Case report

BENEFICIAL EFFECTS OF GONADOTROPIN RELEASING HORMONE ANALOGS IN PULMONARY LYMPHANGIOLEIO-MYOMATOSIS

Simona V. Fica[1], Lia Popescu[2], T. Ciprut[3], Carmen Ardeleanu[4], Dana Terzea[4], Raluca Trifanescu[1], M. Coculescu[*,1]

[1] Department of Endocrinology and 4 Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest
[2] Department of Pulmonary Medicine, "Victor Babes" Hospital, Bucharest,
[3] Department of Radiology, Elias Hospital, Bucharest

OBJECTIVE: To report an unusual cause of respiratory failure in a 33-year old Caucasian woman, diagnosed at 26 years with pulmonary lymphangioleiomyomatosis (LAM) and treated with gonadoliberin analogs (aGnRH) four years.

METHODS: The respiratory failure was diagnosed on functional tests (spirometry, oxymetry, diffusing capacity of carbon monoxide). High resolution chest computed tomographic (HRCT) scan and open lung biopsy with specific immunohistochemistry certified the diagnosis.

RESULTS: The diagnosis of pulmonary LAM was established after one year on chest HRCT and lung biopsy which revealed the proliferation of smooth muscle of pulmonary vessels, positive for actin, desmin, vimentin, estrogen- and progesterone- receptors. Spirometry revealed mixed obstructive and restrictive dysfunction. A correlation between worsening of dyspnea and estradiol peaks occurred during three gestation periods. Despite a short treatment with medroxyprogesterone 10 mg/day and tamoxifen (20 mg/day), the patient's symptoms and pulmonary function tests worsened. aGnRH treatment improved both symptoms and pulmonary function tests during the first year and was associated with a slow decline in pulmonary function tests and stabilization of the cystic lesions during the following 3 years. The patient did not develop LAM-complications such as: pneumothorax, chylothorax, or hemoptysis.

CONCLUSION: Treatment with aGnRH is effective in slowing the evolution of pulmonary LAM.

Key words: estrogen receptors, gonadoliberin analogs, lymphangioleiomyomatosis, actin.

*Correspondence to: Mihai Coculescu, Endocrinology Department, "Carol Davila" University of Medicine and Pharmacy, 34-36 Bd. Aviatorilor, 011863, Bucharest, Romania, Tel/Fax: + 4021 3198718, e-mail: m.coculescu@uni-davila.ro

INTRODUCTION

Pulmonary lymphangioleiomyomatosis (LAM) is a rare, idiopathic, progressive lung disease that almost exclusively occurs in women of childbearing age, rarely in postmenopausal years and exceptionally rare in men (1). Pathologically, it is characterized by a benign, nodular proliferation of immature smooth muscle cells throughout the lungs in the peribronchial, perilymphatic and perivascular areas. This results in obliteration of the respiratory tract and in the development of cysts that mimic emphysema (2, 3). The reported prevalence of LAM is around one per million, although the true prevalence is likely to be greater (1).

LAM has a poor prognosis. Some studies reported that progression of the disease to death due to respiratory failure is common within 8-10 years (2), but other studies reported a survival probability of 71% after 15 years (4).

Various antiestrogen methods have been used for therapy of LAM, such as: progestational agents (5), tamoxifen and oophorectomy (6). The use of interferon α (6,7) and somatostatin was reported in isolated cases. Pulmonary transplantation is used as a last resort (8). However, the surgical procedures rise important risks. As an alternative, gonadotropin releasing hormone analogues (aGnRH) that are equivalent to a chemical oophorectomy have been used by other authors (9, 10) and by ourselves.

CASE REPORT

We present a 33-year old woman initially complaining of one year history of progressive dyspnea on exertion and fatigability. Her past medical history included normal age of menarche, normal menstrual cycle, 1 normal birth a year previously, right breast fibroadenoma operated 4 years previously, emergency myomectomy for subperitoneal uterine leiomyoma, and left ovarian cyst ablation 3 years previously. She had no family history of respiratory or endocrine conditions and she was a lifetime nonsmoker. Physical examination was completely unremarkable. A computed tomography (CT) scan of the chest showed minimal bibasilar interstitial infiltrates. Sequential serum levels of estradiol, progesterone, LH, FSH showed normal hormonal cycling, with correlation between intensification of dyspnea and estradiol peaks. Pulmonary function tests revealed a restrictive pattern with an abnormal gas exchange, as evidenced by a decrease in DLCO (diffusion capacity for carbon monoxide) (Table 1). The patient was thought to have either pulmonary tuberculosis or sarcoidosis. She was started empirically on antituberculous drugs and prednisone for 6 months, without improvement. She had 3 gestations associated with worsening dyspnea and therapeutical abortions were performed.

The diagnosis of LAM was suggested one year later on a repeated chest CT, which showed micronodular interstitial and trabecular infiltrates, multiple cysts

disseminated bilaterally in pulmonary parenchyma, without mediastinal lymph nodes involvement (Fig. 1).

Table 1. Pulmonary function tests

PFTs	Time of diagnosis	MPG +T 1 year	No treatment	No treatment	Start of aGnRH	aGnRH +1 year	aGnRH +2 years	aGnRH +3 years	aGnRH +4 years
VC	57.72	59.17	47	58.1	28.7	57.2	37.2	30.3	40.4
FEV_1	51.2	53.2	35.7	38.4	19.3	23.2	17.2	14.2	11.2
FEV_1/FVC %	88.7	89.8	78	67.9	60	41.7	48.7	48.2	28.5
P_aO_2 (mm Hg)	98.7	97.8	97.9	77.9	77.9	96.1	77.9	80.1	
DLCO	58.7	65.2	57.9	50.7	12	31.7	16.7		
DLCO/VA	77	79.7	63.4	56.3	23.8	36.2	19.6	17.9	

MPG=medroxyprogesterone acetate, T=tamoxifen, aGnRH=gonadotropin releasing hormone analogue, VC=vital capacity, FEV_1=forced vital capacity in one second, P_aO_2=partial pressure of arterial oxygen, DLCO=diffusion capacity for carbon monoxide, DLCO/VA=diffusion capacity corrected for the alveolar volume.

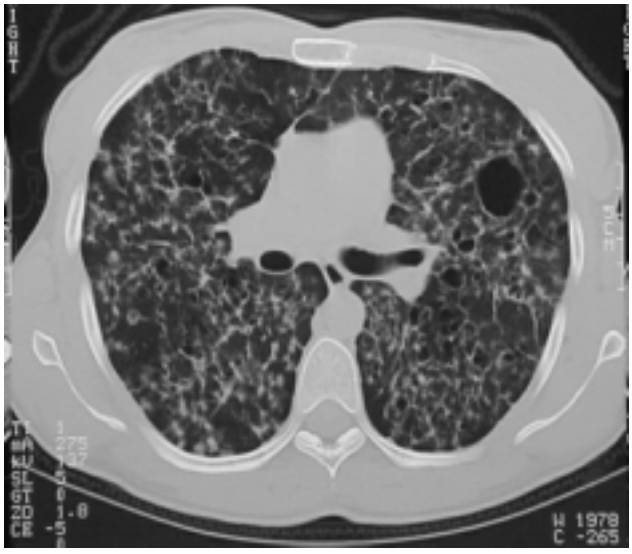


Figure 1. High resolution computed tomography of the lung; December 1998, without any treatment.

The diagnosis of LAM was confirmed by open lung biopsy. The histologic findings were small nests of LAM cells along the pulmonary blood vessels and lymphatics, with infiltration of LAM cells in vessels walls (Fig. 2A). The proliferating LAM cells presented in a nodular, concentric, or parallel pattern of normal smooth muscle cells. Two types of LAM cells were noted: small, spindle-shaped cells and large, epithelioid cells. Mitotic figures and atypical cells were

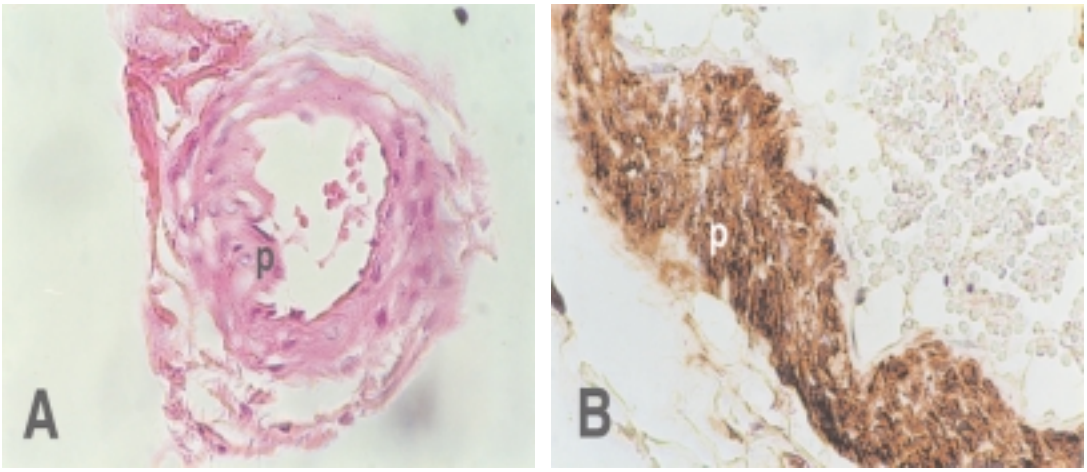
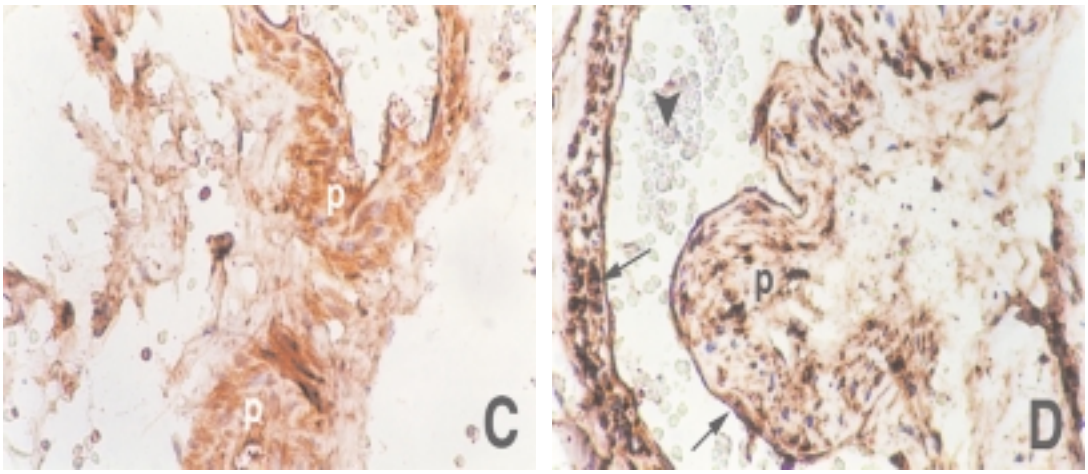
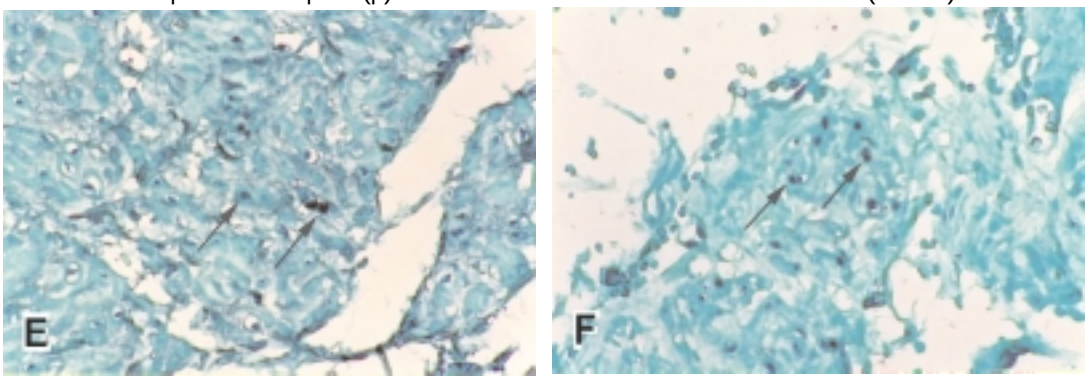


Figure 2A. Histology of blood vessel pads (p), HE, × 400.
Figure 2B. Immunohistochemistry for actin using Avidin Biotin Complex method on lung biopsy, × 400.



Figures 2C and 2D. Immunohistochemistry for desmin (C) and vimentin (D) using Avidin Biotin Complex method on lung biopsy, × 400 (D) Capillary section showing capillary lumen (arrowhead) and perivascular pads (p) immunoreactive for vimentin in LAM cells (arrows).



Figures 2E and 2F. Immunohistochemistry for estrogen receptors (E) and progesteron receptors (F) using Avidin Biotin Complex method on lung biopsy, × 400. Estrogen and progesterone receptor stain the nuclei (arrows).

present, but rare (Fig. 2A). The immunohistochemical staining (performed with Avidin-Biotin peroxidase complex) of the specimens from the lung biopsy, demonstrated smooth muscle components: actin (Fig. 2B), desmin (Fig. 2C) and vimentin (Fig. 2D); estrogen receptors (5% of LAM-positive cells, Fig. 2E), progesterone receptors (10% of LAM-positive cells, Fig. 2F), and proliferating cell nuclear antigen (PCNA) in 5% of LAM-positive cells.

Due to worsening dyspnea, the patient was started on medroxiprogesterone acetate (10 mg/day) and tamoxifen (20 mg/day) without clinical improvement, or any improvement in pulmonary function tests for 3 years (Table 1). During her 4th year of illnes, she was started on a GnRH analog, Triptorelin 3.75-mg s.c. once a month. After 12 months of Triptorelin therapy, the patient showed an improvement of dyspnea on exertion and in pulmonary function tests, improvement that was sustained for over 2 years. Serum estradiol was undetectable, LH was 0.2 mUI/ml, and FSH was 3.02 mUI/ml. High resolution CT of the chest revealed only a slight progression of lesions, with formation of ovoid cysts, some of them 4-5 cm in diameter (Fig. 3A) in the first year of aGnHR therapy and stabilization during the second year (Fig. 3B). DXA bone density scan revealed incipient osteopenia significant for age (BMD L2-L4 =1.013g/cm^2, T score= -1.6 SD, Z score = -1.1 SD) and treatment with calcium and D vitamin was started. The patient did not develop any of the known complications of LAM, such as: pneumothorax, chylothorax, chyloperitoneum, and hemoptysis. Cranial and abdominal CT scans showed absence of meningioma or renal angioleiomyoma.

DISCUSSION

We report improvement of signs and symptoms of LAM after one year of aGnRH treatment, and a slower progression of the disease for the following three years of treatment.

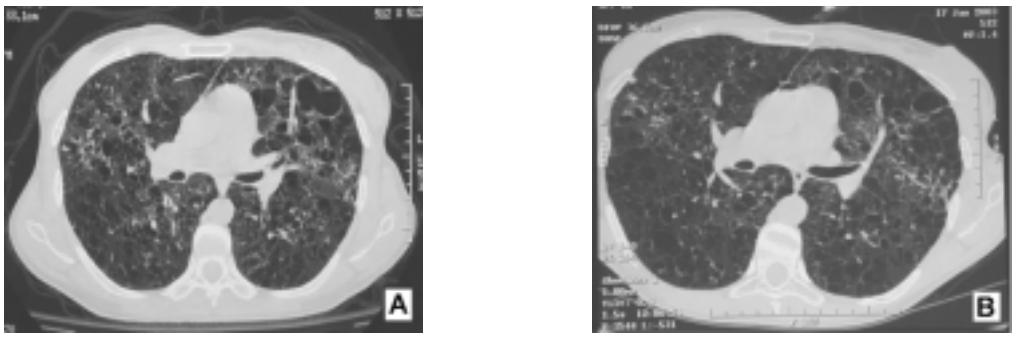


Figure 3. High resolution computed tomography of the lung; November 2000, at the beginning of aGnRH administration (A) and January 2003 (B), under aGnRH therapy for 2 years. Note the multiple cysts (arrow) disseminated bilateral in pulmonary parenchyma and the micronodular interstitial and trabecular hyperplasia, that worsened between 1998 and 2000, but were stable between 2000-2003.

Our patient experienced two comon symptoms of LAM, dyspnea and fatigability. Other clinical features of LAM include hemoptysis, cough and chest pain. A variety of intra- and extrathoracic complications of pulmonary LAM have also been reported: spontaneous pneumothorax, often recurrent or bilateral necessitating pleurodesis, pneumomediastinum, pneumoperitoneum, pneumoretropharynx and subcutaneous emphysema (2); chylothorax due to obstruction of the thoracic duct or rupture of the lymphatics in the pleura or mediastinum by proliferating smooth muscle cells is characteristic of this disorder but is present in only a minority of subjects at diagnosis; chylous ascites, chyluria, chylopericardum have also been reported. Abdominal and pelvic lymph nodes may also be affected. Abdominal, especially renal angiomyolipomas are common, occurring in as many as 50% of patients. They may be very large prior to clinical detection, but only uncommonly affect renal function (1, 2). The pathophysiologic mechanism is thought to be smooth muscle hyperplasia which leads to obstruction of lymphatics and chylothorax, obstruction of the blood vessels and hemoptysis, obstruction of bronchi and diffuse cystic dilatation of the terminal airspace and pneumothorax (11).

Pulmonary function tests are helpful in providing a clue to the diagnosis of LAM. Forty percent of patients have a normal initial spirometry, 44% have obstructive ventilatory impairment and 23% have a restrictive or mixed pattern (4). The lungs are often hyperinflated, with an increase in total lung capacity (TLC), in residual volume (RV), and in RV/TLC ratio. Often there is evidence of airflow limitation with a decreased FEV_1 (forced vital capacity in one second) and FEV_1/FCV (12) and 26% of patients have a positive bronchodilator response (12). Gas exchange is abnormal and the diffusing capacity (DLCO) can be markedly reduced (4). Arterial blood gas analysis shows hypoxemia in 57% patients (12). Our patient had initially started with a restrictive pattern and developed a mixed obstructive and restrictive defect with an abnormal gas exchange and moderate hypoxemia.

HRCT is much more informative and sensitive than routine chest radiography in demonstrating the cystic nature of the disease. The findings of the diffuse, homogeneous, small thin-walled cysts, or of severe destruction of the lung parenchyma due to large cysts is highly suggestive of the diagnosis. The size of the cysts varies from small (less than 1 cm diameter) to bullae (larger than 5 cm diameter). HRCT may also show an increased interstitial pattern, ground glass opacities, presence of pleural or pericardial effusion, pneumothorax and lymph node enlargement (2). Usually, there is a close correlation between the extent of the cystic parenchyma and the disease severity. In our patient, CT revealed only a slight progression of lesions, with formation of ovoid cysts, some of them 4-5 cm in diameter. After starting the treatment with aGnRH, the interstitial infiltrates and the cystic images did not regress, but they remained stable, while the pulmonary function tests showed slight worsening.

The diagnosis of LAM is established by open lung biopsy which demonstrates the presence of LAM cells either by their characteristic histological appearance (proliferation of LAM cells that are atypical smooth muscle cells around bronchovascular structure, into the interstitium, along the axial lymphatics of the thorax and abdomen, and perivascular), or by specific immunostaining for smooth muscle components (α actin, desmin, vimentin). HMB-45 (human melanin black) is positive in many cases (1). This monoclonal antibody labels cells of the melanocyte line, LAM cells and renal angiomyolipoma cells. The percentage of abnormal LAM cells reactive with HMB-45 varies from 17%-67% (12). As an alternative method of diagnosis, transbronchial biopsy in conjunction with HMB 45 staining can be sufficient to make the diagnosis of LAM (13).

The LAM cells are polyclonal in nature and are of two types (2, 3): 1) Small, spindle-shaped cells that are centrally located in the LAM nodules are highly immunoreactive for matrix metaloproteinase-2 (MMP-2), its activating enzyme (MT-1-MMP), and proliferating cell nuclear antigen (PCNA); 2) Large epithelioid cells, that are distributed along the periphery of the nodules and show a high degree of immunoreactivity with HMB-45 antibody and with antibodies against estrogen and progesterone receptors (2). In our case, PCNA was positive, but HMB-45 was negative. It is difficult to establish a relation of these findings with the clinical peculiarity of our case (absence of complications such as pneumothorax), but it is possible that patients who are negative for HMB-45 have a lower risk for recurrent pneumothoraces.

LAM cells can express both estrogen and progesterone receptors (14, 15). In our case, progesterone receptor was expressed more frequently (10% LAM-positive cells) than estrogen receptor (5% LAM-positive cells).

Regarding the role of estrogens, 20% of initial cases of LAM were described in pregnant women and worsening of LAM was observed in 14% of cases (4). The onset of the disease occurs during the childbearing age (1) and only 10% of cases are diagnosed after menopause (4), many of those being associated with estrogen replacement therapy. The clinical course may be longer and more benign after the menopause (16). However, LAM has also been described in male patients (17, 18).

Estrogen and progesterone receptors were selectively expressed in a subpopulation of LAM cells that are larger in size and have a limited ability to proliferate (15). They are localized mainly in the nuclei of large epithelioid LAM cells that are distributed along the periphery of the nodules. These receptors appear to be down-regulated by hormonal therapy (progesterone and tamoxifen), but a correlation between the eficacy of hormonal therapy and the receptors has not been proved, neither for medroxiprogesterone, nor for oophorectomy (15). In our case, there is a relative low expression of the estrogen and progesterone receptors on LAM cells that may explain the response to therapy with aGnRH.

How sex hormones might affect the development and progression of LAM is speculative. Estrogen may amplify the effect of a mutant protein by down regulating tuberin (a 180 kDa protein which acts as a tumor suppressor) or possibly other

protein with GAP (GTP activating protein) that would otherwise compensate for a defect in tuberin activity (1). Differential expression of such proteins would explain the predilection of these lesions for certain tissues. LAM cells that express estrogen receptors also express the protein Bcl-2 that acts as a suppressor of apoptosis or programmed cell death (19). An increase in the ratio of anti-apoptotic proteins such as Bcl-2, Mcl-1 to pro-apoptotic homologue Bax would reduce apoptosis of LAM cells and may represent a way in which estrogen potentiates LAM. Furthermore, the reaction for c-Myc (an apoptosis-related oncoprotein) is positive in all patients. (1).

The pathogenesis of LAM involves genetic factors. LAM occurs sporadically or in association with tuberous sclerosis. There is also an increased association with meningioma (20). LAM may result from mutations of either TSC 1 and TSC 2 genes (21, 22) with expression of a mutant tuberin with abnormal function. Some recent studies found a loss of heterozygosity (LOH) of the wild TSC-2 allele on chromosome 16 in the abnormally pulmonary smooth cells and renal angiomyolipoma cells from patients with sporadic LAM (23). Since a germ line mutation of TSC-2 is unlikely in LAM, patients may be mosaics - that is, they may only carry the TSC-2 mutation in a small population of cells or may have sequential somatic mutations of the TSC-2 gene (22).

Some authors suggest that pulmonary LAM is an ectopic proliferating tissue like a hamartoma (AP) with abnormally proliferating smooth muscle cells that respond to stimulation from circulating overexpressed growth factors. The fibroblast growth factor (24), platelet derived growth factor β-chain and receptors, IGF-1, IGF-2, and their receptors and IGFBP 2,4,6 in spindle cells and IGFBP 5 in epitheliod cells (25), angiotensin II, aberrant HMG I-C (high mobility group protein I-C) transcripts (1), transforming growth factor β_1 and fibronectin (26) have been described in LAM.

Matrix metalloproteinases (MMP_2, MMP_9) are also involved in the pathogenesis of the destructive pulmonary lesions in patients with LAM (27). MMP_2 and MMP_9, both of which can degrade elastin as well as collagen, are probably responsible for the connective tissue destruction and cyst formation in LAM (28).

Lastly, nitric oxide metabolism has been implicated in LAM. Women with LAM had higher exhaled NO than healthy women, but lower than asthmatic women. Immunohistochemical studies showed diffuse NO synthase III expression in the lesional smooth muscle of LAM (29).

The treatment of LAM aims at inhibition of the presumed growth-promoting effects of estrogen on the smooth muscle cells. Progesterone is commonly used in patients without meningiomas (20). The intramuscular depot medroxiprogesterone 400-800 mg/month i.m. is preferred to the oral progesterone 10-20 mg/day. Following intramuscular injection, plasma levels are threefold higher than after oral administration, have little fluctuation and continue to rise smoothly over the first few months (1). A significant reduction in decline of both FEV_1 and DLCO was reported in premenopausal patients treated with progesterone (30). Hormonal

treatment with high doses of medroxiprogesterone acetate may also be beneficial in postmenopausal women (31) and on LAM complications, chylothorax or chylous ascites (32).

The evidence for using Tamoxifen (20 mg/day) as a single agent in LAM is weak. Tamoxifen is a partial agonist at the estrogen receptor and the newer full estrogen receptor antagonists or aromatase inhibitors which block estrogen synthesis may be more effective (33).

Oophorectomy is another alternative treament of LAM. Oophorectomy can be achieved surgically, via radiation of the ovaries and abdomen with 30 Gy (34), or chemically with gonadotrophin releasing hormone agonists. There are no reported beneficial effects of surgical oophorectomy, but the risk of surgery is obvious in condition of respiratory failure and the hormonal effects are similar. In spite of previous radical oophorectomy, there are case reports which have required lung transplantation (8).

GnRH analogs have been used alone and in conjunction with other treatments. Triptoreline (Decapeptyl) 3.75 mg/month, 20-40 months was used with improvement or stabilization of the disease (9). Similar cases were reported with another aGnRH, Goserelin (10). During the 48 months of Triptorelin and Goserelin, our patient showed a good response in the first year and a slow decline in the respiratory function with stable lung lesions thereafter.

Single or double lung transplantation offers the only hope for the cure of pulmonary LAM. The FEV_1 improves from 24% of the predicted value before transplantation to 48% six months after single lung transplantation. Patients survival is similar to the rates seen after lung transplantation to other disorders such as pulmonary fibrosis and emphysema. The main causes of death are acute lung injury (early), infections and bronchiolitis obliterans (later). There is a relatively high frequency of disease-related complications: extensive pleural adhesions leading to moderate to severe intraoperative hemorrhage; spontaneous pneumothorax in the native lung; postoperative chylothorax; recurrent LAM in the donor lung (all male), suggesting that circulating factors may be important (8,35).

In conclusion, in a patient with LAM disease, aGnRH stopped the progression of respiratory failure in the first year of treatment and slowed down the decline during the next three years thereafter, as evidenced by the pulmonary function tests and stabilization of the cysts. Medical treatment with aGnRH seems to be an effective, well tolerated treatment of pulmonary LAM, that preserves in better conditions the quality of life.

Acknowledgments

We express our thanks for the suggestions to Ioana Preston, MD, Assistant Professor Tufts University School of Medicine, Boston, USA, and for technical help to Corin Badiu, MD, Associate Professor of endocrinology and Lidia Pop, MD.

References

1. Johnson S. Rare diseases. 1. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. Thorax 1999;54:254-264.
2. Ferrans VJ, Yu ZX, Nelson WK et al. Lymphangioleiomyomatosis (LAM): a review of clinical and morphological features. J Nippon Med Sch. 2000;67:311-329.
3. Rosai J ed. Rosai and Ackerman's Surgical Pathology. 9th ed. Mosby. 2004.
4. Urban T, Lazor R, Lacronique J et al. Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore) 1999;78:321-337.
5. Denoo X, Hermans G, Degives R et al. Successful treatment of pulmonary lymphangioleiomyomatosis with progestins: a case report. Chest 1999;115:276-279.
6. Klein M, Krieger O, Ruckser R et al**.** Treatment of lymphangioleiomyomatosis by ovariectomy, interferon alpha 2b and tamoxifen–a case report. Arch Gynecol Obstet. 1992;252:99-102.
7. Laverdiere C, David M, Dubois J et al. Improvement of disseminated lymphangiomatosis with recombinant interferon therapy. Pediatr Pulmonol. 2000;29:321-324.
8. Boehler A, Speich R, Russi EW et al. Lung transplantation for lymphangioleiomyomatosis. N Engl J Med. 1996;335:1275-1280.
9. Desurmont S, Bauters C, Copin MC et al. [Treatment of pulmonary lymphangioleiomyomatosis using a GnRH agonist]. Rev Mal Respir. 1996;13:300-304.
10. Rossi GA, Balbi B, Oddera S et al. Response to treatment with an analog of the luteinizing-hormone-releasing hormone in a patient with pulmonary lymphangioleiomyomatosis. Am Rev Respir Dis. 1991;143:174-176.
11. Clementsen PS, Folke K, and Faurschou P. [Lymphangioleiomyomatosis]. Ugeskr Laeger. 1995;157:298-299.
12. Chu SC, Horiba K, Usuki J et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999;115:1041-1052.
13. Bonetti F, Chiodera PL, Pea M et al. Transbronchial biopsy in lymphangiomyomatosis of the lung. HMB45 for diagnosis. Am J Surg Pathol. 1993;17:1092-1102.
14. Logginidou H, Ao X, Russo I et al**.** Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. Chest 2000;117:25-30.
15. Matsui K, Takeda K, Yu ZX et al. Downregulation of estrogen and progesterone receptors in the abnormal smooth muscle cells in pulmonary lymphangioleiomyomatosis following therapy. An immunohistochemical study. Am J Respir Crit Care Med. 2000;161:1002-1009.
16. Baldi S, Papotti M, Valente ML et al. Pulmonary lymphangioleiomyomatosis in postmenopausal women: report of two cases and review of the literature. Eur Respir J. 1994;7:1013-1016.
17. Hu H, Wang W, and Wang X. [Clinical analysis of pulmonary lymphangioleiomyomatosis]. Zhonghua Yi Xue Za Zhi. 2001;81:1256-1260.
18. Kaptanoglu M, Hatipoglu A, Kutluay L et al. Bilateral chylothorax caused by pleuropulmonary lymphangiomyomatosis: a challenging problem in thoracic surgery. Scand Cardiovasc J. 2001;35:151-154.

19. Usuki J, Horiba K, Chu SC et al. Immunohistochemical analysis of proteins of the Bcl-2 family in pulmonary lymphangioleiomyomatosis: association of Bcl-2 expression with hormone receptor status. Arch Pathol Lab Med. 1998;122:895-902.
20. Moss J, DeCastro R, Patronas NJ et al. Meningiomas in lymphangioleiomyomatosis. JAMA 2001;286:1879-1881.
21. Carsillo T, Astrinidis A, and Henske EP**.** Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. Proc Natl Acad Sci U S A. 2000;97:6085-6090.
22. Sato T, Seyama K, Fujii H et al. Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangioleiomyomatosis. J Hum Genet. 2002;47:20-28.
23. Yu J, Astrinidis A, and Henske EP. Chromosome 16 loss of heterozygosity in tuberous sclerosis and sporadic lymphangiomyomatosis. Am J Respir Crit Care Med. 2001;164:1537-1540.
24. Inoue Y, King TE, Jr., Barker E et al**.** Basic fibroblast growth factor and its receptors in idiopathic pulmonary fibrosis and lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2002;166:765-773.
25. Valencia JC, Matsui K, Bondy C et al. Distribution and mRNA expression of insulin-like growth factor system in pulmonary lymphangioleiomyomatosis. J Investig Med. 2001;49:421-433.
26. Evans SE, Colby TV, Ryu JH et al. Transforming growth factor-beta 1 and extracellular matrix-associated fibronectin expression in pulmonary lymphangioleiomyomatosis. Chest 2004;125:1063-1070.
27. Matsui K, Takeda K, Yu ZX et al. Role for activation of matrix metalloproteinases in the pathogenesis of pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med. 2000;124:267-275.
28. Hayashi T, Fleming MV, Stetler-Stevenson WG et al. Immunohistochemical study of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in pulmonary lymphangioleiomyomatosis (LAM). Hum Pathol. 1997;28:1071-1078.
29. Dweik RA, Laskowski D, Ozkan M et al**.** High levels of exhaled nitric oxide (NO) and NO synthase III expression in lesional smooth muscle in lymphangioleiomyomatosis. Am J Respir Cell Mol Biol. 2001;24:414-418.
30. Johnson SR and Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. Am J Respir Crit Care Med. 1999;160:628-633.
31. Zanella A, Toppan P, Nitti D et al. Pulmonary lymphangioleiomyomatosis: a case report in postmenopausal woman treated with pleurodesis and progesterone (medroxyprogesterone acetate). Tumori 1996;82:96-98.
32. Kitaichi M and Izumi T. Lymphangioleiomyomatosis. Curr Opin Pulm Med. 1995;1:417-424.
33. Svendsen TL, Viskum K, Hansborg N et al. Pulmonary lymphangioleiomyomatosis: a case of progesterone receptor positive lymphangioleiomyomatosis treated with medroxyprogesterone, oophorectomy and tamoxifen. Br J Dis Chest 1984;78:264-271.
34. Zahner J, Borchard F, Fischer H et al. [Successful therapy of a postpartum lymphangioleiomyomatosis. Case report and literature review]. Schweiz Med Wochenschr. 1994;124:1626-1632.
35. Pechet TT, Meyers BF, Guthrie TJ et al. Lung transplantation for lymphangioleiomyomatosis. J Heart Lung Transplant 2004;23:301-308.