CASE REPORTS

Pulmunary Lymphangioleiomyomatosis. A case report and review

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Pulmunary Lymphangioleiomyomatosis (P-LAM) is a rare disease that occurs mainly in women of childbearing age.
The most common presenting symptom of the disease is spontaneous pneumothorax .
Histologically, it is characterized by hamartoumatous proliferation of smooth muscle cells around and within the pulmunary lymphatics, venules and airways, that leads to a cystic degeneration of the lung interstitium without predilection of any lung zone.
Extrapulmunary manifestations of P-LAM are renal angiolypomas and enlarged retroperitoneal, paraaortic or pelvic lymphonodes; pathological findings are identical to those found in TSC (Tuberous Sclerosis Complex). TSC1 and TSC2 are two suppressor genes: since loss of heterozigosity of these genes occurs in P-LAM patients, some authors hypotized that P-LAM and TSC have common genetic bases.
The fact that pregnancy is reported to develop the disease process and the cases of postmenopausal women associated with estrogen replacement therapy suggests that an hormonal treatment could be used, althought it results largely ineffective.
In recent years lung transplantation has become a therapeutic approach. Extensive pleural adhesions cause intraoperative problems, but the most important posttransplantation complications are pneumothorax in the native lung or chylothorax or recurrent P-LAM in the lung allograft, even in women who received a transplant from a male donor.
With the improved understanding of genetic biology of P-LAM, new therapies will soon become available.
We report the case of a 35 years old woman, who developed spontaneous pneumothorax . P-LAM was suspected on chest TC scans and was confirmed by a VATS lung biopsy.

KEY WORDS: P-LAM, Pulmunary Lymphangioleiomyomatosis - TSC - Tuberous Sclerosis Complex - Spontaneous Pneumothorax - Lung Diseases - Lung Transplantation - Smooth Muscle.

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Pulmunary Lymphangioleiomyomatosis (P-LAM) is an uncommon chronic debilitating disorder of unknown etiology characterized by "non-neoplastic proliferation of atypical smooth muscle cells" within the lung parenchyma that leads to progressive loss of lung function and, ultimately, to death.

The first report on P-LAM was in 1937 by Burrell[1] and in the same year Von Stössel[2] described a case of a patient with chylous effusion which has been recognized as one of the most prominent clinical features of the disease.[3,4,5,6]

The first significant collection of patients with P-LAM was done by Cornog and Enterline, who reported 6 cases in 1966.[7]

It has been variously called Myomatosis, Leiomyomatosis, Angiomyomatosis hyperplasia, Lymphangiomatous malformation, Diffuse pulmunary leiomyomatosis, Muscular hyperplasia of the lung, Intrathoracic angiomatous hyperplasia.[8]

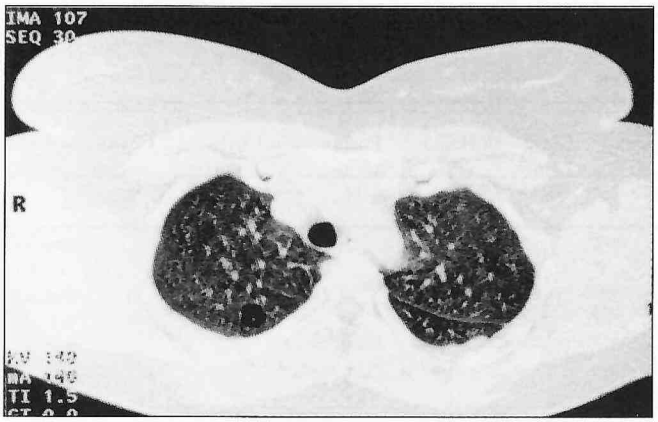
Materials and Methods

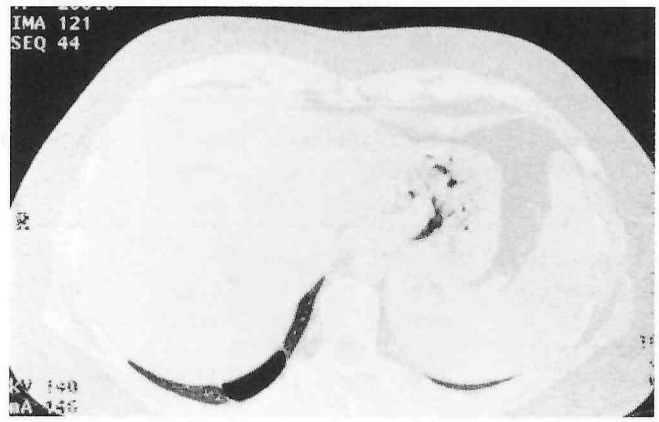
Case report - In november 1998 a 35 years old woman was admitted to our hospital with suspected P-LAM.

The patient had two sons (10 and 12 y. old). She had smoked and was still smoking about ten cigarettes per day. Previously, in 1995, she had developed a left pneumothorax treated with torachostomy on tube drainage. In march 1998 she was again hospitalized for the same pathology and treated again with drainage. CT chest scan showed some "bullae" all over the lungs as thin walled cysts sized from 5 mm to 4 cm with a basilar predominance (Fig. 1 and 2) and a solid hilar mass of 3 cm in diameter defined a bronchial cyst (Fig. 3).

Pulmunary function tests like DCO measured and cardiopulmunary exercise performed were normal.

After a few days we performed a left videothoracoscopic lung biopsy by wedge resection of lingular segment. Biopsied lung tissue was interpreted as a histologically very limited expression of P-LAM (Fig. 4): the smooth muscle





Figs.No 1 – 2 : Sections TC of the chest show thin-walled cysts clearly evident.

cells proliferation was positive for alpha-smooth muscle actin (Fig. 5) in the lung and showed no ER nor PR receptors positivity. Molecular characterization of the HMB-45 reactive Ag was not positive.

As the woman is a young patient and only unfrequently presents shortness of breath in exertion, we have not treated her with hormonal therapy, since this is associated with psychological problems and it is not always successful. Suspected progression of the disease in frequent clinical observations will be confirmed by pulmunary function tests and chest CT scans. A lung transplantation will be provided if end-stage disease develops in the woman. At the same time we are trying to identify her genetic mutations in smooth muscle cells proliferation, with the hope that a future genetic therapy will soon be discovered.

Discussion

Epidemiology - P- LAM is a non familial progressive disease affecting premenopausal women of childbearing age: it's diagnosed in ~1/1.000.000 people, in both Europe and the Unites States and in 46% of women with TSC.[9] Only 16 cases of P-LAM were identified over a period of 10 years in the five teaching hospitals of the University of Colorado Health Sciences Center: caucasians and less commonly asians are afflicted much more than other racial groups.[8,10]

In the majority of the 300 cases reported in literature the mean age at onset of symptoms is 33 years (range 20-44 years):[9,3,8,9,11,12,13,14,15,16] in the youngest woman reported P-LAM was diagnosed at age 9 by lung biopsy.[17]

Only 5% of the P-LAM reported cases are older than age 50 at presentation and the majority of cases occurring in postmenopausal women (even as late as 75 years old) have most often been associated with estrogen replacement therapy by osteoporosis or by bilateral salpingo-oophorectomy. However, P-LAM symptoms can develop after menopause in the absence of exogenous estrogen.[3,8,14,16,18,19,20,21] Several authors also report onset or worsening of the disease while on oral contraceptives.[4,22,23,24,25] Pregnancy has been reported to develop or accelerate the course of the disease.[4,18,19,26,27] Few cases were observed in males[28,29] (one with an extremelly low testosterone level[30]) and in patients of both sexes affected by tuberous sclerosis complex (TSC).[3,4,5,6,8,10,22,31,32,33,34,35] TSC patients with pulmunary involvement may develop pulmunary symptoms during pregnancy too.[36] TSC is inherited as an autosomal dominant tumor suppressor gene syndrome (even up to 68% of the cases may be caused by spontaneous mutations[37]) characterized by mental retardation, seizures, hamartomatous tumors in the brain, heart, skin, lung and kidney, and facial angiofibromas: it was termed by Bourneville "tuberous sclerosis" for the reference to the presence of potato-like central nervous system lesions. Pathologic findings in the lungs and lymph nodes are identical to those found in P-LAM and symptoms are similar.[28,37] TSC1 e TSC2 are suggested to be tumor suppressor genes: TSC2 is on chromosome 16p13 and TSC1 on chromosome 9q34. In a recent study loss of heterozygosity of the TSC2 gene was found by Smoralek in 54% of angiolypomas in patients with P-LAM and was also seen in four lymphonodes in a woman with retroperitoneal LAM.[9] The disease that can occur without evidence is referred to as "sporadic P-LAM" and can be associated with tuberous sclerosis complex (TSC). Loss of heterozygosity (LOH) in the chromosomal region for the TSC2 gene occurs in 60% of TSC associated with angiomyolipomas. Because of the similar pulmunary and renal manifestations of TSC and sporadic P-LAM, some authors hypothesized that P-LAM and TSC have a common genetic basis. TSC2 mutations are more likely to cause sporadic P-LAM than TSC1 mutations: angiomyolipomas resulting from TSC2 mutations more often require surgical removal, either because they are larger than angiomyolipomas resulting from TSC1 mutations, or because they are more likely to be subject to bleeding. Because of the intermingling of smooth muscle cells with normal lung parenchyma, it's difficult to isolate a pure population of pulmunary LAM smooth muscle cells for LOH analysis, whose histological, immunohistochemical and ultrastructural bases are closely related with angiomyolipomas, as well as lymph nodes in P-LAM

TABLE I. - *Clinical manifestations in P-L.A.M. patients.*

Authors	Year	Patients	Mean age (range)	Cough %	Dyspnea %	Chest Pain %	Hemo-ptisis %	Pneumo-thorax %	Chylo-thorax %	Chylo-ascites %
Silverstein (22)	1974	32	39 (18-69)	9	91	18	28	38	78	31
Corrin (5)	1975	28	33 (17-47)	64	86	7	36	43	39	7
Capron (37)	1983	1	34	Y	Y			Y		
Berger (39)	1989	2	35 (33-38)	Y	Y		Y	Y		
Taylor (3)	1990	32	33	41	94	34	44	81	28	6
Tanaka (40)	1995	5	37 (23-49)							
Berkman (41)	1995	1		Y	Y	Y		Y		
Kitaichi (14)	1995	46	32 (20-63)	54	83	30	24	39	11	4
Boheler (32)	1996	Rev.34	29 (5-44)	41	93	25	22	78	22	3
Naalsund (13)	1996	8	36		Y			Y	Y	
Kay (11)	1996	1	44		Y					
Maziak (34)	1996	14	45 (37-58)	100	100		15	57	15	
Yigla (42)	1996	1								
Crausman (43)	1996	16	32 (26-69)	56	100		13	69		
Louis (12)	1997	3	34 (33-36)					Y		
Flieder (44)	1997	1	32					Y	Y	
Hamada (45)	1997	1	40		Y					
Lantuejoul (46)	1997	1	21							
Berner (31)	1997	1	29		Y				Y	
Itami (33)	1997	1	24		Y			Y	Y	
Nagy (47)	1998	1	12	Y	Y					

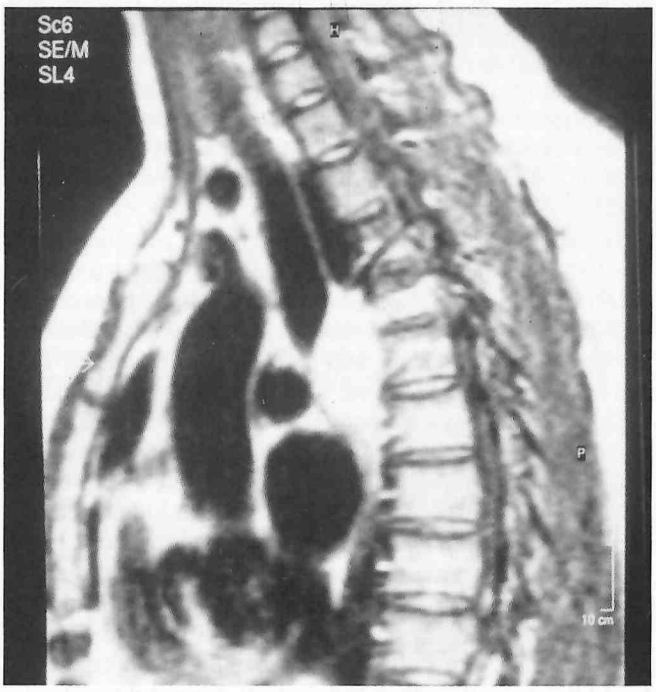


Fig.3. - Chest RMN lateral image showing a cystic mass in the mediastinum, that represents a cystic bronchial malformation.

patients. Since genetic transmission of P-LAM has not been reported, it is possible that P-LAM patients have germ-line TSC2 mutations with limited expression or that they are mosaic for TSC2 mutations[9] with inactivating TSC2 mutations in the lung and in some cases in the kidney, but not in skin, brain, or germ line tissue.

As the symptoms and radiographic and histopathologic features of P-LAM are identical to those in patients with pulmunary involvement of TSC, many authors have suggested that P-LAM may be closely related to or may even be a forme fruste of TSC.[28,34,36,37,38]

Clinical presentation. The classic clinical presentation of P-LAM is distinctive: women of childbearing age present with spontaneous pneumothorax (tab. 1), which is the most common presenting symptom with slowly progressive dyspnea (shortness of breath) on exertion, cough, pleural effusion (chylothorax), chest pain and hemoptisis.[3,4,5,6,8,12,13,14,32,33,40,45,47] Hemoptisis by involvement and total occlusion of the venules (venous hypertension) is of mild to moderate severity and may be life threatening.[8] 50 % of patients develops a pneumothorax at first presentation and 80% develops it in the course of the disease;[3,30,34] pneumothorax is often recurrent[3,5,38] or refractory to conservative therapy with a tube drainage[41] and it may occur in the absence of other clinical or radiological features of the dis-

TABLE II. - *Survival at least 10 years in natural hystory of P-L.A.M*

Authors	Year	Patients	%
Silverstein (22)	1974	32	23%
Taylor (3)	1990	32	78%
Kitaichi (14)	1995	46	40%
Maziak (34)	1996	14	70%

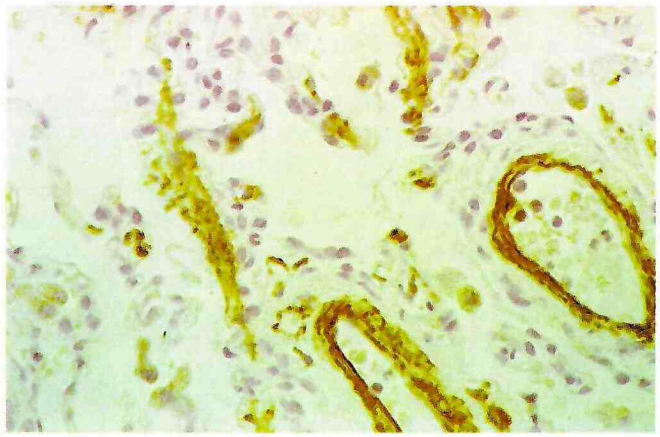


Fig. 4. - A hematoxylin and eosin section of P-LAM patient's lung with smooth muscle cells proliferation (X 50).

ease. In a significant number of P-LAM patients it develops in both chest cavities at different times during their illness.[41,44,46,48] Pneumomediastinum, pneumoretroperitoneum, subcutaneous emphysema[8] and even pneumoretropharinx[49] may also occurr with pneumothorax (which may necessitate pleurodesis in 71%). These patients develop chylous pleural effusions[3,5,14] and chylothorax, which if not present at admission, often (6-20%) develops during the course of the disease.[13,30,32,34,41] Interrupted lymph flow by obstruction of lymphatic channels may also result in several less common manifestations such as chylousascite in approximately 10% of cases,[3,5,9,14,17,30,32] chyloptisis,[50] chyluria,5 chylous pericardial effusion (chylopericardium);[3,8,9,13,21,30,33,41,45,51] low extremity lymphedema are also reported.[8] Chilothorax is due to the obstruction of the thoracic duct and it's revealed by high triglyceride level (greater than 110 mg/dL) with presence of chilomicrons. Some authors explained that the chylous pleural effusion might be caused by rupture of collaterals lymphatics formed by occlusion of the intrapulmunary lymphatics due to the proliferation of smooth muscle cells. Clubbing is apparently uncommon.[4,11,14,32,49,52] Patients with TSC have a similar clinical appearance, because P-LAM is considered as a *forme fruste* of the complete Bouneville disorder.[28,37] Cerebral cortical tubers, cardiac rhabdomyomas, facial angiofibromas, renal angiomyolipomas, which are rare tumors (reported in 40-80% of TS patients) and are usually multiple and bilateral, tend to be solitary and asymptomatic in 15-30% of P-LAM patients.[34] The authors have found renal angiomyolipomas in 40-80% of TSC patients and in15-57% of P-LAM patients, whose grow can reach an enormous size to clinical detection but that only rarely affect renal function.[3,8,34,36] They may be bilateral only in 37% of P-LAM affected subjects[30,32] and associated with flank pain, hematuria or a palpable mass.[34] Extrapulmunary involvement with retroperitoneal, intrabdominal and pelvic angioleiomyomata commonly occurs.[32,34,53,54,55] Clinically (as well as radiographically and pathophysiologically) P-LAM has more resemblance with pulmunary emphysema with significant airflow limitation and it's often clinically misdiagnosed as asthma, chronic obstructive pulmunary disease or bronchitis.[3]

Diagnosis. Due to the varied symptomatology P-LAM is difficult to interpret by clinicians and, as the first symptoms of the disease may occur before an abnormality is detectable by chest-radiographs or pulmunary function tests, there is often a delay between the onset of symptoms and accurate diagnosis: some reported an average length of time with the correct diagnosis of 5±4 years (range 1-13 yrs),[3,34] with an average duration of symptoms of 12,5±9,3 years.[34]

If unilateral spontaneous pneumothorax occurs in a young, apparently healthy fertile woman or if pneumothorax occurs bilaterally, P-LAM diagnosis should be suspected.[41] P-LAM should be highly suspected in any young women who present with recurrent pneumothorax or chylous pleural effusion[56] and progressive airflow limitation (which is not a typical clinical feature of P-LAM).[13,57]

Misdiagnoses include Asthma, Idiopathic pulmunary fibrosis, Chronic obstructive pulmunary disease, Interstitial lung disease of unknown etiology, Sarcoidosis and Tuberculosis. Phsysical examination findings are non specific and include crackles and rhonchi and can be unrevealing or may demonstrate hyperinflation.[14,30]

The most important clues to a diagnosis of P-LAM are characteristic diffuse pulmunary infiltrates on chest radiograph and numerous lung cysts on computed tomography of the chest:[13,57] any disease which reveals cystic changes on chest radiograph or CT such as emphysema[4,14,58] or eosinophilic granuloma may resemble P-LAM.[3,14] Patients with a hystory of smoking must be most carefully evaluated since emphysema may mimic the radiologic pattern of P-LAM.[56] Pneumothorax can be an early feature as chylous pleural effusion.[14,32,33,35,39,47,56,59] Several patients have been found to have P-LAM on CT chest scan after presenting with spontaneous pneumothorax or chylothorax when the pulmunary parenchyma appears to be normal on a chest radiograph.[4,38,39]

Micronodular[33] or reticulonodular[5,14,34,59] opacities which are a non specific occurrence in many interstitial lung diseases are described. Areas of airspace consolidation presumably represent areas of hemorrhage.[4,30,59] The honey-

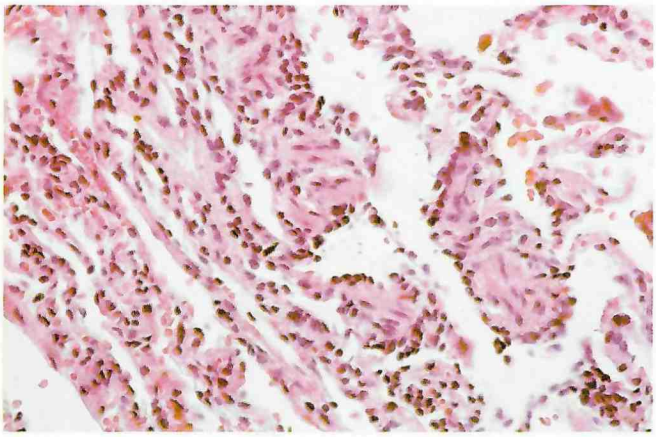


Fig.5. - The presence of alpha-smooth muscle specific actin in these cells confirmes their myoid lineage (X 125).

combing seen in P-LAM is more "delicate" that in other diseases for the absence of significant fibrosis.[4] Some features are interpreted as evidence of recurrent pneumonia[47] as linear opacities (in a reticular pattern without a predominance for any lung zone and with normal lung volumes) resulting from the compression of interstitial tissue by dilated cysts airspaces.[3,14,30] The cysts size may range from less than 0,5 cm to a size as great as 6 cm.[13,30,34,35,59] Hyperinflation with cystis dilatation produces radiolucent lung fields.[3,5,14,59]

Pulmunary function test may be helpful in diagnosis of P-LAM with increased lung volumes[56] and obstructive or restrictive mixed patterns;[3,14] increased gas trapping as well as increase in residual volume is commonly present; often there is decreased forced expiratory volume and vital capacity.[14,30,34] Reduction in elastic recoil forces contributes to airflow limitation but the obstruction is primarily due to airway narrowing rather than to the loss of elastic recoil.[30] Exercise causes an abnormal and excessive ventilatory response with excessive minute ventilation[60] and reduced breathing reserve:[4] the exercise limitation is related to airflow limitation and is reduced primarily in those patients who have large chylous effusions or who have undergone instrumentation of thoracic cavity with or without pleurodesis.[30,61]

There is a markedly reduced diffusing capacity DLCO as a characteristic feature, due to destruction of the alveolar-capillary interface as well as to the presence of ventilation-perfusion abnormalities. Arterial blood gas analysis most often demonstrates hypoxemia without hypercapnia.[13,30]

The evaluation of the lungs on magnetic resonance scans is limited.[60]

Compared to traditional CT, high-resolution computed tomography (HRCT) is much more sensitive to the resolution of the interstitial lung changes to characterize numerous, diffusely distributed, thinwalled cystic airspaces in a better way.[30,35,59,62] These features are not patognomonic for P-LAM, as in Histiocytosis-x they are soaring in lung bases in contrast with the diffuse pattern of P-LAM. For some authors quantitative CT index well correlates with physiologic measurements of airflow, lung volumes, diffusing capacity and exercise performance and may thus provide an useful measure of disease severity.[58] Finally HRCT may reveal good evidence of P-LAM associated lymphoadenopathy or P-LAM complications, such as pneumothorax, pleural effusion, alveolar hemorrhage or lymphatic stasis:[35,59] there is a close correlation between the extent of the cystic parenchimal replacement (measured by quantitative high-resolution chest) and disease severity (determined by spirometry or diffusing capacity). Apart from its potential to assess severity of disease, quantitative TC may also have a role in identifying earlier abnormalities at the onset of the disease, when pulmunary function tests are normal.[63] In P-LAM diagnosis, CT scans of the abdomen may reveal renal angiomyolipomas and enlarged retroperitoneal, paraaortic or pelvic lymph nodes or masses.[35,36] Lymphangiograms may reveal abnormal filling and cystic changes within the lymph nodes.[5,35,64] For a definitive diagnosis of P-LAM, biopsy is required[3,13,52] and it is mandatory to specifically request the pathologist to stain lung tissue specimens for smooth muscle cells: in certain cases this may be sufficient, although such diagnoses heavily depend on the expertise of the clinicians and pathologists involved.[13,57] Sinee the presence of these cells clusters in the pleural effusion is specific and pathognomonic, and since cytologic examination of pleural effusion is less invasive than open lung biopsy, the cytologic examination of the pleural effusion is recommended before thoracotomy in P-LAM suspected patients.[33] If bronchial biopsy is not diagnostic, or conservative management of the pneumothorax is unsuccessful, an open lung biopsy with or without pleurodesis should be performed.[12,13,34,41,57] Thoracoscopic or transbronchial biopsy may obviate the need to violate the integrity of the thoracic cavity by a more invasive biopsy procedure and may thus eliminate a hindrance to future lung transplantation.[13,30,57] When in a lung biopsy specimen the proliferation of smooth muscle cell is fast, early P-LAM lesions are correctly diagnosed.[10,30] In the diagnosis of P-LAM previous published research report the results of fine needle aspiration cytology of a retoperitoneal tumor and paratubar lymph nodes.[31] Lung tissue from P-LAM patients may mimic numerous pathologic entities as idiopathic pulmonary fibrosis, emphysema or any disease that involves smooth muscle hyperplasia.[30] Because P-LAM may involve extraparenchymal sites, such as lymph nodes or abdominal or pelvic masses, a definitive diagnosis of P-LAM can be made from biopsies of such sites. Because of the overlap between P-LAM and TSC discussed previously, patients suspected of suffering from P-LAM should be carefully screened for signs, symptoms, or family history suggesting a diagnosis of TSC. Smooth muscle origin is verified by immunostaining with muscle specific actin antibody[33,47,65] and, more recently, a monoclonal antibody, HMB-45 (melanoma related marker) was found to help the diagnosis. HMB-45 could recognize antigens on the surface of melanoma cell lines and it does not seem to bind to P-LAM cells.[30,66] Not all cells are HMB45 positive, but for some authors HMB45 positivity can be sufficient to estabilish the diagnosis of P-LAM[67,68] in order to exclude other cystic pul-

munary diseases that cause recurrent pneumothorax as Primary spontaneous pneumothorax, Pulmunary eosinophilic granuloma, Pulmunary emphysema and Idiopathic pulmunary fibrosis with apical bullous change.[33,40,46,65]

TSC1 and TSC2 are the gene loci formally assigned to tuberous sclerosis: TSC 2 is located at position 16p13 and it's next to the gene for adult polycystic kidney disease. Loss of heterozygosity at this locus has been demonstrated to be present in renal angiomyolipomas of P-LAM patients and contains the gene for dopamine-B-hydroxylase that catalyzes the conversion of L- dopamine to nor-epinefrine. Thus, putative genes for tuberous sclerosis and P-LAM are involved in the closely related pathways of catecholamine and melanin synthesis. Eumelanin precursors are suspected to have mutagenic effects under influence of insulin-like growth factor 1, epidermal growth factor, adrenal corticosteroids and pituitary hormones. Further cytogenetic studies may help to define the link between these two clinically associated diseases in a better way.

It is unknown whether the smooth muscle cell proliferation results from an abnormality of the proliferating cells or if these cells respond to abnormal stimulation from circulating mediators. The manifestation of P-LAM was thought to have been triggered off by a surge of sex hormones.[12,27,39,46,47,69] The estrogen plays a central role in progression of the disease: P-LAM in fact doesn't present prior to the menarche, rarely after menopause and only in association with hormonal supplementation; the disease is accelerated by pregnancy and abated after oophorectomy:[8] a hormonal stimulus therefore may induce disease proliferation and progression.[39] Progesterone receptor and estrogen receptor have been demonstrated by biochemical means in P-LAM specimens with immunocytochemical method.[27,31,39,46,66,69,70]

The detection of one or both receptors[39,70] clearly demonstrates that endocrine factors are connected with the disease, as clinical behavior suggests. The molecular mechanism of estrogen action is the subject of intense research: the estrogen response element is a palindromic sequence found near the start sites of transcription of many genes whose activation may lead to the activation of autocrine and paracrine stimulatory processes: polypeptide mitogens that mediate the effects of steroid hormones on smooth muscle growth in uterine leiomyomas have been identified and these findings have important implications for growth factor regulation of cellular function in many diseases including P-LAM.[71] There are two reports of recurrence of disease in patients who underwent single lung transplantation for P-LAM:[72,73] in one patient the male donor origin of LAM cells was conformed by karyotype analysis demonstrating the presence of a Y-chromosome. This lends further credence to the idea that humoral factors are important in the development and growth of P-LAM cells.[30] The differential diagnosis is more difficult with Emphysema, Alpha-1-antitrypsin deficiency, Asthma, Chronic extrinsic allergic alveolitis, Pulmunary histiocytosis X, Cystic sarcoidosis (stage IV) as part of a subgroup of cystic interstitial lung disease and panacinar emphysema due to intravenous drug use.[8]

Pathology. P-.LAM is usually diagnosed by open lung, or transbronchial or thoracoscopy biopsy and autopsy.[13] Microscopically there is a cystic degeneration of the lung interstitium: these lesions are the result of the degradation of supportive elastic fibers caused by an imbalance between elastase and alpha-1-antitrypsin which is responsible for the cystic destruction of the lung, mimicing pulmunary emphysema.[30,47,74] There is a diffuse hamartomatous proliferation of smooth muscle around and within the pulmunary lymphatics, venules and airways.[4,5,8,10,12,13,30,32,34,39,41,75,76] Smooth muscle cells are found in the adventitia of terminal bronchi, in the alveolar walls and in the pleura: the proliferating tissue in pulmunary interstitium which may protude into the bronchiolar lumen leads to obstruction and distension of the terminal airspaces[69] and is believed to contribute with the compression of airways to the development of parenchymal cysts and pneumothorax (which where seen in ~5% of women with TSC).[4,5,6,38] Pleura, septa and alveolar walls are involved and thickened, sometimes in a nodular way: breakdown of septa leads to focal emphysema with bullous changes, without predilection of any lung zone.[10,30,34] Concomitant risk factors such as cigarette smoking or dust inhalation may contribute to airway obstruction.[77] Proliferated smooth muscle cells sometimes thicken both pulmunary arteries and veins and cause pulmunary hemorrhage; some degree of hemosiderosis is due to the rupture of dilated and tortuosous venules. In late lesions the smooth muscle accumulation, in association with increased collagen deposit, forms nodular aggregates and the dilated alveolar spaces contain few hemosiderin-laden macrophages.[30] In P-LAM the extrathoracic manifestations are usually confined to the lymphatics above and below the diaphragm: the myoproliferative process may involve the mediastinum with thoracic lymphatics and hilar lymph nodes and retroperitoneum with mesentery: for this reason retroperitoneal lymphonodes are often enlarged.[10,30,32,34,75,76] Dilatation of lymphatic vessels is prominent, especially in the subpleural areas and at some points the walls of the vessels are extremely thin. Cell clusters are seen in the lumina of some lymphatics: the rupture of these thin-walled lymphatics appears to lead to chylous effusion with leaking of the cell clusters into the pleural cavity.[14,33,39] Lymph node involvement is commonly seen histologically, while radiografically this is not a prominent feature.[35] Electron microscopic examination reveals many myofilaments in the smooth muscle of the lung lesions that consist of fusiform cells and dense deposits of collagen fibers.[23] The size of renal angiomyolipomas which may be part of the TSC range from a few millimetres to over 10 cm: angiomyolipomas can also be seen in the pancreas, thyroid adrenals and uterus: hamartomatous lesions are composed by smooth muscle, adipose tissue and blood vessels that have been shown radiographically to be present in nearly 50% or more of patients with P-LAM.[3,30,34,36]

Lung LAM lesions are indistinguishable from those occuring in rare cases of TSC and the proliferation of smooth muscle within the lungs can also occur in association with Benign matastasizing leiomyoma or Interstitial fibrosis. Rare cases of diffuse smooth muscle proliferation of unknown origin are reported.[11] It's also well known that hypertrophy and hyperplasia of smooth muscle occur in

many types of chronic pulmunary diseases, including Emphysema, Eosinophilic granuloma and Idiopathic interstitial fibrosis.

Therapy. The major hindrance to the research necessary to achieve this goal is the rare and sporadic nature of the disease.[30]

The predilection of P-LAM for premenopausal women has led to the assumption that hormonal factors play an important role in the pathogenesis of the disease. Several authors have suggested that assays and immunohistochemical tests for estrogen and progesterone receptors in lung-biopsy specimens might be used to determine the most appropriate hormonal treatment for P-LAM. Steroid receptor determination should be performed in all these rare cases as suggested by other authors.[78] ER and PR content of lung tissue may be a way for clarifying the relationship of P-LAM to Bourneville syndrome and to distinguish these two disorders.[39]

Since patients with both PR and ER positive breast tumors have better prognosis because of the higher response to hormonal therapy, many clinicians have used hormonal manipulation for the therapy ofP-LAM such as oophorectomy[3,10,14,24,64,79] (or radioablaction of the ovaries), progesterone[3,10,12,14,16,17,21,25,27,80,81,82] tamoxifene or other antiestrogen agents.[3,10,14,26,30,83,84] Antiestrogen therapy has become the primary form of medical treatment and the administration of luteinizing -release hormone analogues or various combinations of these treatments have been attempted.[16,17,19,25,80,85,86] Hormonal manipulation therapy by surgery, irradiation and chemiotherapy produced variable results.[30,39,47,57,70] It was not successful[3,5,14,22,26,32,64,80,85] on pulmonary parenchymal changes which appeared to be stationary or progressive, but had beneficial effects on chylothorax or chylous ascites.[3,14,30,57] Definitive conclusions should not be drawn from these reports because responses have been variable to hormonal treatments that are not acceptable in a young patient: for this reason lung transplantation is considered a consistent therapy for P-LAM.[8,9,10,30,32,34,47,72,73,81,82] Unfortunately P-LAM patients who undergo transplantation often have severe airway obstruction with severe hyperinflation and are stll at high risk for pneumothorax. Marked hemodynamic instability combined with the ethical dilemma of transplantation for a systemic disease that may recur, makes the issue of lung transplantation for P-LAM a complicated one and does not allow to consider it a definitive therapy.[30] The first successful transplantation (a combined heart-lung transplantation) for lymphangioleiomyomatosis was performed in 1983[82] and a single lung transplantation was performed in 1988.[81] The mean interval of 11 years between the onset of symptoms and the time of lung transplantation is in accordance with the natural hystory of P-LAM. A FEV 1 below 25 to 30 % of the predicted value might be used as referral guideline for lung transplantation.[32] Lymphoadenopaty due to P-LAM should not be considered a contraindication to lung transplantation; however, lymphoadenopathy may lead to diagnostic confusion in the posttransplantation period if this condition is not recognized beforehand. Lung transplantation is not a controindication in P-LAM patients with TS, even if they present with end-stage P-LAM. However, some patients with TS are mentally retarded, a fact that might lead to problems in compliance with treatment after transplantation. Authors report 34 end-stage P-LAM patients treated at 16 transplantation centers, each having experience with only one or a few patients.[32] The most important post-transplantation complications of P-LAM patients were episodes of pneumothorax in the native lung after single-lung transplantation in 5 patients and chylothorax resolved by thoracic-duct ligation. Drainage of pleural fluid collections can be hazardous as it may lead to protein loss and it's not always necessary. Chemical or surgical pleurodesis has been performed with variable success in preventing recurrent pneumothorax and pleural effusion. Although such procedures may complicate future lung transplantation, these may be necessary to control symptoms. Survival rates after lung transplantations are similar between patients who underwent transplantation for systemic versus isolated disease and the deaths were due to acute lung injury, hemorrhage, dehiscence of the bronchial anastomosis with sepsis, or, some months later, to infections, or bronchiolitis obliterans.[32,87] Because both P-LAM and bronchiolitis obliterans may be characterized by an obstructive spirometric pattern, disease recurrence should be included in the differential diagnosis when pulmunary function deteriorates after transplantation. Patients who undergo transplantation often have severe airway obstruction with severe hyperinflation, receive instrumentation of the thoracic cavity or pleurodesis and remain at high risk for pneumothorax: these characteristics increase intraoperative and postoperative risks. The possibility of recurrent P-LAM in male donor's lung too implicates new aspects for lung transplantation which cannot be considered a definitive therapy.[10,26,72,73] Hormonal treatment was continued after transplantation in 8 patients at four centers and was discontinued in 18 patients at 9 centers: in all the patients who had received some kind of hormonal treatment, end-stage disease developed.[32] The use of monoclonal antibody HMB45 can be a valuable tool to detect even small proliferation of smooth muscle cellsbiopsies obtained from patients after transplantation (also being highly specific and sensitive for the diagnosis of P-LAM).[40,67,88] Recurrent P-LAM is described in the lung allograft where the proliferated smooth muscle cells are of donor origin and the smooth muscle proliferation of the allografted lung was multifocal: these findings point out to systemic causative factor in the recipient.The morbidity of transplantation underscored the need to elucidate the pathogenic mechanism involved in P-LAM in order to formulate rational strategies for treatment. The involvement of lung and regional lymph nodes raises speculations that P-LAM might be the result of local cytokine effects transferred by lymphatics as it does not seem to be metastatic.[10]

The possibility of recurrent P-LAM raises the question whether patients with P-LAM are disqualified for transplantation: we know that lung transplantation for respiratory failure resulting from systemic disease as Sarcoidosis and Scleroderma remains controversial: further investigations in this direction have to be performed.[10]

Finally, alpha-interferon has also been tried out without

benefit, as it has many side effects. Today only oophorectomy and treatment with progestational agents appear to provide reliable benefit. In a meta-analysis of 30 treated cases prior to the widespread tissue destruction,a combination therapy was performed with oophorectomy and either progesterone and/or tamoxifen. Chemical oophorectomy with LHRH analogs may replace surgical oophorectomy, although currently data are lacking.[72] When renal angiomyolipomatas develop symptoms, nephrectomy, partial nephrectomy or arterial embolization may be necessary.[36]

With improved understanding of the natural history of P-LAM as well as of genetic, molecular and cellular biology, new therapies will soon become available.

Prognosis. Most patients die by progressive deterioration of respiratory function within several years (mean time: 10 years) after the onset of disease and have a slowly declining clinical course; (more recent observations show that some patients are still alive 13 and 20 years after the onset of P-LAM).[3,4,5,6,22,30,41]

The disease is thought to be inexorably progressive with a median survival of 8 to 10 years from diagnosis, with 22 to 78% of women succumbing to progressive respiratory failure after a mean of 8,5 years from diagnosis. In the most recent large case series there was an apparent improvement in survival perhaps by hormonal interventions or better supportive treatments or an earlier stage diagnosis of the disease (Tab II). A long term (20 years) survival has been also reported.[3,14,30]

As P-LAM can be treated with different approachs and lung transplantation is available, these patients may be live longer and, in time, extrathoracic manifestations may be revealed.[34]

The overall actuarial one year and two year survival rates after lung transplantation for P-LAM reported in the St.Louis International Lung Transplantation Registry for P-LAM are 69% and 58% respectively and are similar to other diseases. Among the 34 patients with transplantation for P-LAM reported from 16 centers (27 single lung transplantation, 6 bilateral, 1 heart-lung transplantation) 19 were alive at a mean of 33±20 mounths after transplantation;[32] others report that 50% were still alive in 3 yrs.[72] Recurrence disease in male donor's lung[72,73] supports the idea that humural factors are important in the development and growth of the P-LAM cells. Other complications specific to P-LAM transplantation are present as pneumothorax after single lung transplantation in native lung, or infections in the native lung which may contain many large cysts, or chylothorax by leakage of chyluos fluid from dilated and torn lymphatic vessels in the mediastinum. However, no severe functional impairment was reported since the transplanted lung was predominant and sufficient for ventilation and perfusion.[32] Postoperative complications were similar to these occurred in transplantations for other diseases, as pneumonia, acute rejection and bronchiolitis obliterans.

Among patients with TSC, P-LAM is the third-most-frequent cause of TSC related death after renal disease and brain tumors. Pulmunary function and histologic pattern are predictive of survival[14] as elevated total lung capacity and reduced FEV1/FEV ratio were associated with poor survival (2 to 5 years) after initial examination; furthermore, a predominantly cystic pattern of histopathology predicts a worse prognosis than a predominantly muscolar pattern but we don't know whether these patterns represent two distinct histopathologies or different stages in the disease evolution.[8]

A reasonable approach to the P-LAM patients follow up is subjective evaluation, full pulmunary function testing (spirometry, lung volumes and DLCO) and CXR at 6 months intervals with more extensive or invasive procedures such as exercise testing and/or HRCT scans at 12 mouths intervals. The wide variation in the rate of deterioration in patients with P-LAM may necessitate adjustments of these intervals for individual patients. Furthermore, patients should be advised to utilize contraceptive meaures.

Conclusions

Our reported P-LAM case must be considered as a "sporadic" one .

Our investigation didn't reveal any pulmunary symptoms among parents or sisters or sons.

Physical examination findings and radiographic presentation are not specific for P-LAM. Suspected P-LAM on chest CT was confirmed by a lung biopsy with a wedge resection on VATS. Such a procedure is less invasive than the open lung biopsy and eliminates a hindrance to future lung transplantation; furthermore, it is the best method to have adeguate tissue for the histopathologic diagnosis .

Our patient's histopathologic finding is an early one and we use a combination of subjective, radiographic and physiologic parameters to follow up the young woman and to capture all the aspects of future manifestations of her disease.

We have subscribed our patient in a registry created by a working group for P-LAM (convened in March 1995), with a tissue bank and a funding mechanism for P-LAM-related research: Sue Byrnes is its Executive Director (10105 Beacon Hills Drive, Cincinnati, OH, 4524; fax-phone: 513-777 6889)

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