Eur Respir J, 1996, 9, 402–405
DOI: 10.1183/09031936.96.09030402
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European Respiratory Journal
ISSN 0903 - 1936

Extrathoracic angiomyolipomas in lymphangioleiomyomatosis

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ABSTRACT: Pulmonary lymphangioleiomyomatosis (LAM) is a rare disorder that affects women and can lead to serious respiratory impairment. Since Bourneville's tuberous sclerosis (TS) was first reported, the striking similarities between the two entities have led many to believe that LAM is a *forme fruste* of TS. This is suggested by reports that angiomyolipomas, rare tumours in themselves, are reported in 40–80% of TS patients and occur in 15–30% of LAM patients. A retrospective chart review was conducted of 14 patients that presented to our institution with a diagnosis of LAM. We sought to document the clinical manifestations, particularly the incidence and location of extrathoracic tumours, in order to further support the hypothesis that LAM is a *forme fruste* of TS.

Twelve patients had premenopausal onset of symptoms and two postmenopausal. The diagnosis was confirmed histologically (n=12) and/or by computed tomography (CT) scan of the thorax (n=12). Imaging investigations revealed extrathoracic tumours in 12 of 14 patients (86%). Eight of the 14 patients (57%) had renal tumours consistant with angiomyolipomas (bilateral in five patients). Only one patient had renal symptoms (flank pain and haematuria). All had normal serum creatinine, one had a reduced creatinine clearance. Extrathoracic nonrenal tumours were discovered in the pancreas, adrenals and uterus, findings previously unreported in LAM.

In summary, the incidence of extrathoracic tumours in lymphangioleiomyomatosis patients is much higher than previously reported in the literature. This increased association supports the theory that lymphangioleiomyomatosis and tuberous sclerosis represent part of a spectrum of a similar disease process.

Eur Respir J., 1996, 9, 402–405.

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Keywords: Angiomyolipomas
lymphangioleiomyomatosis
tuberous sclerosis

Received: May 16 1995
Accepted after revision October 11 1995

Pulmonary lymphangioleimyomatosis (LAM) is a rare disorder characterized by proliferation of smooth muscle elements of the bronchioles, venules and lymphatics in the lung parenchyma. Smooth muscle proliferation can also be found in extrapulmonary sites. Although LAM is classified as a distinct clinical entity, the same pathological process can be seen in approximately 1% of patients with tuberous sclerosis [1]. Renal angiomyolipomas have been found in 40–80% of tuberous sclerosis patients [2–4]. However, renal angiomyolipomas are being found increasingly in patients with LAM (15–30%) [2, 5].

We have noticed a number of patients with LAM to have associated tumours of the kidney as well as additional extrathoracic masses. Such patients appeared to be asymptomatic from their extrapulmonary lesions. We suspect that the current literature underestimates the association between the two which, because of their asymptomatic nature, may be overlooked. With the various treatment regimens for LAM and with availability of lung transplantation, these patients may be living longer and, therefore, with increasing time extrathoracic manifestations may be uncovered. We therefore wish to report the clinical manifestations including extrathoracic tumours in 14 cases of LAM referred to our institution over the last 10 yrs.

Methods

The medical records of all patients who presented to our institution with LAM between 1984–1994 were reviewed. Patients had been referred for management or for assessment for lung transplantation. Data were collected with regard to demographics, mode and date of initial presentation, biopsy results, complications, imaging (chest radiograph, computed tomography (CT), ultrasound), extrathoracic manifestations and pulmonary function tests.

Flow-volume curves were obtained by maximal forced expiratory manoeuvres using a Morgan Spiroflow 12 L dry rolling-seal spirometer. The best of three expiratory manoeuvres was used to obtain forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Lung volumes were obtained by the helium dilution method. Predicted values for these paramenters were calculated using the Intermountain prediction equations [6].

The data are presented as absolute value or mean±standard deviation.

Table 1. – Duration of disease since correct diagnosis and findings on presentation in 14 patients with LAM

Pt No.	Symptom duration yrs	Disease duration yrs	Haemoptysis	Cough	Dyspnoea	Pneumothorax	Chylothorax
1	36	9	Y	Y	Y	Y	N
2	25	10	N	Y	Y	Y	N
3	6	3	N	Y	Y	Y	N
4	5	4	N	Y	Y	N	Y
5	22	2	N	Y	Y	Y	N
6	7	1	N	Y	Y	N	N
7	13	4	N	Y	Y	Y	N
8	11	1	N	Y	Y	Y	N
9	4.5	2	N	Y	Y	Y	N
10	8	4	N	Y	Y	N	N
11	11	10	N	Y	Y	N	Y
12	4	1	N	Y	Y	Y	N
13	14	13	Y	Y	Y	N	N
14	8	7	N	Y	Y	N	N

LAM: Lymphangioleiomatosis; N: no; Y: yes.

Results

During the 10 year period, 14 adult women presented to our institution with LAM. Six patients were referred for lung transplant assessment, two patients for management of complicated pneumothoraces, and six patients for continuing management. The average age was 45±6 yrs (range 37–58 yrs). Four of the patients have since died, one following lung transplant, one of progressive respiratory failure and two of trauma.

Clinical presentation

Table 1 shows the findings at presentation and the duration of symptoms prior to diagnosis and at the time of initial assessment. The average length of time to diagnosis was 7.4±8.1 yrs (range 1–27 yrs), with the average duration of symptoms being 12.5±9.3 yrs (range 4–36 yrs), and the average length of time with the correct diagnosis being 5.1±4.0 yrs (range 1–13 yrs). Ten patients have survived at least 10 yrs from diagnosis. Twelve of the patients had premenopausal onset of symptoms (one presented at time of pregnancy). Only two patients were diagnosed with LAM at their initial presentation to their doctor.

At the time of presentation two patients complained of haemoptysis and all had progressive dyspnoea, unproductive cough and shortness of breath on exertion. Seven patients developed pneumothoraces at first presentation, one with a chylothorax. One patient developed a pneumothorax 22 yrs following the initial presentation.

Complications

Ten patients (71%) had pleurodesis during the course of their illness (seven bilateral) for various reasons (table 2): eight for pneumothoraces, one for pleural effusion and one for chylothorax. All patients had multiple pneumothoraces prior to pleurodesis. Three patients went on to require pleurectomy and only one had a decortication.

Table 2. – Frequency of pneumothoraces, associated pleurodesis and lung function studies in 14 patients with LAM

Pt	Pneumothoraces		Pleurodesis		Pulmonary function tests			%pred	FEV1/FVC
No.	Left	Right	Left	Right	TLC	$T_{L,CO}$	FEV1	FVC	%
1*	4	3	Y	Y	-	13	27	38	88
2†	5	2	Y	Y	109	40	20	27	39
3†	5	5	Y	Y	93	25	29	42	53
4•	0	0	Y	Y	65	32	62	55	87
5	0	1	N	N	110	30	82	100	69
6	1	4	N	Y	150	31	38	79	37
7†	2	4	Y	Y	110	21	32	47	44
8	2	2	N	N	105	41	34	63	42
9	3	2	Y	Y	-	-	-	-	-
10	0	0	N	N	135	28	30	80	31
11•	0	0	N	Y	141	21	20	55	28
12	4	2	Y	Y	-	-	-	-	-
13	3	3	Y	Y (2)	-	-	20	28	36
14	0	0	N	N	105	42	86	100	52

*: decortication; †: pleurectomy; •: pleurodesis for reasons other than pneumothoraces. LAM: lymphangioleiomyomatosis; TLC: total lung capacity; $T_{L,CO}$: transfer factor of the lungs for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; Pt: patient; % pred: percentage of predicted value; Y: yes; N: no.

No pleural space complications occurred in two patients. Pulmonary function results were available for 12 patients. The results of the other two patients were unavailable as one died and one was followed elsewhere. Of the 12 patients with spirometry, 10 showed an obstructive pattern. Vital capacity was reduced in 10 out of 12 patients. Total lung capacity was preserved or increased in 9 out of 10 patients measured. Diffusion capacity was measured in 11 patients, and was less than 45% predicted in all.

Diagnostic techniques

Twelve of the patients had a open lung biopsy consistent with the diagnosis of LAM. Two of these patients had an initial misdiagnosis (eosinophilic granuloma, "nonspecific") and were subsequently found to have LAM upon repeat open lung biopsy. Two of the patients had the diagnosis of LAM based on history and CT.

All 14 patients demonstrated a diffuse reticular pattern on chest radiographs. High resolution CT studies of the chest (n=12) revealed diffuse multiple thin-walled cysts ranging in size from a few millimetres to 6 cm.

Extrathoracic findings

Twelve of the 14 patients (86%) had extrathoracic abnormalities (table 3). Eight patients (57%) had kidney tumours (fig. 1), five of which were bilateral. All of the kidney tumours had relatively pathognomonic appearance of angiomyolipomas. Renal angiomyolipomas were shown on CT examinations to be masses of complex appearance with irregular solid enhancing components, mixed with areas of fatty attenuation. Sonographic evaluation showed lesions ranging from homogenous echogenic masses to complex tumours of solid appearance with areas of mixed echogenicity. The lesions ranged in size from a few millimetres to over 10 cm. One patient was symptomatic with haematuria and flank pain. All had normal creatinine levels and only one had a reduced creatinine clearance.

Table 3. – Extrathoracic tumours or masses discovered in 14 patients with LAM

Location		Frequency n
Renal	bilateral	5
	unilateral	3
Adrenal		1
Retroperitoneal		2
Liver		1
Thyroid		1
Pancreas		1
Uterus		1
None		2

LAM: lymphangioleiomyomatosis.

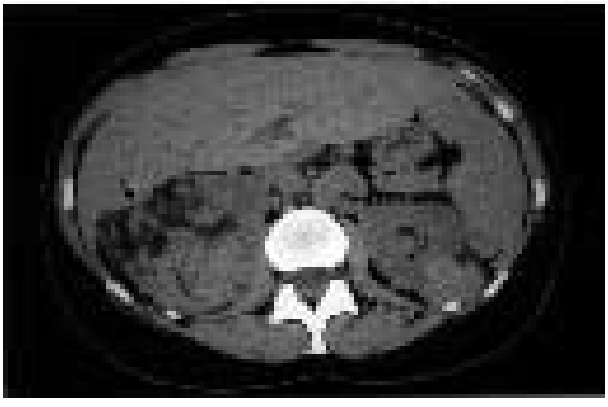

Fig. 1. – Axial unenhanced computed tomography (CT) of the kidneys of a 40 year old woman with lymphangioleiomyomatosis (LAM) showing typical bilateral angiomyolipomas with fat components (arrows).

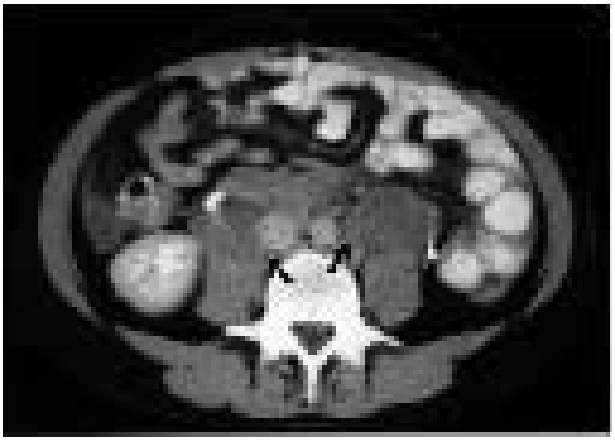

Fig. 2. – Axial enhanced computed tomography (CT) image in the mid-abdomen of a 30 year old woman with lymphangioleiomyomatosis (LAM). There are bilateral cystic masses (arrows) of the retroperitoneum displacing the ureters. These probably represent malformations of the lymphatics.

Two patients had cystic retroperitoneal masses consistent with malformations secondary to lymphatic obstruction (fig. 2). Extrathoracic nonrenal tumours or masses were noted in the pancreas, thyroid, adrenals and uterus. The pancreatic mass was biopsied and had histological findings of an angiomyolipoma. Four patients with extrathoracic abnormalities had normal kidneys. One patient with tumours of the kidney had melanin deposits on her face, with a CT of her head showing subependymal calcified tubers without hydrocephalus. This patient had no obvious mental deficiency, and no other extrathoracic manifestations. Two patients (14%) had no evidence of extrathoracic manifestations. The lack of other findings was confirmed on autopsy.

We did not find either CT scan or ultrasound to be more sensitive than the other in detecting abdominal lesions. It is our current practice to obtain an ultrasound of the kidneys once the diagnosis is made.

Discussion

LAM is a rare idiopathic disease that progressively affects the lungs of women. Lung biopsies are diagnostic, with the characteristic findings of proliferation of smooth muscle involving the lymphatics, airways and blood vessels, with loss of parenchyma leading to honeycombing [7]. However, high resolution CT findings have become relatively pathognomonic and accepted as diagnostic of LAM [8].

Angiomyolipomas are rare tumours accounting for 1–2% of all renal tumours [9]. In contrast, angiomyolipomas of the kidney are found in 40–80% of tuberous sclerosis patients and multiple bilateral angiomyolipomas are reported to occur exclusively in these patients [2, 3, 10–12]. The previously reported association of angiomyolipomas with LAM was 15–30% [2, 5]. In LAM, the extrathoracic manifestations are usually confined to the lymphatics above and below the diaphragm. In our series, 8 of 14 patients (57%) had renal tumours consistant with angiomyolipomas, of which five were bilateral. This is the first report suggesting the association of angiomyolipomas occurring in the pancreas in patients with LAM. All but one of the extrathoracic manifestations were asymptomatic and none required any treatment interventions.

The extrathoracic findings in our population were discovered through imaging techniques and only confirmed histologically in one instance (pancreas). Hence, applying a pathological diagnosis to all the extrathoracic findings seen would not be appropriate. Furthermore, it is possible that such findings are coincidental. For example, the adrenal and thyroid abnormalities may well represent coincidental benign tumours without a relationship to LAM. The abnormalities in the uterus may simply represent fibromas, emphasizing the difficulty in correlating extrathoracic tumours with LAM. It is also possible that one of our patients had tuberous sclerosis; nevertheless, excluding this patient still leaves a high proportion of subjects with extrathoracic abnormalities.

Our experience suggests that prolonged survival is possible. Approximately 70% of our group have survived at least 10 yrs, with a mean duration of symptoms of 12 yrs (range 4–36 yrs). TAYLOR *et al*. [13] reported similar findings, with 78% of their patients (n=32) surviving at least 10 yrs. This is in contrast to the earlier experience with 32 patients, as reported by SILVERSTEIN *et al*. [14]. Follow-up data were available for 29 of the 32 patients; three had survived more than 10 yrs at the time of the report, whereas 20 patients had died between 6 months and 12 yrs after the onset of pulmonary disease. Various hormonal manipulations have been attempted, with no apparent correlation between the status of progesterone and oestrogen receptors and the response to hormonal therapy [13]. Three of our 14 patients have progressed symptomatically to necessitate lung transplantation. Only one patient has died as a direct result of her respiratory disease. All 14 patients have been on various treatments at one time or another.

We suspect that, as these patients are living longer, the incidence of discovering extrathoracic lesions increases. As most are asymptomatic, many may go undocumented. The majority of the literature proposes that renal angiomyolipomas in association with pulmonary LAM is a *forme fruste* of tuberous sclerosis [1–3, 15–17]. Although LAM is a distinct clinical entity, the same pathological findings can be seen in association with tuberous sclerosis in 1% of these patients [1, 18]. Whilst STOVIN *et al*. [18] have proposed that LAM and tuberous sclerosis are probably not different aspects of the same disease process but seem to be two different disorders, CORRIN *et al*. [7] regarded the pathology as identical but noted intriguing differences in sex distribution and family history. We believe this increased association of extrathoracic tumours with LAM supports the theory that LAM and tuberous sclerosis represent a spectrum of a similar disease process.

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