Extrapulmonary Lymphangioleiomyomatosis (LAM): Clinicopathologic Features in 22 Cases

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We describe the lesions of extrapulmonary lymphangioleiomyomatosis (LAM) affecting the lymph nodes of the mediastinum and retroperitoneum in 22 women (mean age ± SD, 42.4 ± 10.5 years). In most of these patients, the diagnosis of extrapulmonary LAM preceded that of pulmonary LAM, usually by 1 to 2 years. Eleven patients had distinct symptoms, including chylous pleural effusion and/or ascites, abdominal pain, and palpable abdominal masses. In the other 11 patients, the masses caused no symptoms. Well-circumscribed, encapsulated masses, measuring up to 20 cm in size, occurred in the mediastinum in 2 patients, the upper retroperitoneum in 15, extensive areas of the retroperitoneum in 2, and the pelvis in 3. The masses exceeding 3 cm in diameter contained large, multiple cysts filled with yellow-tan chylous fluid. Histologically, the masses were characterized by a proliferation of smooth muscle cells (LAM cells) arranged in fascicular, trabecular, and papillary patterns, which were associated with slit-like vascular channels. The LAM cells varied from small, spindle-shaped cells to large epithelioid cells. Immunohistochemical studies showed a strong reactivity of most LAM cells for α-smooth muscle actin and smooth muscle myosin heavy chain and a weak to moderate reactivity of a lesser number of cells for desmin and nonmuscle myosin heavy chain II-B. A reaction for HMB-45 and estrogen and progesterone receptors was observed mainly in epithelioid LAM cells. These patterns of reactivity are similar to those observed in pulmonary LAM. However, the chylous cysts are not a feature of pulmonary LAM and are thought to result from obstruction of lymphatics. HUM PATHOL 31:1242-1248. Copyright © 2000 by W.B. Saunders Company

Key words: **extrapulmonary, immunohistochemistry, lymphangioleiomyomatosis, lymph node, mediastinum, retroperitoneum.**

Abbreviations: **α-SMA, α-smooth muscle actin; H & E, hematoxylin and eosin; LAM, lymphangioleiomyomatosis; NMHC II-B, nonmuscle myosin heavy chain II-B; SMMHC, smooth muscle myosin heavy chain; AFIP, Armed Forces Institute of Pathology; MA, monoclonal; PA, polyclonal; ER, estrogen receptor; PR, progesterone receptor; CT, computed tomography.**

The diagnosis of lymphangioleiomyomatosis (LAM), a disease of young women, usually is based on recognition of its pulmonary manifestations. These consist of proliferation of abnormal smooth muscle cells (LAM cells) and progressive destruction of pulmonary tissue, with formation of diffusely distributed parenchymal cysts.[1] However, LAM also can involve the mediastinal and retroperitoneal lymph nodes and axial lymphatics.[2] The LAM cells are considered to be related to smooth muscle cells in the walls of lymphatic vessels.[3,4] The majority of patients with pulmonary LAM also develop angiomyolipomas, most of which are localized in the kidneys.[5-7] LAM cells are immunohistochemically distinguishable from other types of smooth muscle cells by their reactivity with HMB-45 antibody,[8] a mouse monoclonal antibody that recognizes a glycoprotein (gp 100) that is present in premelanosomes of cells of melanocytic lineage.[9] The abnormal smooth muscle cells in angiomyolipomas also show reactivity with HMB-45 antibody.[5,7,10] Receptors for estrogen and progesterone have been demonstrated in LAM cells.[11-14] However, they are not detectable in all patients with this disease.[14]

The morphologic changes of extrapulmonary LAM have been described in detail only in a small number of individual case reports.[2,5,15-17] The purpose of this report is to describe the clinical manifestations and the histopathologic and immunohistochemical features of extrapulmonary LAM in 22 patients in whom histologic examination was necessary to establish the correct diagnosis of these lesions. These patients formed part of our series of 188 patients with LAM.

MATERIALS AND METHODS

The study group consisted of 22 patients in whom histologic studies were necessary to establish the diagnosis of extrapulmonary LAM. These were part of a series of a total of 188 cases of LAM referred to the Pulmonary Critical-Care Medicine Branch and the Pathology Section of the National Heart, Lung and Blood Institute (n = 138) from 1995 to 1999, and to the Department of Pulmonary and Mediastinal Pathology of the Armed Forces Institute of Pathology (AFIP) (n = 50) from 1972 to 1999, for clinical and/or histologic evaluation. Studies were approved by the Institutional Review Boards of the National Heart, Lung, and Blood Institute and

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the AFIP. The clinical and imaging studies, the location of the masses, the gross anatomic findings, and the follow-up data were obtained from the patients' files. Special attention was paid to whether or not the patients had developed pulmonary LAM and/or angiomyolipomas.

The tissues studied were obtained surgically from 18 patients, by needle biopsy from 3, and at autopsy from 1 (a patient who also had tuberous sclerosis). The histologic sections from each case (hematoxylin & eosin, Masson trichrome, and Movat pentachrome stains) were independently reviewed by two of us (K.M. and W.D.T.). Sections immunostained for α-smooth muscle actin (α-SMA), HMB-45, or hormone receptors were available in 3 cases. In 9 other cases, paraffin sections of formalin-fixed extrapulmonary LAM lesions were available for study. The sections were treated with an antigen retrieval solution (Citra, BioGenex, San Ramon, CA), immunostained by using the immunoperoxidase method (EnVision System, DAKO, Carpinteria, CA), and then counterstained with hematoxylin as described previously.[14]

The immunostaining was performed by using a series of monoclonal (MA) and polyclonal (PA) antibodies that recognized the following antigens or markers: α-SMA (MA; dilution, 1:200); desmin (MA; dilution, 1:100); smooth muscle myosin heavy chain (SMMHC) (MA; dilution, 1:100); nonmuscle myosin heavy chain II-B (NMHC II-B) (PA; dilution, 1:1000); HMB-45 (MA; dilution, 1:100); estrogen receptor (ER) (MA; dilution, 1:25), progesterone receptor (PR) (PA; dilution, 1:50) and CD34 (MA; dilution, 1:200). The antibody against NMHC II-B was a gift from Dr R.S. Adelstein, National Heart, Lung, and Blood Institute, National Institute of Health. All other antibodies were obtained from DAKO. For immunohistochemical negative control procedures, the primary antibody was either omitted or replaced by a suitable concentration of normal immunoglobulin G of the same species (mouse or rabbit). These control procedures gave negative results.

RESULTS

Clinical Findings

The clinical findings in the 22 patients with extrapulmonary LAM are summarized in Table 1. All patients were women, ranging from 22 to 67 years of age (mean ± SD, 42.4 ± 10.5 years) and all but 2 patients (patients 2 and 6) were in the reproductive age. One of the 2 patients with a mediastinal mass (patient 21) had chylothorax, and 2 patients (patients 18 and 22) with extensive retroperitoneal LAM had chylous ascites. Of 20 patients with abdominal masses, 11 (55%) had no clinical symptoms referrable to the lesions of extrapulmonary LAM, which were diagnosed during the course of studies for the evaluation of pulmonary LAM in 4 patients or other associated conditions in 7 patients. These conditions are listed in Table 1. One of these patients (patient 14) was found to have totally asymptomatic intraabdominal lesions of LAM when she underwent a Caesarean section, and another patient (patient 9) had similar lesions demonstrated by computed tomography (CT) during follow-up studies for a previous diagnosis of Hodgkin's disease. The

TABLE 1. Clinical and Pathologic Findings in 22 Women With Extrapulmonary LAM

Case No.	Age	Clinical Findings	Associated Conditions	Location of Lesions	Specimen	No. of Masses	Maximum Dimension (cm)	Follow-up (years)
1	39	RPL adenopathy	P-LAM*	Upper RP	NB	Multiple	3	4.5
2	53	RPL adenopathy	P-LAM†	Upper RP	E-LAM	1	4	6
3	34	L renal mass	P-LAM, AML, TS*	Hilus of L kidney	E-LAP	5	2.5	4
4	30	Abdominal pain	P-LAM, uterine LM‡	Pelvis	E-LAP	4	12	11
5	53	None	P-LAM‡	Upper RP	E-LAP	1	2.5	3.5
6	60	Mass in R diaphragm	P-LAM‡	Lower Med	NB	1	3	4.5
7	45	RPL adenopathy	P-LAM‡	Upper RP, Mes	E-LAP	3	2.5	5
8	49	Abdominal mass	P-LAM‡	Upper RP	E-LAP	1	5	13
9	30	None	Hodgkin's disease‡	Pelvis	E-LAP	3	1	5
10	34	L renal mass	AML, TS, P-LAM, Splenic LA‡	Hilus of L kidney	E-LAP	1	1	7
11	39	R pleural effusion	P-LAM†	Upper RP	E-LAM	2	1	1.5
12	43	Abdominal mass	P-LAM‡	Mes	E-LAP	1	8	11
13	37	Unknown	P-LAM‡	Lower RP, pelvis	E-LAP	Multiple	1	3
14	37	None	Caesarean section, ES, P-LAM‡	Upper RP, Mes	E-LAP	3	20	6
15	41	Pelvic mass	P-LAM†	Pelvis	E-LAP	1	7	1.5
16	50	Abdominal mass	ES, P-LAM1	Upper RP	E-LAP	2	4	1
17	45	RPL adenopathy	Unknown	Upper RP	NB	Multiple	2	—
18	22	Chylous ascites	Chylothorax‡	Pelvis, lower/upper RP, Mes	E-LAP	Multiple	2	—
19	38	RPL adenopathy	AML, P-LAM	Upper RP	Autopsy§	Multiple	3	Died at 7
20	51	Abdominal mass	P-LAM, AML‡	mesentery	E-LAP	1	15	—
21	67	Chylothorax	P-LAM†	Upper Med	E-LAP	Multiple	2	—
22	36	Chylous ascites	P-LAM†	Pelvis, lower/upper RP, med	E-LAP	Multiple	4	—

Abbreviation: AML, angiomyolipoma; Dis., disease; E-LAp, excision of laparotomy; ES, endosalpingiosis; LA, lymphangioma; LAM, lymphangioleiomyomatosis; LM, leiomyomata; L, left; Med, mediatinum; Mes, mesentery; NB, needle biopsy; OLB, Open lung biopsy; P-LAM, pulmonary LAM; R, right; RP, retroperitoneum; and RPL, retroperitoneal TS, tuberous sclerosis.

The diagnosis of P-LAM was made before (*), semitaneously with (†), or after (‡) that of extrapulmonary LAM,

§ Autopsy showed severe P-LAM.

other 9 (45%) patients in this group had signs or symptoms, including a palpable abdominal mass, abdominal pain, and chylous ascites, which appeared directly related to the lesions of extrapulmonary LAM (Table 1). Two patients (patients 3 and 10) had tuberous sclerosis. Both patients developed pulmonary and extrapulmonary LAM and angiomyolipomas of the kidneys. The latter lesions were detected in only 2 other patients (patients 19 and 20).

Imaging and Gross Anatomic Findings

As demonstrated by CT and ultrasonography, 2 patients had masses in the mediastinum, 15 in the upper retroperitoneum, including the mesentery and hilus of the kidneys, 3 in the pelvic areas, and 2 in large areas extending from the upper retroperitoneum into the pelvis (Table 1). In 1 of the latter 2 patients, lymphangiography showed in the pelvis a plexus of dilated lymphatic vessels, with marked stasis and pooling (Fig 1).

At the time of preoperative or operative evaluation, the masses were considered to be single in 8 (36%) patients and multiple in 14 (64%). Grossly, the masses were well demarcated and encapsulated and ranged from 1 to 20 cm in greatest dimension (mean, 5.3 cm); however, masses in the mesentery tended to be larger (mean diameter, 11.8 cm). The cut surfaces of all masses showed soft, yellow-tan, lobulated tissue without necrosis or hemorrhage. The masses exceeding 3 cm in diameter tended to show prominent cystic changes, with LAM tissue lining the walls of the cysts. The cystic spaces in many masses were filled with milky, pale, yellow-tan fluid.

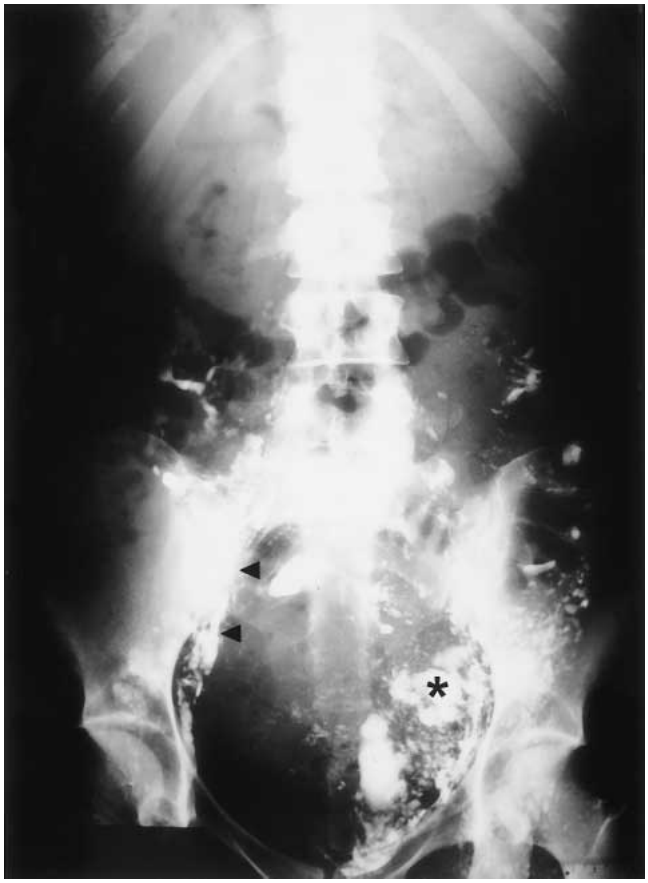

FIGURE 1. Lymphangiogram of patient 22 with extrapulmonary LAM involving large areas of the retroperitoneum, showing a plexus of dilated lymphatic vessels (arrowheads), with marked stasis and pooling (asterisk), in the pelvis.

Histologic Findings

The specimens from all patients showed essentially similar histologic features. These were characterized by a proliferation of LAM cells. Some of these cells were organized in a haphazard manner, whereas others formed fascicles, plump trabecular bundles, anastomosing cords, and irregular papillary patterns (Fig 2A, B). Slit-like channels lined by flattened endothelial cells were present throughout the masses. These channels were empty or contained small numbers of lymphocytes and erythrocytes. However, in 1 patient (patient 8), they contained large numbers of inflammatory cells (Fig 2C). The LAM cells were morphologically heterogeneous, with a spectrum ranging from small to medium-sized, spindle-shaped cells to large epithelioid cells. The latter had a clear cytoplasm and round to oval nuclei with distinct nucleoli (Fig 2D). No mitotic activity was identified in LAM cells in any of the patients. Small aggregates of lymphoid cells were present in all masses except in 1 that was studied only by needle biopsy (Fig 2A). These aggregates resembled lymphoid follicles, and some of them actually had follicular centers. Other inflammatory cell infiltrates were not prominent in the stroma of LAM cells in any of the cases. In 11 cases, LAM cells infiltrated the fatty tissue surrounding the fibrous capsule of the mass (Fig 2C). Necrosis was not observed in any case. Focal hemorrhage was present in 3 cases (patients 5, 8, and 11). Two masses resected from the upper retroperitoneum showed an association of LAM with epithelial inclusions resembling the cells of Fallopian tube mucosa (endosalpingiosis). These 2 patients (patients 14 and 16) will be reported separately.

Immunohistochemical Findings

A positive reaction for HMB-45, in the form of cytoplasmic granules, was observed in many of the LAM cells in 11 of the 12 cases examined by this method (Fig 3A, B). The lesion in the remaining patient was reported to be HMB-45–negative. However, tissue from this patient was not available for study by us. The percentage of HMB-45–positive LAM cells varied from case to case (range, 5% to 50%; mean, 15.6%), as determined by counting in 5 high-power (×400) fields. Most HMB-45–positive LAM cells were of the epithelioid type. All masses showed a positive reaction for the 4 muscle markers used in the study. However, the patterns of reactivity for these markers differed from one another. Staining for α-SMA and SMMHC was observed in almost all LAM cells in every case, whereas that for desmin was weaker and detected in approximately 80% of the LAM cells. The reaction of LAM cells for α-SMA and SMMHC was cytoplasmic and was mostly localized

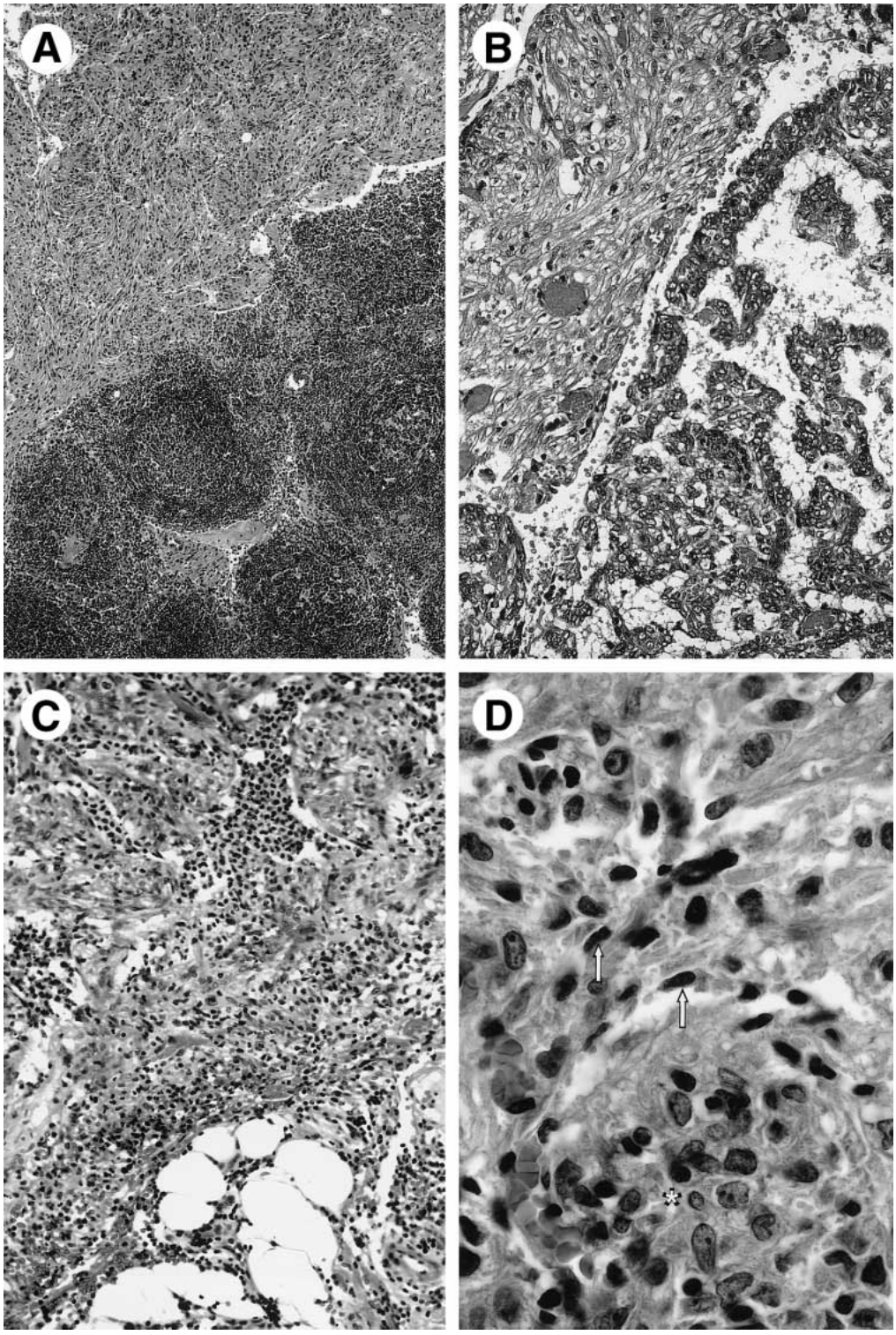

FIGURE 2. Histology of extrapulmonary LAM. (A) LAM cells proliferate in fascicles, which are separated by narrow lymphatic channels. Note aggregates of lymphoid cells forming follicular centers. Patient 9. (H&E, original magnification ×100.) (B) In this area, LAM cells form plump trabecular bundles and irregular papillary patterns. Patient 4. (H&E, original magnification ×250.) (C) Lymphatic channels among the fascicles of LAM cells are filled with inflammatory cells. Note invasion of LAM cells into fatty tissue surrounding the lesion. Patient 8. (H&E, original magnification ×250.) (D) Heterogeneity of LAM cells. Note large epithelioid LAM cells with distinct nuclei (asterisk) and smaller, round to oval cells (arrows). Patient 9. (H&E, original magnification ×1,000.)

in peripheral portions of the cells (Fig 3C, D). In contrast, the reaction for desmin was cytoplasmic and frequently distributed in the perinuclear areas (Fig 3E). Staining of the LAM cells for NMHC II-B was weak to moderate, and strongest in areas adjacent to the plasma membranes (Fig 3F). LAM cells with an epithelioid morphology showed a positive reaction for this protein (which is known to be present in a variety of cells other than muscle[18]). Endothelial cells covering the surfaces of the fascicles were strongly positive for NMHC II-B (Fig 3F). The reaction for ER and PR was detected in the nuclei of LAM cells in 3 of the 6 cases examined, and was localized mainly in cells of the epithelioid type (Fig 3G, H). Immunostaining with CD34 highlighted endothelial cells lining slit-like channels and spaces among the fascicles of LAM cells (Fig 3I).

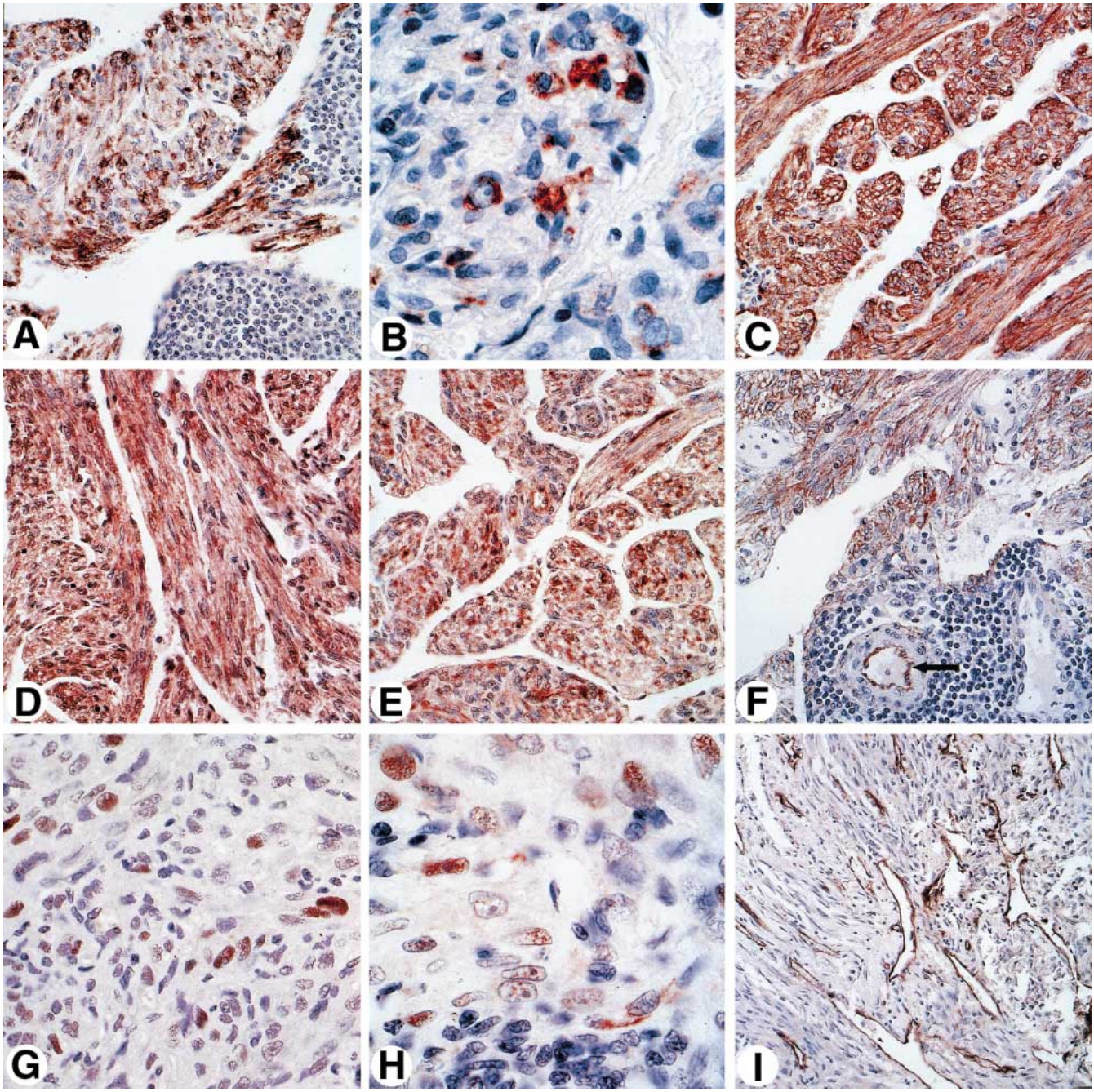

FIGURE 3. Immunohistochemical reactivity of lesions of extrapulmonary LAM (immunoperoxidase with hematoxylin counterstain). (A and B) HMB-45. The reaction in LAM cells is granular and cytoplasmic. The percentage of HMB-45–positive cells is approximately 50% in patient 12 (A), but only 5% in patient 5 (B). (Original magnifications, A: ×400; B: ×1,000.) (C and D) α-SMA (C) and SMMHC (D). The reaction for these 2 markers is strong in many LAM cells and is frequently localized in the peripheral portions of the cytoplasm. (Original magnification, each, ×400.) (E) Desmin. The reaction is frequently distributed in the perinuclear areas. (Original magnification, ×800.) (F) NMHC II-B. The reaction is weak but is strongest in areas adjacent to the plasma membranes. Blood vascular endothelial cells give a stronger reaction (arrow). (Original magnification ×400.) (G and H) ER (G) and PR (H). The nuclei of some of the epithelioid LAM cells are positive for these hormone receptors. A reaction for ER is weaker than that for PR. Patient 21. (Original magnification, G, ×630; H, ×1,000.) (I) CD34. The reaction highlights endothelial cells covering the surfaces of the fascicles. Patient 12. (Original magnification ×250.)

Patient Follow-up

Clinical follow-up data were available in 17 patients. Clinical, roentgenographic, and histologic studies were performed to evaluate the possibility that these patients also had pulmonary LAM. The latter was discovered before evaluation for extrapulmonary LAM in 1 patient (patient 1). Pulmonary and extrapulmonary LAM were recognized simultaneously in 3 patients (pa-

tients 2, 11, and 15). In the other 13 patients (patients 3 through 10, 12 through 14, 16, and 19), the diagnosis of pulmonary LAM was established after that of extrapulmonary LAM, usually within 2 years. However, in 1 patient (patient 14), the manifestations of pulmonary LAM have remained minimal for the 6 years that have elapsed since the diagnosis of extrapulmonary LAM. One patient (patient 19) died of severe pulmonary LAM 7 years after the initial diagnosis, and the other 16 patients are alive, with follow-up periods ranging from 1 to 13 years (mean, 5.5 years).

DISCUSSION

The current study describes the morphologic features of extrapulmonary LAM and shows that they differ in several important respects from those of pulmonary LAM and angiomyolipomas. Most of the lesions of extrapulmonary LAM occurred in lymph nodes along the lymphatic vessels of the mediastinum and retroperitoneum. These findings are in accord with previous reports by Chu et al,[6] who found a high frequency (77%) of involvement of abdominal and retroperitoneal lesions involving lymph nodes in their series of patients with pulmonary LAM. Nevertheless, Urban et al[19] found a lower incidence (24%) of abdominal lymphadenopathy in their patients. The incidence of extrapulmonary LAM in our 188 patients could not be calculated because a number of these patients were studied before the advent of high-resolution CT. However, the patients reported by Chu et al[6] actually are an unselected subset of patients who underwent comprehensive diagnostic studies by our group.

Although the size of the lesions observed in the current study varied from case to case, the masses occurring along the mesentery were much larger than those in other sites. Such masses, especially those exceeding 3 cm in diameter, were well circumscribed and had prominent cysts that were filled with chylous fluid. The LAM cells ranged from round or spindle-shaped cells to larger epithelioid cells. These variations were similar to those found in pulmonary LAM.[1,8,14] However, the LAM cells in extrapulmonary lesions, in contrast to those in the lungs, tended to form fascicles and papillary patterns rather than nodules. In spite of the absence of mitotic activity and cellular atypia, LAM cells in extrapulmonary lesions invaded adjacent fatty tissue beyond the capsule in half of the masses. Immunohistochemically, most of the LAM cells showed a positive reaction for muscle markers, whereas only the subpopulation of LAM cells with an epithelioid morphology showed reactivity for HMB-45 and hormone receptors. These observations are similar to those that we have reported in pulmonary LAM.

It was surprising to find that in 13 of the 17 patients in whom follow-up data were available, the diagnosis of extrapulmonary LAM preceded that of pulmonary LAM. This is attributable to the fact that the clinical manifestations of pulmonary LAM were absent or minimal in these patients, and that the corresponding radiographic changes (early cystic lesions) are evident on high-resolution CT study but not on routine roentgenograms of the chest.

Extrapulmonary LAM was observed in 3 major locations: the posterior mediastinum, the upper retroperitoneal areas close to the abdominal aorta (including the mesentery and renal arteries), and the pelvic cavity. These predominant locations of LAM were related to the anatomic distribution of lymphatic vessels. The abdominal lymphatics drain into the intestinal lymphatic trunks or into 1 of the 2 lumbar trunks that converge into the cisterna chyli, from which the thoracic duct originates. Tributaries of the lumbar trunks include the renal and the iliac lymphatic vessels, which partially drain the genitals, the bladder, and the lower limbs.

We believe that the dilation of lymphatic vessels observed in the current study occurs as a consequence of obstruction to the flow of lymph or chyle. This obstruction probably is a consequence of compression of thin-walled lymphatic vessels, particularly those in lymph nodes by proliferating LAM cells. It is clear that the lesions of extrapulmonary LAM differ from those of pulmonary LAM in that the cysts in the former involve the lymphatics, whereas in the latter they affect the airways. In pulmonary LAM, we have not observed cystic spaces representing greatly dilated lymphatic vessels. The cystic dilation of the air spaces in pulmonary LAM is thought to be caused, at least in part, by the activity of matrix metalloproteinases that are produced by LAM cells.[20,21] It remains to be determined whether a comparable process also contributes to the dilatation of the lymphatic vessels in extrapulmonary LAM.

The lesions of extrapulmonary LAM described in the current study also differ clearly from angiomyolipomas. HMB-45–positive cells are found in both of these lesions; however, angiomyolipomas are further characterized by the presence of abundant adipose tissue and by disorganized components of blood vessels.[5,7,10] We did not observe accumulations of adipose tissue within the lesions of extrapulmonary LAM. Furthermore, this tissue did not contain remnants or fragments of blood vessels. Therefore, we regard angiomyolipomas as an unusual but distinct expression of the proliferative capacity of LAM cells. Angiomyolipomas have been reported in up to two thirds of the patients with pulmonary LAM, and most of these lesions are present in the kidneys.[6] As in the case of other retroperitoneal lesions of LAM, we were not able to determine the incidence of angiomyolipomas in our series of 188 patients because a number of these patients were studied before the development of high-resolution CT techniques. However, angiomyolipomas were diagnosed on the basis of either biopsy or nephrectomy in at least 22 of these 188 patients. The incidence of angiomyolipomas in patients with LAM has been reported to be as high as 60% (see Chu et al[6] for review). This incidence was found in a group of 35 patients (included among our total of 188 cases) studied by ultrasonography and high-resolution CT. In contrast to these findings, Urban et al[19] found angiomyolipomas in only 32% of patients studied by similar techniques. Angiomyolipomas were detected in

only 4 of the 22 patients with extrapulmonary LAM. The reason for these differences is not known. The frequent occurrence of extrapulmonary lesions and angiomyolipomas emphasizes the systemic nature of LAM and the importance of lymph node involvement as a factor in determining the extent of extrapulmonary lesions.

In summary, we have described clinical, histopathologic, and immunohistochemical features of 22 cases of extrapulmonary LAM. The morphologic and immunohistochemical heterogeneity of LAM cells in extrapulmonary LAM is similar to that in pulmonary LAM. The size of the lesions of extrapulmonary LAM is largely determined by the development of multiple cysts containing chylous fluid, rather than by the degree of proliferation of LAM cells. These cysts are thought to be formed as consequences of obstruction to the flow of lymph or chyli.

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