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Lymphangioleiomyomatosis of the Pelvic Lymph Nodes Detected Incidentally During Surgical Staging of Gynecological Malignancies: Comprehensive Clinicopathological Analysis of 17 Consecutive Cases from a Single Institution

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Abstract. *Background/Aim: Lymphangioleiomyomatosis (LAM) belongs to the perivascular epithelioid cell tumor (PEComa) family. The relationship between LAM and tuberous sclerosis complex (TSC) is of particular concern in a subset of women with clinically occult LAM involving the pelvic lymph nodes. This study aimed to investigate the clinicopathological features of incidental nodal LAM detected during the surgical staging of gynecological tumors. Patients and Methods: During the study period of 10 years, we identified 17 patients with pelvic nodal LAM that was incidentally detected during surgery for gynecological neoplastic lesions. We conducted immunostaining to assess the diagnostic utility of a panel of PEComa markers. Results: Two of the 17 patients (11.8%) were diagnosed with TSC before surgery without any pulmonary symptoms. During the follow-up, both patients developed pulmonary and extrapulmonary LAMs. All affected nodes were multiple and unilateral in the pelvic region. The mean nodal size was 5.4 mm, and the mean proportion of the area involved in the LAM was 34.1%. In two patients with TSC, the largest affected node measured 19.3 mm and 7.6 mm, respectively, and the proportion of the area replaced by LAM was 99% and 90%, respectively. The most frequently expressed markers were human melanoma black 45 and cathepsin K, which showed 100% positivity in all the examined cases. Conclusion: While most small nodal LAMs incidentally discovered during surgery have insignificant prognostic value, larger nodal LAMs occupying most of the nodal parenchyma at reproductive age should raise awareness of pulmonary and extrapulmonary LAMs as well as TSC.*

Lymphangioleiomyomatosis (LAM) is a member of the family of lesions known collectively as perivascular epithelioid cell tumors (PEComas) (1, 2). Other members of this family include angiomyolipoma (AML), transcription factor E3 (TFE3) translocation-associated PEComa, and clear cell myelocytic tumors. LAM cells consistently express melanogenesis-related markers and smooth muscle markers, which are commonly observed in PEComas (1). Conventional and TFE3 translocation-associated PEComas arise in various organ systems, whereas LAM is restricted to specific anatomical locations (3-5). LAM most commonly affects the lungs, where it behaves as a low-grade but destructive disease, leading to progressive respiratory failure (6). Additionally, LAM can be found in the lymphatic vessels and lymph nodes of the mediastinum, retroperitoneum, and pelvic cavity (7). The clinical manifestations, behavior, and histological features of extrapulmonary LAM differ from those of pulmonary LAM, despite the similar immunophenotype of LAM cells (8).

Extrapulmonary LAM may be associated with PEComa family tumors or various manifestations of tuberous sclerosis complex (TSC). Notably, it remains unclear whether all patients with extrapulmonary LAM also have pulmonary LAM or are at risk of developing it. Therefore, the potential relationship between LAM and TSC is of particular concern in a unique subset of women with clinically occult LAM involving the pelvic lymph nodes, which is detected incidentally during the surgical staging of uterine and ovarian malignancies. In this

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study, to better understand the clinical behavior of nodal LAM, we investigated the clinicopathological characteristics of incidental pelvic nodal LAM detected during the surgical staging of gynecological neoplastic lesions. Additionally, we performed immunostaining for a panel of markers commonly employed in diagnosing PEComas to assess their utility in nodal LAM.

Patients and Methods

Case selection and data collection. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (protocol number: 2024-07-028; approval date: July 11, 2024). We searched institutional databases for cases matching the keywords "lymphangioleiomyoma" and "lymphangioleiomyomatosis" that occurred between January 2013 and December 2022. We identified 44 consecutive patients with LAM involving various organs. Two board-certified pathologists specializing in gynecological oncology (Y.L. and H.S.K.) thoroughly reviewed all available hematoxylin and eosin-stained slides to confirm the pathological diagnosis of LAM, collect pathological information, and assess the presence of sufficient lesional tissue for immunohistochemical staining. Seventeen of the 44 cases were confirmed as pelvic nodal LAM incidentally detected during surgical staging for gynecological malignancies and premalignant lesions, while 27 cases of LAM arising in the lungs (18 cases), retroperitoneum (three cases), pancreas (two cases), stomach (two cases), supraclavicular lymph node (one case), and recurrent laryngeal nerve lymph node (one case) were excluded from this study. The following clinical information was obtained from electronic medical records: patient age at the time of diagnosis; clinical history of TSC, pulmonary LAM, and extrapulmonary LAM; primary indication for surgical staging and procedure; current status and survival data; and postoperative follow-up duration. The following pathological data were also collected: number of sampled and affected nodes, laterality, location, and size of affected nodes; percentage of microscopic area replaced by LAM; microanatomical topography of LAM; concurrent nodal lesions; and concurrent uterine lesions.

Immunostaining. Immunostaining was performed using a Bond-max automated immunostainer (Leica Biosystems, Deer Park, IL, USA) and Bond Polymer Refine Detection (Leica Biosystems) (9-25). Briefly, 4-μm-thick, formalin-fixed, paraffin-embedded tissue sections were deparaffinized in xylene and rehydrated using a graded alcohol series. After antigen retrieval, the sections were incubated with primary antibodies against human melanoma black 45 (HMB45; dilution, 1:80; clone, HMB45; Agilent Technologies, Santa Clara, CA, USA), melan A (dilution, 1:80; clone, A108; Agilent Technologies), cathepsin K (dilution, 1:500; clone, EPR19992; Abcam, Waltham, MA, USA), microphthalmia-associated transcription factor (MiTF; prediluted; clone, 34CA5; Biocare Medical, Pacheco, CA, USA), desmin (dilution, 1:200; clone, D33; Agilent Technologies), estrogen receptor (ER; dilution, 1:200; clone, 6F11; Leica Biosystems), progesterone receptor (PR; dilution, 1:1,800; clone, 16; Leica Biosystems), and D2-40 (dilution, 1:100; clone, D2-40; Agilent Technologies). After chromogenic visualization, slides were counterstained with hematoxylin, dehydrated, cleared, and mounted. Positive and negative controls were stained concurrently. Positive controls included cutaneous nodular malignant melanoma for HMB45, melan A, cathepsin K, and MiTF; uterine leiomyoma for desmin; luminal A-type invasive breast carcinoma for ER and PR; and peritoneal epithelioid malignant mesothelioma for D2-40. Negative controls were prepared by substituting non-immune serum for the primary antibodies, resulting in undetectable staining. Each immunostained slide was scored by two board-certified pathologists. Staining intensities for all examined proteins were designated as negative, weak, moderate, or strong, and staining proportions were determined in 5% increments across a 0%-100% range and classified as focal (<50%) or diffuse (≥50%).

Results

Clinical features. We identified 17 patients with pelvic nodal LAM that was incidentally discovered during surgical staging of gynecological malignancies. Table I presents the detailed clinical characteristics of the patients. The mean patient age was 52.1 years (range=41-74 years). Two of the 17 patients (11.8%; cases 7 and 16) had been diagnosed with TSC prior to undergoing gynecological surgery. None of the patients presented respiratory signs or symptoms related to pulmonary LAM at the time of diagnosis. However, during the follow-up period, these two patients developed both pulmonary and extrapulmonary LAM affecting the uterus and kidneys. Regarding the primary indications for surgical staging, 10 patients (58.8%) underwent total hysterectomy for endometrial carcinoma, and radical hysterectomy was performed in three patients with endocervical adenocarcinoma (17.6%). Additionally, two patients (11.8%) underwent surgical staging for ovarian carcinoma, and one patient (5.9%) for uterine rhabdomyosarcoma. Endometrioid carcinoma was the most common histological type (9/17, 52.1%). Other recorded types included two cases of human papillomavirus-independent gastric-type endocervical adenocarcinoma, one case of mixed serous and clear cell endometrial carcinoma, and one case of uterine rhabdomyosarcoma. Bilateral pelvic lymph node dissection was performed in all but one patient, who underwent sentinel lymph node biopsy. Postoperative follow-up information was available for all patients, with a mean follow-up period of 31.7 months (range=6-67 months). One patient (case 15), who died of uterine rhabdomyosarcoma six months after surgery, was the only mortality recorded during the follow-up period. The remaining 16 patients were followed up for more than a year and are currently alive. Twelve of these patients have shown no evidence of recurrent disease, while four experienced persistent systemic metastases. Table II summarizes the clinical features of these 17 patients.

Pathological features. Table III details the pathological characteristics of the patients. The mean number of lymph nodes sampled was 12 (range=4-26). In over half of the patients (9/17, 52.1%), LAM affected multiple lymph nodes, with right-sided and unilateral involvement (15/17, 88.2% for both). The mean size of the affected nodes was 5.4 mm (range=1.0-19.3 mm), and the mean proportion of the

Table I. *Clinical characteristics of 17 patients with incidental pelvic or para-aortic lymphangioleiomyomatosis (LAM).*

Case No	Age (years)	TSC	Pulmonary LAM	Extrapulmonary LAM	Primary indication for for surgical staging	Surgical staging procedure	Survival status	Follow-up (months)
1	55	No	No	No	Endocervical UAC	RH, PLND	ANED	12
2	47	No	No	No	Endocervical GAC	RH, BSO, PLND, PALND, OMT	ANED	36
3	42	No	No	No	Endocervical GAC	RH, BS, PLND	AWD	30
4	66	No	No	No	Cervical HSIL	TH, BSO, PLND	ANED	14
5	43	No	No	No	Endometrial EC	TH, RS, LSO, PLND	ANED	53
6	41	No	No	No	Endometrial EC	TH, RS, LSO, PLND	ANED	43
7	41	Yes	Yes	Yes (kidney and uterus)	Endometrial EC	TH, RS, LSO, PLND	ANED	40
8	56	No	No	No	Endometrial EC	TH, BSO, PLND	AWD	43
9	48	No	No	No	Endometrial EC	TH, BS, PLND	ANED	41
10	70	No	No	No	Endometrial mixed SC and CCC	TH, BSO, PLND, OMT, PRT, APP	AWD	26
11	53	No	No	No	Endometrial EC	TH, PLND, OMT, PRT	ANED	26
12	55	No	No	No	Endometrial EC	TH, BSO, SLNB	ANED	31
13	41	No	No	No	Endometrial EC	TH, BS, PLND	ANED	15
14	52	No	No	No	Endometrial EC	TH, BSO, PLND	ANED	12
15	74	No	No	No	Uterine RMS	TH, BSO, PLND, OMT, PRT	DOD	6
16	43	Yes	Yes	Yes (kidney and uterus)	Ovarian CCC	TH, RSO, PLND, OMT, PRT, APP	ANED	67
17	59	No	No	No	Ovarian HGSC	TH, BSO, PLND, PALND, OMT, PRT, APP	AWD	43

ANED: Alive with no evidence of disease; AWD: alive with disease; APP: appendectomy; BS: bilateral salpingectomy; BSO: bilateral salpingo-oophorectomy; CCC: clear cell carcinoma; DOD: died of disease; EC: endometrioid carcinoma; GAC: gastric-type adenocarcinoma; HGSC: high-grade serous carcinoma; HSIL: high-grade squamous intraepithelial lesion; LSO: left salpingo-oophorectomy; OMT: omentectomy; PALND: para-aortic lymph node dissection; PLND: pelvic lymph node dissection; PRT: peritonectomy; RH: radical hysterectomy; RMS: rhabdomyosarcoma; RS: right salpingectomy; RSO: right salpingo-oophorectomy; SC: serous carcinoma; SLNB: sentinel lymph node biopsy; TH: total hysterectomy; TSC: tuberous sclerosis complex; UAC: usual-type adenocarcinoma.

intranodal microscopic area replaced by LAM was 34.1% (range=5%-99%). In the two patients with TSC, the greatest dimensions of affected lymph nodes were 19.3 mm and 7.6 mm, and the areas occupied by LAM were 99.0% and 90.0%, respectively. Figure 1 illustrates the histological and immunohistochemical features of nodal LAM. LAM lesions consisted of bland epithelioid or spindle cells with eosinophilic cytoplasm, similar to normal smooth muscle cells. Epithelioid LAM cells exhibited a nested or nodular architecture (Figure 1A) and demonstrated varying degrees of cathepsin K immunoreactivity (Figure 1B). The nests of LAM cells were surrounded by cleft-like lymphatic spaces highlighted by D2-40 immunostaining (Figure 1C). Lesional cells showed reactivity for HMB45 (Figure 1D), MiTF (Figure 1E), desmin (Figure 1F), and ER (Figure 1G). In four cases (23.5%), LAM cell clusters were located adjacent to metastatic carcinoma cells and glands (Figure 1H and I), and it was considered possible that metastatic carcinoma cells could be overlooked due to their sparse presence. In one instance, metastatic endocervical adenocarcinoma cells were obscured by proliferating LAM cells. Spindle cell areas of LAM lesions displayed a fascicular growth pattern with a less distinct lymphatic endothelial lining. There was no evidence of nuclear enlargement, pleomorphism, prominent nucleoli, or brisk mitotic activity. Additionally, no necrosis or hemorrhage was observed. Although LAM predominantly involved the nodal parenchyma, it also extended into the subcapsular sinus and extranodal lymphatic vessels or soft tissue in some cases.

Immunostaining results. Table IV presents the results of immunostaining, which was performed in all but one case due to an insufficient nodal tissue sample. The most commonly expressed markers in LAM were HMB45 and cathepsin K, with 100% positivity in the 16 cases analyzed. LAM cells displayed diffuse and strong cytoplasmic immunoreactivity for both markers, with a granular staining pattern. The mean staining proportion for cathepsin K (94.4%; range=70%-100%) was higher than that for HMB45 (59.1%), which had a wider proportional range (5%-100%). High positivity rates were also noted for MiTF and desmin (93.8% for both). MiTF showed nuclear and cytoplasmic expression, while desmin was confined to the cytoplasm. D2-40 staining highlighted the lymphatic endothelial lining in all but one case (93.8%). The positivity rates for ER and PR were 81.3% and 68.8%, respectively, with variable staining intensities and

proportions. Melan A was the least frequently expressed marker, showing focal weak-to-moderate immunoreactivity in six cases (37.5%). Differences in immunostaining patterns were noted between epithelioid and spindle cell lesions. Spindle LAM cells (Figure 2A) exhibited faint MiTF immunoreactivity (Figure 2B) but strong cytoplasmic expression of cathepsin K (Figure 2C) and desmin (Figure 2D). In contrast, epithelioid LAM cells (Figure 2E) showed uniform and strong nuclear MiTF expression (Figure 2F), moderate-to-strong perinuclear cathepsin K immunoreactivity (Figure 2G), and weak desmin expression (Figure 2H). Table V summarizes the pathological and immunophenotypic features of incidental nodal LAM cases.

Discussion

In patients without signs or symptoms of pulmonary LAM, some studies suggest that nodal LAM presence indicates a high likelihood of developing pulmonary LAM (26, 27). Matsui *et al*. (26) analyzed 22 Japanese patients with nodal LAM and reported that the diagnosis preceded that of pulmonary LAM by 1-2 years, with half of the patients being asymptomatic. Similarly, Chu *et al*. (27) found that in 27 out of 35 patients (77.1%) with pulmonary LAM, imaging revealed retroperitoneal lymphadenopathy. In contrast, Rabban *et al*. (8) reported that in all 26 patients studied, the nodal LAM was occult with a mean size of 3.5 mm, and none had a history of pulmonary LAM or respiratory failure. They concluded that nodal LAM does not necessarily correlate with TSC or pulmonary LAM when incidentally detected during staging surgery for gynecological or urinary tumors (8). Similarly, Schoolmeester and Park (7) also showed that none of their 19 patients had a history of TSC, renal AML, or pulmonary LAM, and none exhibited clinical manifestations of pulmonary LAM. This suggests that incidentally discovered nodal LAM may not predict the development of pulmonary LAM. Taken together, the clinical relevance of nodal LAM in predicting pulmonary LAM remains controversial. Although a few studies have examined the prognostic significance of small incidental LAM detected in lymph nodes resected for unrelated purposes, nodal LAM still appears to exhibit two distinct clinical behaviors (7). In most patients, it is a non-aggressive, incidental finding with insignificant prognostic value, while in a few cases, it represents a precursor to destructive LAM, such as pulmonary LAM or multiple extrapulmonary LAMs. Therefore, we aimed to analyze the clinicopathological characteristics of incidental pelvic nodal LAM with respect to its association with the development of pulmonary LAM.

In this study, among the 17 patients with incidental nodal LAM, two (11.8%) developed pulmonary, renal, and uterine LAM. This proportion was higher than that in a previous study (2/61; 3.3%) (28). However, our findings do not necessarily indicate a direct association between pelvic LAM and the development of TSC, pulmonary LAM, or multiple extrapulmonary LAMs. Both affected patients (41 and 43 years old) were younger than the mean age of 52.1 years, and

Table II. *Summary of clinical characteristics of 17 patients with incidental pelvic or para-aortic lymphangioleiomyomatosis (LAM).*

Characteristic	Number of cases (%)
Mean age (range; years)	59 (41-74)
Clinical diagnosis of tuberous sclerosis complex	
Yes	2 (17.8)
No	15 (88.2)
Pulmonary LAM	
Yes	2 (17.8)
No	15 (88.2)
Extrapulmonary LAM	
Yes	2 (17.8)
No	15 (88.2)
Primary indication for surgical staging	
Cervix	
Gastric-type adenocarcinoma	2 (17.8)
Usual-type adenocarcinoma	1 (5.9)
High-grade squamous epithelial lesion	1 (5.9)
Endometrium	
Endometrioid carcinoma	9 (52.9)
Mixed serous and clear cell carcinoma	1 (5.9)
Uterus	
Rhabdomyosarcoma	1 (5.9)
Ovary	
High-grade serous carcinoma	1 (5.9)
Clear cell carcinoma	1 (5.9)
Surgical staging procedure	
Uterus	
Total hysterectomy	14 (82.4)
Radical hysterectomy	3 (17.6)
Adnexa	
BSO	8 (47.1)
RSO	1 (5.9)
RS and LSO	3 (17.6)
BS	3 (17.6)
Lymph node	
PLND	14 (82.4)
PALND	0 (0.0)
PLND and PALND	2 (11.8)
SLNB	1 (5.9)
Omentectomy	6 (35.3)
Appendectomy	3 (17.6)
Peritonectomy	5 (29.4)
Survival status	
Alive with no evidence of disease	12 (70.6)
Alive with disease	4 (23.5)
Died of other cause	0 (0.0)
Died of disease	1 (5.9)
Mean follow-up (range; months)	31.7 (6-67)

BS: Bilateral salpingectomy; BSO: bilateral salpingo-oophorectomy; LSO: left salpingo-oophorectomy; PALND: para-aortic lymph node dissection; PLND: pelvic lymph node dissection; RS: right salpingectomy; RSO: right salpingo-oophorectomy; SLNB: sentinel lymph node biopsy.

Table III. *Pathological characteristics of 17 patients with incidental pelvic or para-aortic lymphangioleiomyomatosis (LAM).*

Case No	Number of sampled nodes	Number of affected nodes	Laterality of affected nodes	Location of affected nodes	Size of affected nodes (mm; largest if multiple)	Proportion of area replaced by LAM (%)	Microscopic topography of LAM	Concurrent nodal lesion	Concurrent uterine lesion
1	7	2	Unilateral (right)	Pelvic	1.4	15	NP	None	None
2	19	3	Unilateral (right)	Pelvic	5.0	20	ENST	Metastatic carcinoma (1/19, 2 mm)	None
3	26	3	Bilateral	Pelvic	3.0	10	NP	Metastatic carcinoma (2/26; <1 mm)	None
4	5	1	Unilateral (right)	Pelvic	1.5	5	SCS	None	AM
5	15	4	Unilateral (right)	Pelvic	7.0	50	NP, ENLV	None	None
6	7	2	Unilateral (right)	Pelvic	6.7	40	NP, ENST	None	None
7	4	4	Unilateral (right)	Pelvic	7.6	90	NP, ENST, ENLV	None	AM, LM
8	10	2	Unilateral (right)	Pelvic	4.7	10	NP	None	AM, LM
9	15	10	Bilateral	Pelvic	5.3	70	NP, ENST, ENLV	None	AM
10	16	1	Unilateral (right)	Pelvic	1.0	5	SCS	None	AM, LM
11	11	1	Unilateral (left)	Pelvic	5.5	20	NP	Metastatic carcinoma (1/11; 8 mm)	AM
12	8	1	Unilateral (right)	Pelvic (right obturator sentinel)	1.3	5	NP	None	AM
13	7	1	Unilateral (left)	Pelvic	7.0	25	NP, ENST	None	AM
14	8	1	Unilateral (right)	Pelvic	7.3	40	NP	None	LM
15	15	1	Unilateral (right)	Pelvic	1.8	5	NP	None	LM
16	8	3	Unilateral (right)	Pelvic	19.3	99	NP	Metastatic carcinoma (1/8; 9 mm)	None
17	23	1	Unilateral (left)	Pelvic	6.8	70	NP, ENLV	None	LM

AM: Adenomyosis; ENLV: extranodal lymphatic vessel; ENST: extranodal soft tissue; LM: leiomyoma; NP: nodal parenchyma; SCS: subcapsular sinus.

their affected nodes (19.3 mm and 7.6 mm) were much larger than those of other patients. The proportions of microscopic areas replaced by LAM were 99.0% and 90.0%, respectively. In a previous study by Schoolmeester and Kay (7), the largest nodal LAM (25 mm) was also locally aggressive. The authors emphasized lesion size as a key clinical prognostic factor, rather than the total number or distribution of lesions. Similarly, Matsui *et al*. (26) found that patients who developed pulmonary LAM had nodal LAMs measuring at least 10 mm. A review by Jaiswal *et al*. (29) also highlighted that patients with nodal LAMs of at least 10 mm either had concurrent pulmonary LAM or developed it later. Thus, it is reasonable to assume that larger LAM lesions, extensive (≥90%) involvement of the nodal area, or both may help predict the development of pulmonary LAM or other PEComa family tumors. Given the locally destructive nature of pulmonary LAM and its association with respiratory failure, screening and early detection of large nodal LAM could improve patient outcomes by facilitating earlier intervention.

Histologically, LAM involving extranodal soft tissue can resemble intravenous leiomyomatosis and angiomyomatous hematoma (8), as all three exhibit benign spindle cell proliferation with smooth muscle differentiation. The presence of large dilated veins surrounding leiomyomatous nodules favors the diagnosis of intravenous leiomyomatosis. Nodal angiomyomatous hamartoma is characterized histologically by the partial replacement of normal nodal parenchyma with proliferating smooth muscle cells and disorganized blood vessels. The presence of irregularly distributed, thick-walled vessels within a dense fibrocollagenous stroma supports the diagnosis of angiomyomatous hamartoma. Concurrently, nodal LAM cells frequently coexist with metastatic carcinoma cells, which might be overlooked due to their minimal quantity or because they are obscured by proliferating LAM cells. In this study, two cases of endocervical adenocarcinoma, one case of endometrial endometrioid carcinoma, and one case of ovarian clear cell carcinoma metastasized to the pelvic lymph nodes, where LAM lesions were incidentally detected. While the

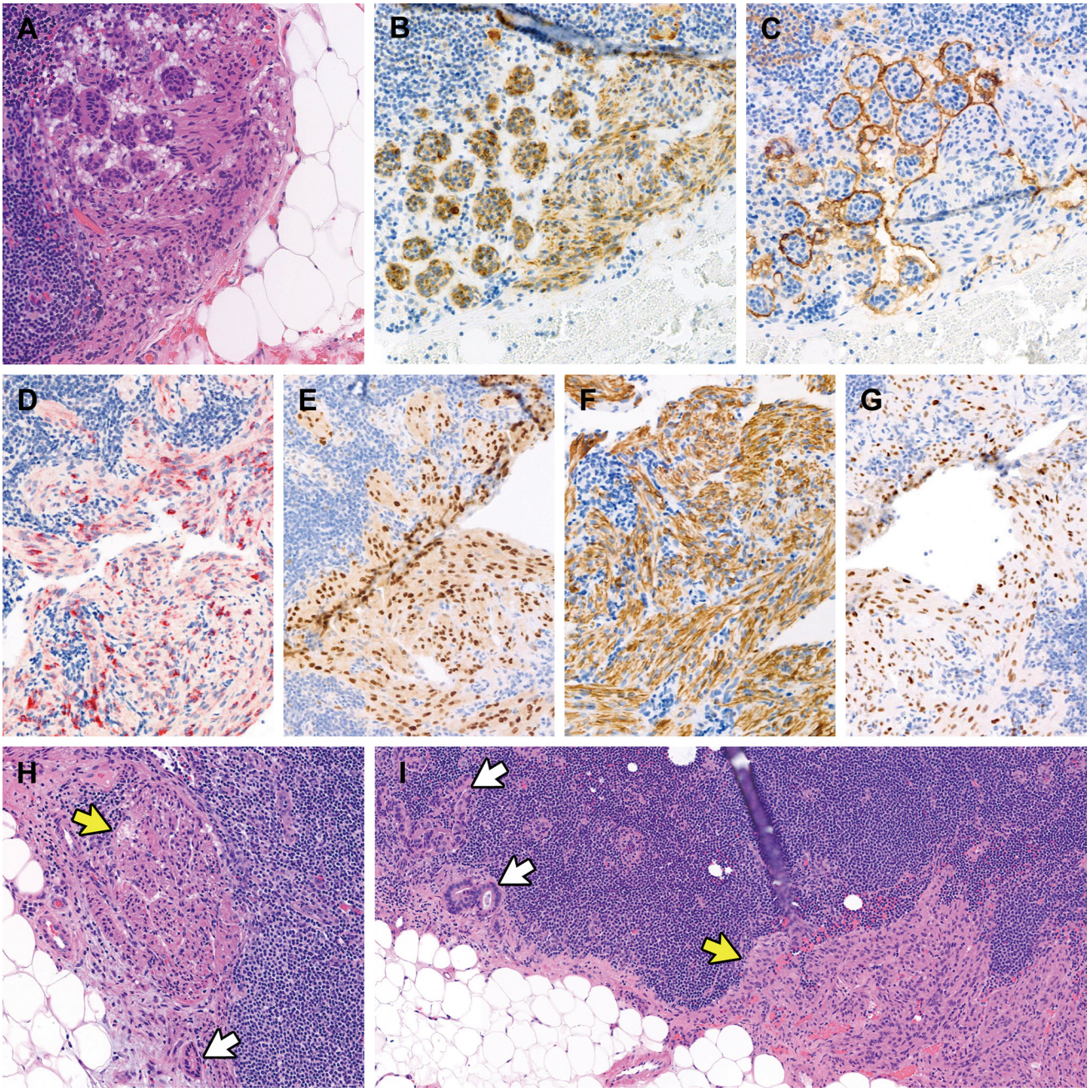

Figure 1. *Histological and immunophenotypical features of incidental nodal lymphangioleiomyomatosis (LAM). (A) Epithelioid LAM exhibits a nested or nodular architecture and demonstrates varying degrees of immunoreactivities for (B) cathepsin K. (C) The LAM cell nests are surrounded by cleft-like lymphatic spaces, highlighted by D2-40 immunostaining. The lesional cells also react with (D) human melanoma black 45, (E) microphthalmia transcription factor, (F) desmin, and (G) estrogen receptor. (H and I) The LAM cell clusters (yellow arrows) are located closely adjacent to metastatic carcinoma cells and glands (white arrows), which can be overlooked because of their small quantity.*

histological diagnosis of nodal LAM is generally straightforward, immunostaining for melanocytic and smooth muscle markers can further confirm the diagnosis (30). Previous studies have shown that HMB45 and MiTF exhibit higher diagnostic sensitivity than other markers, such as melan A (7, 8). In this study, we performed immunostaining for cathepsin K, which has recently been recognized as a sensitive marker for pulmonary LAM and PEComas (31, 32). Although Uehara *et al*. (33) reported that varying degrees of cathepsin K immunoreactivity were observed in less than 50% of the

Table IV. *Immunophenotypes of 17 patients with incidental pelvic or para-aortic lymphangioleiomyomatosis (LAM).*

Case No	HMB-45	Melan-A	MiTF	Cathepsin K	Desmin	ER	PR	D2-40
1	DSP (60%)	FMP (5%)	DSP (100%)	DSP (100%)	DSP (100%)	DSP (60%)	Negative	DSP (100%)
2	DSP (90%)	Negative	FSP (10%)	DSP (100%)	DSP (100%)	FSP (40%)	DSP (100%)	DSP (100%)
3	DSP (100%)	Negative	DSP (100%)	DSP (100%)	Negative	Negative	Negative	FSP (40%)
4	FSP (30%)	FWP (30%)	DSP (100%)	DWP (90%)	DSP (100%)	FSP (30%)	Negative	DSP (100%)
5	FSP (30%)	Negative	DSP (60%)	DSP (100%)	FSP (40%)	FWP (20%)	DSP (80%)	DSP (100%)
6	DSP (100%)	Negative	DSP (80%)	DSP (100%)	DSP (100%)	Negative	FSP (30%)	DWP (100%)
7	DSP (60%)	Negative	DSP (80%)	DSP (100%)	DSP (100%)	DSP (80%)	DSP (100%)	DSP (100%)
8	FSP (10%)	Negative	DSP (100%)	DSP (100%)	DSP (80%)	FMP (40%)	FSP (10%)	FMP (30%)
9	FSP (20%)	Negative	DSP (100%)	DSP (100%)	DSP (70%)	FSP (30%)	FSP (30&)	DSP (100%)
10	NA	NA	NA	NA	NA	NA	NA	NA
11	DSP (80%)	Negative	FSP (20%)	DSP (100%)	DSP (60%)	FSP (10%)	FSP (10%)	DSP (100%)
12	DSP (100%)	Negative	NA	DWP (100%)	DSP (100%)	NA	NA	NA
13	DSP (70%)	FMP (5%)	DSP (100%)	DSP (100%)	DSP (100%)	FWP (40%)	DSP (100%)	DSP (100%)
14	DMP (60%)	FWP (10%)	DSP (100%)	DSP (30%)	DSP (60%)	DSP (80%)	FWP (30%)	DSP (100%)
15	DSP (100%)	FWP (10%)	DSP (100%)	DSP (100%)	DSP (80%)	FSP (10%)	Negative	DSP (100%)
16	FSP (5%)	Negative	DSP (100%)	DSP (90%)	FSP (10%)	FWP (10%)	DSP (100%)	FSP (10%)
17	FSP (30%)	FSP (30%)	FSP (30%)	DSP (100%)	DSP (90%)	FSP (30%)	FSP (10%)	DSP (100%)

DSP: Diffuse strongly positive; FSP: focal strongly positive; FMP: focal moderately positive; FWP: focal weakly positive; NA: not applicable.

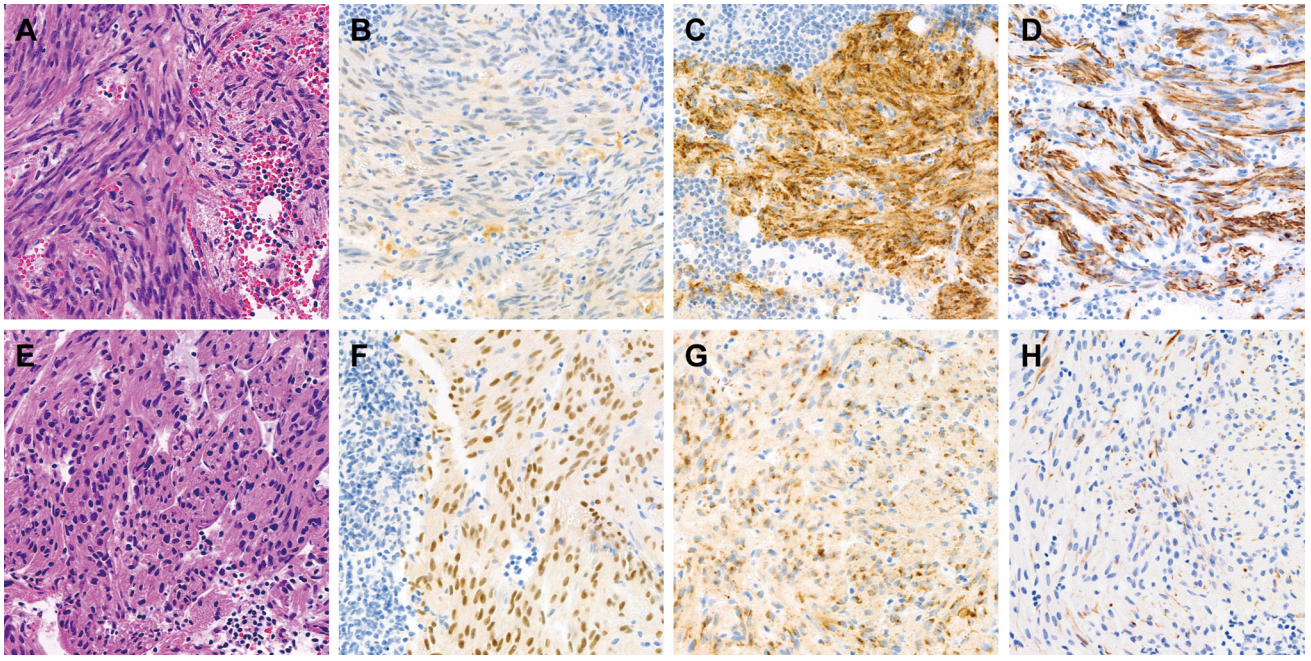

Figure 2. *Distinct immunostaining patterns between areas of (A-D) spindle cell and (E-H) epithelioid morphology in nodal lymphangioleiomyomatosis (LAM). (A) Spindle-shaped LAM cells demonstrate (B) subtle immunoreactivity for MiTF and diffuse and strong cytoplasmic expression for (C) cathepsin K and (D) desmin. Conversely, (E) epithelioid LAM cells exhibit (F) consistent and strong nuclear expression for MiTF, (G) perinuclear dot-like immunoreactivity for cathepsin K, and (H) focal and weak expression for desmin.*

lesion areas, moderate-to-strong cathepsin K immunoreactivity was observed in more than 50% of the lesion areas in most cases. More importantly, cathepsin K was found to be more consistently expressed in LAM cells than in MiTF and desmin cells, which exhibited different expression patterns between epithelioid and spindle cell morphologies. Moreover, MiTF expression was more diffuse and strongly positive in epithelioid LAM cells, whereas spindle cell lesions displayed faint MiTF expression. Desmin was uniformly positive in areas of spindle cell morphology with strong intensity;

Table V. *Summary of pathological and immunophenotypical characteristics and immunophenotypes of 17 patients with incidental pelvic or para-aortic lymphangioleiomyomatosis (LAM).*

Characteristic	Number of cases (%)
Mean number of sampled nodes (range)	12 (4-26)
Number of affected nodes	
Single	8 (47.1)
Multiple	9 (52.9)
Laterality of affected nodes	
Unilateral	15 (88.2)
Bilateral	2 (11.8)
Location of affected nodes	
Pelvic	17 (100.0)
Para-aortic	0 (0.0)
Pelvic and para-aortic	0 (0.0)
Mean largest size of affected nodes (mm; range)	5.4 (1.0-19.3)
Mean proportion of area replaced by LAM (%; range)	34.1 (5.0-99.0)
Microscopic topography of LAM	
Confined to the subcapsular spaces	2 (11.8)
Nodal parenchyma	15 (88.2)
Extranodal soft tissues	4 (23.5)
Extranodal lymphatic vessels	4 (23.5)
Concurrent lesion involving lymph nodes	
Metastatic carcinoma	4 (23.5)
Endosalpingiosis	0 (0.0)
Endometriosis	0 (0.0)
Reactive lymphoid hyperplasia	0 (0.0)
Concurrent uterine lesion	
Adenomyosis	8 (47.1)
Leiomyoma	6 (35.3)
HMB45	
Positive	16 (100.0)
Negative	0 (0.0)
Melan-A	
Positive	6 (37.5)
Negative	10 (62.5)
MiTF	
Positive	15 (93.8)
Negative	1 (6.3)
Cathepsin K	
Positive	16 (100.0)
Negative	0 (0.0)
Desmin	
Positive	15 (93.8)
Negative	1 (6.3)
ER	
Positive	13 (81.3)
Negative	3 (18.8)
PR	
Positive	11 (68.8)
Negative	5 (31.3)
D2-40	
Positive	15 (93.8)
Negative	1 (6.3)

ER: Estrogen receptor; PR: progesterone receptor; HMB-45: human melanoma black 45; MiTF: Microphthalmia-associated transcription factor.

however, in epithelioid lesions, desmin immunoreactivity was focal and weak. Conversely, cathepsin K was strongly and diffusely expressed in both areas. These findings support the notion that a panel of multiple markers is necessary for the definitive diagnosis of LAM. Further investigations using larger cohorts of nodal LAM are necessary to clarify the positive rates, sensitivities, and specificities of markers and to evaluate the differences in their expression patterns.

One potential mechanism for LAM cell proliferation may be linked to sex hormones, potentially induced by an altered hormonal environment in patients with gynecological malignancies. Endometrial endometrioid carcinomas can induce a hyperestrogenic state. Given that endometrioid carcinoma and LAM typically show strong immunoreactivity for hormone receptors, sex hormones are believed to play a role in the pathogenesis of both conditions. Some researchers have hypothesized that pronounced ER and PR expression could correlate with the severity of pulmonary LAM in pregnant women (34). In this study, pulmonary LAMs in two patients with TSC exhibited strong immunoreactivity for hormone receptors, and metastatic carcinoma cells from the endometrium and ovary were detected in the lymph nodes impacted by LAM lesions. The frequent involvement of pelvic lymph nodes in LAM and its identification during gynecological surgery suggest that an altered hormonal environment may contribute to LAM pathogenesis. Further research is needed to elucidate the relationship between sex hormone levels and LAM development.

Study limitations. First, this study involved patients with incidental pelvic nodal LAM diagnosed and treated at a single institution, thereby constraining the reproducibility of the findings. A fundamental limitation of single-institution studies is their restricted external validity. Additionally, the exclusion of patients with LAM manifesting in other organs and tissues resulted in a relatively small cohort size, precluding a comparative analysis. Second, the molecular analysis required to investigate the pathogenic mechanisms of nodal LAM linked to gynecological malignancies was not within the scope of this research. Third, due to the limited sample size, the statistical significance of the expression status of the immunohistochemical markers could not be analyzed.

Conclusion

In summary, most small nodal LAM lesions, incidentally discovered during surgical staging for gynecological tumors, appear to have insignificant prognostic value. However, some cases with large nodal LAM occupying a substantial portion of the nodal parenchyma may raise awareness of the potential development of pulmonary and extrapulmonary LAM in women of reproductive age. A small number of metastatic carcinoma cells and glands might be overlooked in patients with

nodal LAM. Immunostaining was conducted using eight melanocytic and smooth muscle markers; of these, cathepsin K was the most frequently expressed. While MiTF and desmin are also useful for diagnosis, variations in their expression patterns were observed depending on cellular morphology. Further research with larger cohorts is required to better understand the pathogenesis and clinical implications of NLAM.

Conflicts of Interest

None of the Authors declare conflicts of interest or financial ties regarding this study.

Authors' Contributions

All Authors made substantial contributions to the conceptualization and design of this study, including collection, analysis, interpretation, and validation of the data, drafting of the manuscript, critical revision of the manuscript, and approval of the final version to be published.

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