Does lymphatic obstruction/lymphostasis precede ("primary") rather than follow early or late ("secondary") the pleiomorphic cellular proliferative (hyperplastic, neoplastic, '"metastatic") phase of each disease? Within the limitations of current lymphatic imaging protocols and accurate inclusive reporting of clinical details of these rare conditions,

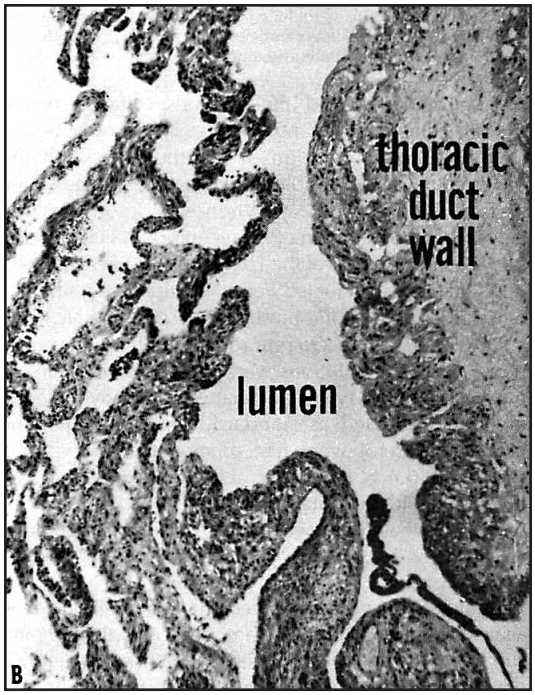

Fig. 1. Photomicrograph of a thoracic duct appearing grossly normal but exhibiting extensive obstructive intraluminal proliferation of smooth muscle cells in an autopsy examined specimen from a patient with LAM (H&E x40). (Reproduced from ref. 9 with permission and modified legend.)

support for the "primary" view comes from various multimodal imaging techniques. Conventional oily contrast lymphography, lymphscintigraphy, and MRI have all been used to document the frequent anatomic and functional abnormalities in the central lymphatic system (thoracic duct and larger tributary collectors) and specifically lymphatic obstruction, lymphostasis, lymph reflux, collateralization, and external fistulae in both LAM and GSD (1-7). Histologic and immunohistochemical reports from biopsy, surgical, and autopsy specimens with and without lymphatic-specific staining (1,2,8,9) further delineate microscopic lymphatic abnormalities – increased numbers, lymphangiectasia, thickened walls, intramural and extramural obstruction, and dysplasia in the lung and lymphatic collectors (*Fig. 1*), and regional lymph nodes (LAM) and in bone (GSD) (normally lacking lymphatics), associated with tissue fibrosis.

On the other hand, the "proliferative theory" posits that lymphatic obstruction is secondary and a much later life- threatening event. Driven by a variety of "triggers" – gene mutations, wound/fracture healing, vascular growth factors and assorted hormones and cytokines – albeit inconsistently documented, lymphatic, vascular accessory cell, smooth muscle (pericyte), and pluripotential stem cells are turned on to the proliferative mode, and in the walls and lumen of pulmonary and extrapulmonary lymphatics produce vessel narrowing and obstruction. This proliferative process is viewed by some as not only neoplastic but actually fulfilling the definition of cancer (10), particularly as cells and cell clusters migrate through the interstitium, enter the lymph circulation, deposit in lymph nodes, accumulate in body cavity fluids, and circulate in the blood stream to arrive or arise in distant and even select locations (e.g., bone), thereby behaving like true "metastases" but "benign" by most other criteria. What is known about the proliferative potential (hyperplasia, dysplasia, neoplasia) of the primary and metastatic lesions and masses in LAM (10,11) and GSD (2,12) and are *in vitro* cultures an accurate reflection of *in vivo* biologic behavior? Indeed, some lesions (and patients) remain stable for long periods of time without treatment, circulating VEGF-C and -D levels are often elevated, and clinical improvement with lesion regression has been reported with the use of targeted anti-(vascular) growth factor therapy in both LAM and GSD and recurrence with discontinuation of these agents. Furthermore, is proliferation of the putative responsible/errant (non-lymphatic) cell type (vascular smooth muscle) a primary event? What is that cell of origin and its relationship to other parenchymal or mesenchymal cells – e.g., in the lung and airways or in the bony skeleton or encircling and extramurally obstructing these lymphatic

channels? How interchangeable and transformable are cell types by transdifferentiation? Is not the (lymph)angioblast one of the most primitive "stem cells"? Our interest in these questions began in 1982, when we encountered a young woman presenting in extremis with a giant cervicomediastinal lymphangioma associated with extensive bony lesions (osteoclastic "metastases") throughout her skull and skeleton. The primary mass of chylous and non-chylous cystic structures wrapping around the lungs and heart was meticulously resected almost in its entirety from jaw to diaphragm. We subsequently cultured lymphatic endothelial cells from the mass and observed for the first reported time what we termed "'lymphangiogenesis' (in contrast to hemangiogenesis) *in vitro*". Clusters of these cells sprouted tubes in tissue culture spontaneously without added growth factors or special matrix and survived for many generations (12). Her disorder would subsequently be recognized to fall under the diagnosis of GSD (12,13). Remarkably, 35 years later, her disease remains stable without recurrence of the primary cervicomediastinal tumor and with neither expansion not regression of her widespread "benign metastatic" bone lesions. A bold surgeon's debulking of the primary tumor (and no other treatment) abruptly halted the "proliferative" stimulus and the metastatic process!

Relatively unexplored is the concept that the "proliferative stimulus" in LAM and GSD might be secondary to a hidden "primary" but as yet inadequately studied lymphatic obstructive process? Lymphatic obstruction itself leads to the known sequelae of "lymphostasis" which could mimic the "proliferative theory." Mechanistically, lymphostasis with high protein (lymph)edema fluid accumulation and the associated loosening of the sol-gel extracellular matrix, stimulates vigorous lymphangiogenesis and even lymphatic cellular transdifferentiation and cellular migration as part of a more generalized or even selective/targeted tissue overgrowth phenomenon. The sequelae of lymphatic obstruction in a variety of organs as well as in the limbs are by now well-recognized. These "lymphostatic disorders" were elegantly characterized by Földi and colleagues more than a half century ago (14), further conceptualized by us (*Fig.2*) in the 1980's (15), and underlying molecular mechanisms are currently being investigated. Just as during obstruction of blood vascular flow, internal stress and elevated intraluminal pressure in anatomically or functionally obstructed lymphatic vessels act as potent stimuli to (lymph)angiogenesis/vasculogenesis with increasing smooth muscle remodeling in the hypertensive vessel wall. With persistence of lymphostasis, a sequence of events is set into motion characterized by accumulation of high protein lymphedema, immune dysregulation, inflammation, susceptibility to infection, and soft tissue overgrowth - with fibrous and adipose deposits – accompanied by vigorous lymph- (and often also hem-) angiogenesis and later, angiotumorigenesis. Warty overgrowths and benign tumors appear and in rare instances, angiosarcoma and other malignancies as cells transition [epi(endo)thelial- mesenchymal transition – EMT] into altered migrating phenotypes capable of entering the lymph circulation with dissemination to the bloodstream and distant sites (13,15).

The suggested fundamental shift in perspective about both LAM and GSD would stimulate different and innovative approaches to early evaluation, treatment and even prevention that might also alleviate other features of these diseases – in the lung and bones – that follow the common pathway of "lymphostasis". This line of thinking was reinforced at the 2nd International Conference of the Lymphatic Malformation Institute in Atlanta in June 2016 (16), when review of the comprehensive database registry for GSD revealed that chylothorax with progressive lung disease and other chylous reflux complications were the chief causes of death and serious morbidity rather than the distinctive

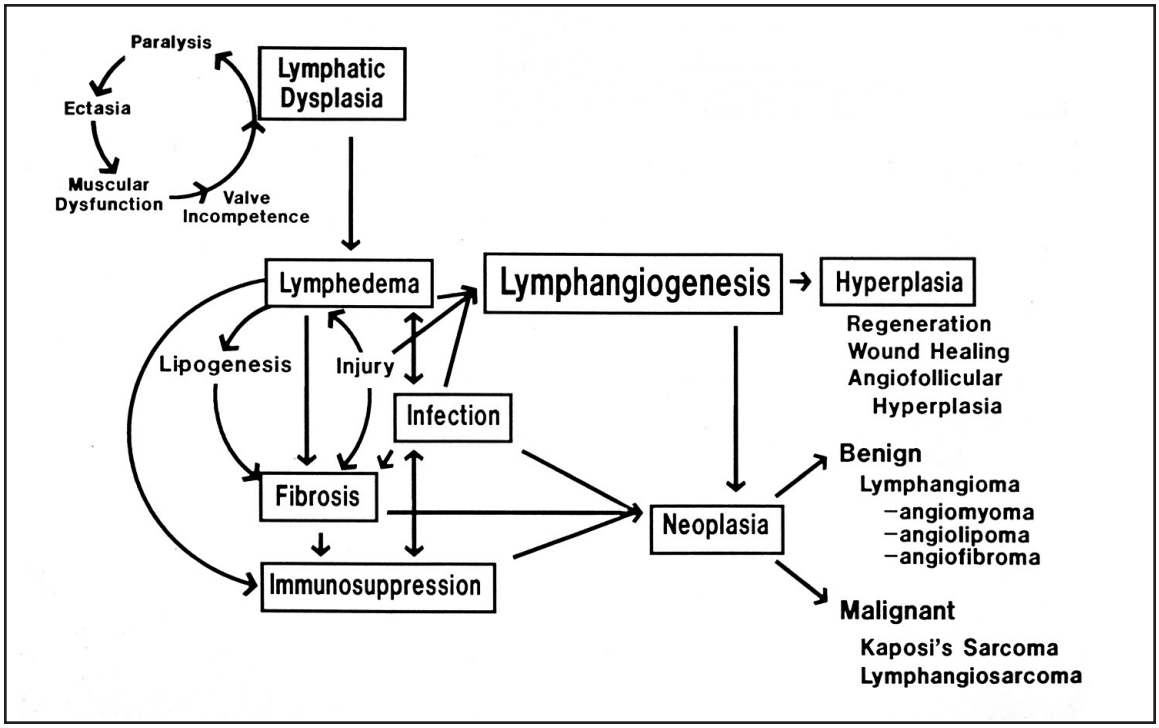

Fig. 2. Schematic diagram proposing pathophysiologic links between lymphangiogenesis and lymphangiodysplasia, hyperplasia, and neoplasia in the setting of lymphostasis. During a latent period, lymphatic dysplasia produces ectasia, muscular dysfunction, paralysis, and valve incompetence culminating in persistent high-protein lymphedema. Subsequently, superimposed opportunistic infection, immunosuppression, and injury with recurrent lymphangitis promote persistent lymphedema, intense angiogenesis, lipid deposition and fibrosis, and on rare occasions malignant vascular neoplasia. This sequence of events may occur as a local phenomenon in peripheral lymphedema or in a multitude of isolated or generalized visceral disorders characterized by scar formation, angiohyperplasia, and neoplasia. (Reproduced with permission from ref. 15)

"disappearing bone." There was a call for early diagnosis and early intervention when these "secondary lymphatic complications" first appear and even "preventive" lymphatic imaging screening beforehand (but could these actually be "primary"?). In this light, as mentioned earlier, the limited but often temporary success of therapy with anti-proliferative agents like rapamycin (sirolimus) in both disorders could perhaps be viewed as attacking the secondary effects of lymphatic obstruction/lymphostasis, which include proliferation of a variety of cell types particularly lymphatic endothelium (i.e., secondary lymphangiogenesis/ lymphvasculogenesis) and pericytes. Indeed, continued chylous reflux into the lung [what Dori and Itkin have called "lung perfusion" (a special form of lymphedema) seen on magnetic resonance lymphograms] (17) may initiate progressive pulmonary dysfunction, proliferation of diverse cell types, and pathologic changes in both LAM and GSD. Furthermore, lymph and particularly chylous lymphostasis/reflux surrounding or within bone may also stimulate the aggressive osteoclast proliferation responsible for "disappearing bones" in GSD. Eliminating the lymph reflux by interventional lymphatic sclerosis therapy or lymphovenous decompression (diversion) would be predicted to abort this chain of events. Interestingly, older articles referred to LAM as chylous lung

disease and GSD as "chyle in bone" but these terms were later abandoned as specific non-lymphatic cell types (myoepithelial cells, pericytes, or osteoclasts) and molecular events became the focus of investigation and even targeted treatment.

Until non-invasive lymphatic imaging is carried out more widely, earlier in the course of disease, and with enhanced spatial and temporal resolution of dynamic images – and this would seem to be indicated now – the nature of these disorders and approaches to management based on preventing or reversing the life-threatening lymphatic abnormalities will likely remain elusive. If the "primary" lymphatic obstructive hypothesis holds true or applies much earlier in the disease than currently suspected, then screening of lymphatic abnormalities even before they manifest clinically – particularly chylous and non-chylous reflux and "lung perfusion" – by biplanar lymphangioscintigraphy preferably with SPECT-CT localization is indicated. Furthermore, image-guided radiologic (lymphatic sclerosis) (17) or operative interventions such as lymphatic decompressive (lymphatic-venous) shunts (18) or "tumor debulking" (12) should be considered earlier in the course of these diseases rather than focusing on controlling (with attendant adverse side effects) the secondary proliferative effects of lymphatic obstruction and lymphostasis in affected organs.

In summary, the fundamental unanswered question remains: are these primarily lung, bone, or congenital or acquired lymphatic/vascular disorders? Is lymphatic obstruction with or without lymph reflux, lymphatic overgrowth, or tumor formation (with "metastasis") simply secondary to parenchymal involvement and transdifferentiation of cell types in the primary neoplastic process or is it the primary phenomenon? Moreover, the overlapping biomarkers and processes that define neoplasia, cancer, and embryonic development of the lymphatic system as well as the seeming contradiction of terms that underlie the expression "benign metastasizing lymphangioma" remain unresolved. Without improvement in understanding and this possible paradigm shift, introduction of novel therapies will not be available that might improve prognosis, quality of life, and life expectancy for patients afflicted with these perplexing disorders. Lymphologists all over the world need to bring together their experience, knowledge, technology and skills (particularly in diagnostic and interventional imaging and decompressive lymphatic surgery) to positively impact patients with LAM and with GSD.

CONFLICT OF INTEREST AND DISCLOSURE

The author declares that no competing financial interests exist.

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