Published in final edited form as:

Am J Surg Pathol. 2015 October ; 39(10): 1404–1410. doi:10.1097/PAS.0000000000000470.

Incidental Nodal Lymphangioleiomyomatosis Is Not a Harbinger of Pulmonary Lymphangioleiomyomatosis: A Study of 19 Cases with Evaluation of Diagnostic Immunohistochemistry

J. Kenneth Schoolmeester, MD¹ and Kay J. Park, MD²

¹Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

²Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Lymphangioleiomyomatosis (LAM) is a proliferation of perivascular epithelioid cells typically affecting the lung as a low grade, destructive and progressive disease, but may also be found in lymph nodes and other organs. LAM is sometimes seen as an incidental finding in lymph node dissections performed for staging of gynecologic tumors. To our knowledge, no study has investigated the clinical significance of incidental nodal LAM in relation to subsequent development of pulmonary LAM. We identified 19 patients from our institution with LAM in lymph nodes. Follow up was available for 100% of patients and ranged from 3 to 123 months (mean 33.8 months). All were women and ages ranged from 35 to 71 years (mean 56.3). None had a history of tuberous sclerosis, renal angiomyolipoma or pulmonary LAM. LAM involvement spanned 1 to 6 nodes (mean 2) ranging from 1 to 100% of the total excised lymph nodes. The single largest focus of nodal LAM ranged from 1 to 9 mm (mean 4.3) in 18 patients without evidence of persistent or recurrent nodal LAM. In the one patient with persistent local nodal LAM, the greatest diameter was 25 mm. Affected lymph node sites were regional pelvic and retroperitoneal chains routinely sampled in staging operations. An immunohistochemical panel of HMB45, A103 and β -catenin was evaluated in 18 cases. HMB45 showed strong, but usually focal staining in every case compared to A103 which was very focally expressed (39%) or negative. β -catenin showed strong, diffuse cytoplasmic and membranous (nuclear) reactivity in 100% of cases. At last clinic visit, all 19 patients had no manifestations of pulmonary LAM. In an absence of signs of symptoms of extranodal LAM, patients with incidentally discovered nodal LAM smaller than 10 mm are not at risk for developing pulmonary LAM.

Introduction

Lymphangioleiomyomatosis or LAM is a constituent of the PEComa family of tumors, a family defined by a neoplastic proliferation of perivascular epithelioid cells (also called LAM cells in the thoracic literature)(1). Other members in the PEComa family include angiomyolipoma (AML), conventional PEComa (which includes “sugar tumors” and “clear

Corresponding Author: J. Kenneth Schoolmeester, Mayo Clinic, 200 First Street, Rochester, MN 55905, 507-284-2511, schoolmeester.john@mayo.edu.

The authors have no conflict of interest or funding sources to disclose.

cell myomelanocytic tumors”) and *TFE3* translocation-associated PEComa. LAM, like AML, occurs in specific anatomic sites while conventional PEComa and *TFE3* translocation-associated PEComa may arise in many organ systems(2–8). LAM is most commonly diagnosed in the lung where it behaves as a low grade, destructive and progressive lung disease(9). LAM is also found in lymphatics and lymph nodes of the thorax, pelvis and retroperitoneum, sometimes with equally low grade and destructive behavior(10, 11). Patients with pulmonary LAM are typically young women of reproductive age, but rare cases of pulmonary LAM have been described in men(12). Like other members of the PEComa family, there is an association with tuberous sclerosis (TS) and pulmonary LAM is estimated to develop in 4–5% of women with TS(13, 14). However, the vast majority of patients with pulmonary LAM do not have TS or do not have clinically overt signs of TS despite frequent concurrence of AML of the kidney in 16–60% of cases(11, 15).

In patients entirely without signs or symptoms of pulmonary LAM, some investigators have proposed that the presence of nodal LAM may be a high risk indicator for the development of pulmonary LAM. A study of 22 patients with nodal LAM(15), the largest to date, found that a diagnosis of nodal LAM preceded development of pulmonary LAM by 1 to 2 years in 11 patients who were otherwise asymptomatic and in another 9 patients who had signs or symptoms related solely to abdominopelvic nodal LAM. The size of nodal LAM in that study tended to be large, ranging from 10 to 200 mm (mean 53) and total quantity of LAM lesions numbered 1 to 5. Another cohort of 35 patients with pulmonary LAM found coinciding retroperitoneal lymphadenopathy in 77% and pelvic lymphadenopathy in 11% by CT and/or ultrasound although lymph node size ranges were not stated(11). While there is evidence to link large, bulky nodal LAM as either a harbinger or simultaneously occurring lesion of pulmonary LAM, no study has specifically examined the prognostic significance of small, incidental LAM occasionally identified in lymph nodes resected for unrelated purposes. To better understand the clinical behavior of incidental nodal LAM, we studied a large group of patients, each with follow up and most of duration exceeding the 1 to 2 year range quoted for expected development of pulmonary LAM(15). We also evaluated the utility of HMB45, A103 and β -catenin immunohistochemical (IHC) stains in nodal LAM. Diagnosis of LAM in the lung or lymph node may be facilitated by demonstrating expression of melanocytic protein markers HMB45 or A103, but these stains may sometimes be focal or even negative(16). Recently, 28 cases of pulmonary LAM were shown to consistently express β -catenin in a strong and diffuse membranous and cytoplasmic pattern(17). The authors proposed that β -catenin may be a superior marker to traditional IHC in the diagnosis of pulmonary LAM. We evaluated the application of this finding to nodal LAM.

Materials and Methods

Cases of LAM involving lymph nodes were retrieved from Memorial Sloan Kettering Cancer Center’s (MSK) Department of Pathology. Terms “lymphangiomyomatosis” and “lymph node” were used for a search of cases spanning 2004 to 2014. 19 cases were identified. 18 (cases 1–17 and 19) of these were patients whose clinical workup, operative treatment, pathologic evaluation and postoperative management were performed at MSK. One patient (case 18) had her staging surgery performed at another institution, but all slides

processed from this procedure were reexamined at MSK prior to her receiving postoperative therapy. All H&E slides were rereviewed to confirm the patients' diagnoses. Clinicopathologic data and follow up were obtained from the MSK computerized medical record system.

Each case was re-examined to confirm LAM involvement of lymph nodes and any other clinical relevant lesions. These other lesions were the primary purpose of surgery in 18 patients. Nineteen patients had varying degrees of lymph node involvement. The site(s) and total of all surgically sampled lymph nodes, site(s) and total of affected lymph nodes, the largest single focus of LAM as measured by its greatest linear microscopic diameter (done by physically measuring the focus on the glass slide), the mean of the greatest linear microscopic diameter of all LAM in lymph nodes if more than one focus was found (foci in close proximity to one another were considered physically distinct if they were 1 mm or more apart) were recorded.

IHC was performed using a panel of three antibodies: HMB45 (clone HMB45, no dilution, Ventana Medical Systems, Tucson, AZ), A103 (clone A103, no dilution; Ventana Medical Systems) and β -catenin (clone 14, no dilution, Ventana). The Optiview detection system (Ventana) was utilized with positive and negative controls as necessary.

Immunoreactivity for each stain was graded as either strong (S), weak (W) or absent (0) and then focal/patchy or diffuse.

Results

Clinical and follow up data are summarized in Table 1. The 19 patients with nodal LAM were women aged 35–71 years (mean 56.3). None had a history of TS, renal AML or pulmonary LAM. Eighteen patients had surgery for tumors involving the reproductive tract organs, 16 of these tumors were various forms of Müllerian carcinoma, 1 was an adult granulosa cell tumor and the other was leiomyomata (this latter patient, case 7, had a history of sarcoidosis and leukemia which was the clinical basis for lymph node sampling). The remaining patient (case 19) had a laparoscopic resection of a lymph node that was clinically suspected to be lymphoma; she had no history of gynecologic neoplasia.

Follow up was available for 100% of patients and ranged from 3 to 123 months (mean 33.8 months). At last clinic visit, 17 patients were alive with no evidence of pulmonary or nodal LAM, 1 patient had died of serous carcinoma at 23 months post-operation but had no evidence of pulmonary or nodal LAM prior to her death and the last patient (case 19) showed regional persistence of nodal LAM with no evidence of pulmonary LAM. Case 19 was treated with an aromatase inhibitor and initially showed a radiologic decrease in node size at 2 months, but 4 months later had a rebound increase in affected node size.

With the exception of cases 7 and 19, lymph node sampling was performed as part of surgical staging. The pathologic findings are shown in Table 2. All lymph node dissections were from pelvic and retroperitoneal chains including the external and internal iliac, common iliac, para-aortic and aortic lymph nodes and are listed how they were labeled by the submitting surgeon. In some cases, only a regional name was supplied such as "pelvic"

lymph nodes. Total lymph nodes excised from each patient ranged from 3 to 52 nodes (mean 22.3). LAM involvement comprised 1 to 6 nodes (mean 2) ranging from 1 to 100% of the total excised lymph nodes.

Analyzing the 18 patients without evidence of recurrent or persistent nodal LAM, the single largest focus of nodal LAM ranged from 1 to 9 mm (mean 4.3). Similarly, the mean of the largest dimension of all LAM identified in a patient's lymph node(s) ranged from 1 to 7 mm (mean 3.4). Case 19 had a notably larger nodal LAM lesion than the other 18 patients — the greatest diameter was 25 mm and the mean of the largest dimension of all LAM in her lymph nodes was 14 mm.

The histologic findings of nodal LAM were in keeping with PEComa family of tumors. The perivascular epithelioid cell (PEC), can be epithelioid(Fig. 1A) or spindled(Fig. 1B), but the cytoplasm consistently shows a clear to granular and eosinophilic quality that is classically associated with the PEComa family. In nodal LAM, there was often a mixture of both epithelioid and spindled forms(Fig. 1C), but finding just one morphology was also common. In its epithelioid form, LAM tended to have a nested, lobulated and vaguely swirling architecture that was separated by prominent, sharply defined or cleft-like lymphatic spaces. The spindled form took on a more fascicular growth pattern while preserving the nested or somewhat swirling appearance, but the lymphatic vasculature was less prominent. Bands of dense hyaline collagen were sometimes found intermixed. Neither mitotic activity nor necrosis was seen. Distribution of LAM within the lymph node compartments was variable. Some cases were limited to the subcapsular sinus or hilum(Fig. 1D) while others showed node involvement with extranodal extension(Fig. 1E) or frank effacement or replacement of the lymph node parenchyma(Fig. 1F). Aside from the physical extent of PEC proliferation, there were no morphologic differences in case 19 compared to the other 18 cases.

IHC findings are listed in Table 3. Tissue blocks were available for IHC in 18 cases. HMB45 was positive in every case with a strong, but inconsistently either patchy or diffuse pattern(Fig. 2A). A103 was expressed in 7 cases (39%) and was always focal, sometimes labeling no more than 3 or 4 lesional cells. β -catenin was positive in all cases and showed a consistently extensive, strong and diffuse expression in a cytoplasmic and membranous pattern(Fig. 2B). No nuclear expression was identified.

Other lesions identified in lymph nodes include one case with endosalpingiosis and another with endometriosis.

Discussion

Contrasting our findings with observations of prior studies(10, 11, 15), it is evident that nodal LAM exhibits two distinct patterns of proliferation: one which is inert and shows no potential for locally or systemically destructive behavior and the other which is a harbinger or synchronous lesion of pulmonary LAM. What drives nodal LAM to a more aggressive state is unclear. Based on our cohort, other than lesion size, there was no outstanding clinical, anatomic distribution or morphologic feature that could distinguish the 18 patients in which LAM did not recur to the one patient that did or in comparison to all other studies

of aggressive nodal LAM. However, the significance of lesion size cannot be underappreciated since an expansile, occlusive and destructive growth of perivascular epithelioid cells is the very cause of complications in both the lung and lymph node(9). Investigators have speculated a role for sex hormones owing to the routinely strong IHC expression of estrogen and progesterone receptor in LAM as well as the finding of increased severity of symptoms and disease in pregnant patients with LAM(18). Further, Yu *et al*(19) cultured cells from a renal AML in a patient with pulmonary LAM found that both ER α and ER β receptors are present and that these cells show proliferation when exposed to hormonal stimulation. This same group also noted that tamoxifen, a selective estrogen receptor modulator, was effective as estrogen in stimulating growth in the same perivascular epithelioid cell culture. Tamoxifen's capacity to act as both estrogen agonist and antagonist in various human tissues(1) highlights the importance of hormonal stimulation in the release of potent growth factors such as ERK and c-myc.

Other studies have focused on lymphangiogenesis and its role in the progression of LAM. Using antibodies for two vascular endothelial growth factors Flt-4 (a marker specific to lymphatic endothelial cells) and VEGF-C, Kumasaka and colleagues(20) assessed patterns of lymphatic production in cases of pulmonary LAM and nodal LAM. They demonstrated an abundance of lymphatic vessels in LAM, both encircling and enmeshed with the lesional cells. This was in comparison to CD31 expression which was far lower. This same group followed this study with another examining the role these vessels may play in possible dissemination or metastasis of LAM such as from the lung to a lymph node or vice versa(21). They targeted the lymphatic abnormalities associated with pulmonary and nodal LAM such as chylous effusions, chylous ascites and chylous cyst formation. Clusters of LAM, enveloped by lymphatic endothelial cells, were found in all chylous specimens. These cell clusters were specifically seen in intra-LAM lymphatic spaces and were then suggested that through LAM-associated lymphangiogenesis small clumps of lesional cells may enter the lymphatic circulation where they may circulate to other organs.

Other data support a metastatic mechanism for the migration of LAM. Karbowiczek *et al*(22) utilized microsatellite markers and *TSC2* gene mutations to analyze a patient with recurrent LAM following single-lung transplantation. They discovered a matching microsatellite signature and an identical somatic one base pair deletion in exon 18 of *TSC2* in pulmonary and nodal LAM cells in the patient's primary and recurrent LAM. The authors concluded that despite the histologically benign appearance of LAM, it is capable of metastasizing in a subset of patients.

Our data add that it is not the quantity or distribution of nodal lesions that is clinically prognostic, but the largest size of an individual lesion. All 18 patients without recurrent or persistent LAM were under 10 mm in greatest dimension with an average greatest diameter size of 4.3 mm. The finding of 10 mm is relevant when reviewing other reports of nodal LAM that have shown aggressive behavior. In the study of 22 patients by Matsui and colleagues(15), all patients who subsequently or simultaneously developed pulmonary LAM had nodal manifestations of at least 10 mm. Further, a literature review(23) found similarly large nodal LAM of at least 10 mm was either the initial presenting sign of pulmonary LAM or coexisted with pulmonary LAM. Patient 19 in our series whom had locally aggressive

nodal LAM had lesions which measured 25 mm in greatest diameter with an average largest dimension in all her lymph nodes of 14 mm. Whether the size of the lesion is reflective of its internal capacity to proliferate or is being driven by an external source is unknown. Given the proliferative associations of sex hormones and the prevalence of nodal LAM in gynecologic tumor resections identified in our institution, one may reason that an underlying altered hormonal environment induced by a hormone-producing tumor may be a possible explanation. Some gynecologic tumors in our series are capable of producing hyper-estrogenic states such as adult granulosa cell tumor or may be the consequence of a hyper-estrogenic environment such as low grade endometrioid carcinoma. However, such cases were the minority in our cohort and we did not appreciate this trend.

The diagnosis of nodal LAM is usually straightforward. Most cases can be identified by H&E due to the particular morphology and distribution of perivascular epithelioid cells in the lymph node, but in some settings IHC can be helpful. Flavin and authors(17) examined the role of aberrant β -catenin signaling in TS(24), specifically examining the diagnostic value of β -catenin IHC in pulmonary LAM, and compared expression of HMB45 to β -catenin in 28 cases. They found that all 28 cases demonstrated intense β -catenin labeling with a high specificity and a superior overall immunoreactivity to HMB45. We undertook a similar IHC comparison in our series of nodal LAM and found that HMB45 and β -catenin were the more consistently positive markers in nodal LAM (100% of cases) than A103 (39%). Between HMB45 and β -catenin, we believe the latter is the better marker from an interpretation standpoint: HMB45, while strong, was often punctate and focal in contrast to the diffuse, strong cytoplasmic, nonnuclear pattern of β -catenin.

Some cases of nodal LAM may cause difficulty in the setting of a premenopausal patient with replacement of lymph node(s) by LAM. In this scenario, a diagnosis of leiomyomatosis peritonealis disseminata could be considered in the limited differential. A patient with leiomyomatosis peritonealis disseminata classically presents with multiple small nodules smaller than 10 mm scattered on the peritoneum and in the omentum(25). The histologic features are in keeping with leiomyomata: a fascicular arrangement of uniformly bland smooth muscle cells. IHC can be helpful, but it is important to recognize that some smooth muscle tumors may exhibit focal expression of HMB45(26). Therefore, A103 or β -catenin would be our immunostain of choice. Since LAM may often be negative for A103, we believe the diffuse pattern of β -catenin is preferable to confirm a suspected diagnosis of LAM.

In summary, we presented 19 patients with nodal LAM, all with long term follow up at a single institution, and found no evidence of aggressive behavior or development of pulmonary LAM in 18 patients whose lesion(s) measured no greater than 10 mm. We also advocate the use of β -catenin IHC in diagnostically difficult cases for its ease of interpretation.

Acknowledgments

This abstract was presented at the 2015 USCAP Annual Meeting, Boston, MA.

References

1. Finlay G. The LAM cell: what is it, where does it come from, and why does it grow? *Am J Physiol Lung Cell Mol Physiol*. 2004; 286:L690–693. [PubMed: 15003933]
2. Argani P, Aulmann S, Illei PB, et al. A distinctive subset of PEComas harbors TFE3 gene fusions. *Am J Surg Pathol*. 2010; 34:1395–1406. [PubMed: 20871214]
3. Doyle LA, Hornick JL, Fletcher CD. PEComa of the gastrointestinal tract: clinicopathologic study of 35 cases with evaluation of prognostic parameters. *Am J Surg Pathol*. 2013; 37:1769–1782. [PubMed: 24061520]
4. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol*. 2005; 29:1558–1575. [PubMed: 16327428]
5. He W, Cheville JC, Sadow PM, et al. Epithelioid angiomyolipoma of the kidney: pathological features and clinical outcome in a series of consecutively resected tumors. *Mod Pathol*. 2013; 26:1355–1364. [PubMed: 23599151]
6. Schoolmeester JK, Dao LN, Sukov WR, et al. TFE3 Translocation-associated Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract: Morphology, Immunophenotype, Differential Diagnosis. *Am J Surg Pathol*. 2015; 39:394–404. [PubMed: 25517951]
7. Schoolmeester JK, Howitt BE, Hirsch MS, et al. Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. *Am J Surg Pathol*. 2014; 38:176–188. [PubMed: 24418852]
8. Sukov WR, Cheville JC, Amin MB, et al. Perivascular epithelioid cell tumor (PEComa) of the urinary bladder: report of 3 cases and review of the literature. *Am J Surg Pathol*. 2009; 33:304–308. [PubMed: 18971775]
9. McCormack FX, Travis WD, Colby TV, et al. Lymphangioleiomyomatosis: calling it what it is: a low-grade, destructive, metastasizing neoplasm. *Am J Respir Crit Care Med*. 2012; 186:1210–1212. [PubMed: 23250499]
10. Urban T, Lazor R, Lacronique J, et al. Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)*. 1999; 78:321–337. [PubMed: 10499073]
11. Chu SC, Horiba K, Usuki J, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. *Chest*. 1999; 115:1041–1052. [PubMed: 10208206]
12. Aubry MC, Myers JL, Ryu JH, et al. Pulmonary lymphangioleiomyomatosis in a man. *Am J Respir Crit Care Med*. 2000; 162:749–752. [PubMed: 10934115]
13. Castro M, Shepherd CW, Gomez MR, et al. Pulmonary tuberous sclerosis. *Chest*. 1995; 107:189–195. [PubMed: 7813275]
14. Bisceglia M, D'Alessandro V, Simeone A, et al. Selected case from the Arkadi M. Rywlin International Pathology Slide Seminar: Sporadic lymphangioleiomyomatosis. *Adv Anat Pathol*. 2010; 17:445–452. [PubMed: 20966650]
15. Matsui K, Tatsuguchi A, Valencia J, et al. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol*. 2000; 31:1242–1248. [PubMed: 11070117]
16. Johnson SR, Cordier JF, Lazor R, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J*. 2010; 35:14–26. [PubMed: 20044458]
17. Flavin RJ, Cook J, Fiorentino M, et al. beta-Catenin is a useful adjunct immunohistochemical marker for the diagnosis of pulmonary lymphangioleiomyomatosis. *Am J Clin Pathol*. 2011; 135:776–782. [PubMed: 21502434]
18. Oprescu N, McCormack FX, Byrnes S, et al. Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: a population-based registry. *Lung*. 2013; 191:35–42. [PubMed: 23007140]
19. Yu J, Astrinidis A, Howard S, et al. Estradiol and tamoxifen stimulate LAM-associated angiomyolipoma cell growth and activate both genomic and nongenomic signaling pathways. *Am J Physiol Lung Cell Mol Physiol*. 2004; 286:L694–700. [PubMed: 12922981]

20. Kumasaka T, Seyama K, Mitani K, et al. Lymphangiogenesis in lymphangioleiomyomatosis: its implication in the progression of lymphangioleiomyomatosis. *Am J Surg Pathol.* 2004; 28:1007–1016. [PubMed: 15252306]
21. Kumasaka T, Seyama K, Mitani K, et al. Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangioleiomyomatosis. *Am J Surg Pathol.* 2005; 29:1356–1366. [PubMed: 16160479]
22. Karbowniczek M, Astrinidis A, Balsara BR, et al. Recurrent lymphangiomyomatosis after transplantation: genetic analyses reveal a metastatic mechanism. *Am J Respir Crit Care Med.* 2003; 167:976–982. [PubMed: 12411287]
23. Jaiswal VR, Baird J, Fleming J, et al. Localized retroperitoneal lymphangioleiomyomatosis mimicking malignancy. A case report and review of the literature. *Arch Pathol Lab Med.* 2003; 127:879–882. [PubMed: 12823048]
24. Mak BC, Kenerson HL, Aicher LD, et al. Aberrant beta-catenin signaling in tuberous sclerosis. *Am J Pathol.* 2005; 167:107–116. [PubMed: 15972957]
25. Kurman, RJ. International Agency for Research on Cancer., World Health Organization. WHO classification of tumours of female reproductive organs. Lyon: International Agency for Research on Cancer; 2014.
26. Simpson KW, Albores-Saavedra J. HMB-45 reactivity in conventional uterine leiomyosarcomas. *Am J Surg Pathol.* 2007; 31:95–98. [PubMed: 17197924]

Figure 1.

Nodal LAM can have an epithelioid appearance consisting of nests or bundles of uniform perivascular epithelioid cells with typical grainy, eosinophilic to clear cytoplasm round or ovoid nuclei with small nucleoli. Collagen bundles are sometimes intermixed in nodal LAM (A, 400X). Nodal LAM can also be spindled with perivascular epithelioid cells showing similar cytoplasmic and nuclear qualities as their epithelioid counterparts, but with elongated, spindled nuclei and a fascicular growth pattern (B, 200X). In some cases, there is a blending of both epithelioid and spindled forms, but cytologic atypia, mitotic activity or necrosis is not seen (C, 400X). Even in its incidental form, nodal LAM shows a spectrum of proliferation: from a single deposit in the subcapsular sinus (D, 40X) to predominantly an extranodal lesion with only focal involvement of the lymph node (E, 40X) or near replacement of a small lymph node (F, 20X).

Figure 2.

Nodal LAM's immunohistochemical expression of HMB45 is typically focal with a granular or gritty quality that fills just a portion of the cytoplasm (A, 400X). β -catenin consistently strongly and diffusely labels the cytoplasm of nodal LAM, often with an accentuated membranous pattern, that sharply distinguished the lesion from nonneoplastic tissue (B, 200X).

Table 1

Clinical data and follow up of patients with nodal LAM

Case	Age (years)	TS or AML	Primary Indication for Surgery	Follow Up
1	45	No	Clear cell carcinoma of ovary	NED, 123 months
2	61	No	High grade serous carcinoma of ovary	NED, 30 mos.
3	50	No	High grade serous carcinoma of ovary	NED, 94 mos.
4	71	No	Serous carcinoma of uterus	NED, 23 mos.; Died of serous carcinoma
5	59	No	Endometrioid carcinoma of uterus	NED, 60 mos.
6	46	No	Endometrioid carcinoma of uterus	NED, 46 mos.
7	35	No	Leiomyomata of uterus, history of sarcoidosis and leukemia	NED, 46 mos.
8	52	No	Adult granulosa cell tumor of ovary	NED, 29 mos.
9	67	No	MMMT of uterus	NED, 31 mos.
10	46	No	Clear cell carcinoma of ovary	NED, 22 mos.
11	59	No	SCC of cervix	NED, 15 mos.
12	71	No	Mixed serous and endometrioid carcinoma of uterus	NED, 26 mos.
13	45	No	Mucinous carcinoma of ovary	NED, 10 mos.
14	64	No	Endometrioid carcinoma of uterus	NED, 8 mos.
15	59	No	Endometrioid carcinoma of uterus	NED, 8 mos.
16	51	No	High grade serous carcinoma of fallopian tube	NED, 5 mos.
17	58	No	Endometrioid carcinoma of uterus	NED, 3 mos.
18	71	No	Mixed serous and endometrioid carcinoma of uterus	NED, 42 mos.
19	60	No	Nodal LAM	AWD, 21 mos. Treated with AI; node size decreased 2 mos. after, but then increased 4 mos. later

Tuberous sclerosis (TS); renal angiomyolipoma (AML); malignant mixed Mullerian tumor (MMMT); squamous cell carcinoma (SCC); aromatase inhibitor (AI); no evidence of nodal or pulmonary LAM (NED); alive with nodal LAM (AWD)

Table 2

Pathologic findings of nodal LAM

Case	Quantity of Affected Node(s) (% Total)	Total Sampled Nodes	Site(s) of Affected Nodes	Sites of Sampled Nodes	Largest Single Focus of LAM	Average of Largest Dimension of All LAM Foci	Other Lesions
1	1 (3%)	32	R. external iliac	B. external iliac, B. hypogastric, B. obturator, B. common iliac, B. paraaortic, interaortocaval	3 mm	2 mm	Endosalpingiosis
2	1 (2%)	42	R. obturator	B. external iliac, B. hypogastric, B. obturator, B. common iliac, B. paraaortic, interaortocaval	4 mm	3 mm	None
3	3 (8%)	36	L. external iliac, R. paraaortic	B. external iliac, B. hypogastric, B. obturator, B. paraaortic	3 mm	2 mm	None
4	1 (4%)	24	R. pelvic	B. pelvic, B. paraaortic	5 mm	3 mm	None
5	1 (3%)	35	L. obturator	B. external iliac, B. hypogastric, B. obturator, B. pelvic, paraaortic	3 mm	3 mm	None
6	1 (3%)	38	L. pelvic	B. pelvic, R. external iliac, B. paraaortic, L. common iliac, subaortic	6 mm	5 mm	None
7	3 (30%)	10	L. common iliac, L. external iliac, L. obturator	B. external iliac, B. internal iliac, B. obturator, L. common iliac	9 mm	6 mm	None
8	1 (4%)	24	R. obturator	B. external iliac, B. obturator, B. common iliac, B. paraaortic	5 mm	4 mm	None
9	6 (29%)	21	R. pelvic, R. paraaortic	L. external iliac, B. pelvic, B. paraaortic	5 mm	4 mm	None
10	1 (3%)	30	L. external iliac	B. external iliac, B. hypogastric, B. obturator, B. common iliac, B. paraaortic	3 mm	2 mm	Endometriosis
11	2 (2%)	11	L. external iliac, L. common iliac	B. external iliac, B. hypogastric, B. obturator, B. common iliac, B. aortic	4 mm	2 mm	None
12	2 (25%)	8	B. obturator	R. external iliac, B. obturator,	3 mm	4 mm	None
13	3 (6%)	52	R. paraaortic	B. pelvic, B. paraaortic	1 mm	1 mm	None
14	2 (13%)	16	L. hypogastric	B. external iliac, B. hypogastric, B. obturator, B. common iliac, B. aortic	5 mm	5 mm	None
15	1 (33%)	3	R. external iliac	B. external iliac	2 mm	1 mm	None
16	2 (11%)	18	L. external iliac	L. external iliac, L. obturator, B. paraaortic, L. common iliac	3 mm	2 mm	None
17	3 (75%)	4	B. external iliac	B. external iliac	7 mm	5 mm	None
18	1 (1%)	17	L. pelvic	B. pelvic, B. paraaortic	7 mm	7 mm	None
19	3 (100%)	3	L. common iliac, L. pelvic	L. common iliac, L. pelvic	25 mm	14 mm	None

B. (bilateral); R. (right); L. (left)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Immunohistochemical findings of nodal LAM

Case	HMB45	A103	β -catenin
1	S, diffuse	0	S, diffuse
2	S, patchy	0	S, diffuse
3	S, patchy	0	S, diffuse
4	S, diffuse	S, focal	S, diffuse
5	S, patchy	0	S, diffuse
6	S, diffuse	0	S, diffuse
7	S, diffuse	S, focal	S, diffuse
8	S, patchy	0	S, diffuse
9	S, diffuse	S, focal	S, diffuse
10	S, patchy	0	S, diffuse
11	S, patchy	W, focal	S, diffuse
12	S, patchy	0	S, diffuse
13	S, diffuse	S, focal	S, diffuse
14	S, patchy	W, focal	S, diffuse
15	S, patchy	0	S, diffuse
16	S, patchy	0	S, diffuse
17	S, patchy	S, focal	S, diffuse
18	ND	ND	ND
19	S, patchy	0	S, diffuse

Strong (S); weak (W); negative (0); ND (not done)