Eur Respir J, 1994, 7, 1013–1016
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European Respiratory Journal
ISSN 0903 - 1936

CASE REPORT

Pulmonary lymphangioleiomyomatosis in postmenopausal women: report of two cases and review of the literature

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Pulmonary lymphangioleiomyomatosis in postmenopausal women: report of two cases and review of the literature. S. Baldi, M. Papotti, M.L. Valente, M. Rapellino, E. Scappaticci, B. Corrin. ©ERS Journals Ltd 1994.

ABSTRACT: Pulmonary lymphangioleiomyomatosis, a disease largely confined to women in their reproductive years, is reported in two postmenopausal patients. Nine similar cases in the literature are reviewed. In older women, the disease appears to be similar to that described in younger women, with the possible exception that the clinical course may be longer and more benign after the menopause.

It would appear that hormonal factors play a role in the development of the disease both before and after the menopause, and that hormonal treatment may be beneficial in the older women.

Eur Respir Rev., 1994, 7, 1013–1016.

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Keywords: Lymphangioleiomyomatosis, pathology.

Received: July 12 1993
Accepted after revision December 5 1993

Pulmonary lymphangioleiomyomatosis (PLAM) is an uncommon disorder of unknown cause characterized by a proliferation of immature smooth muscle, which results in well-defined, thin-walled cystic lesions [1]. The chief symptom is progressive dyspnoea. Chylous effusions, pneumothoraces and haemoptyses are characteristic complications. Radiographically, the lungs initially show a reticular pattern, but unlike fibrotic lungs they appear enlarged and, ultimately, show widespread honeycombing [2]. Computed tomography (CT) scan typically displays thin-walled cystic air spaces surrounded by relatively normal lung parenchyma [3]. Functionally, obstructive or restrictive changes, with impairment of pulmonary carbon monoxide diffusion capacity (DLCO) may be present [2, 4].

PLAM may be part of a more inclusive syndrome, in which muscle associated with extrapulmonary lymphatics and lymph nodes is excessive. When present, pulmonary involvement is a prominent feature of the lymphangioleiomyomatosis syndrome, but instances exist where the lungs are spared and the lesions are confined to extrapulmonary sites, notably thoracoabdominal lymph nodes and lymphatics [5]. Such patients are reputed to live longer than those on whom the lungs are affected [5].

Whatever the extent of the disease, it is notable that the patient is always female, and generally in the reproductive years. Because of this, a hormonal basis is suggested. Occasionally reports of the disease affecting postmenopausal women [6–13] are, therefore, of interest. We describe two further postmenopausal women with PLAM.

Case report No. 1

A 59 year old woman, who had no children, and was 8 yrs postmenopausal, was admitted to hospital in February 1990 with an 8 month history of dyspnoea on exertion. She had never smoked or taken oral contraceptives, and denied having had any previous pulmonary symptoms. Physical examination was unremarkable. Chest radiographs showed an increase in interstitial marking, more evident at the lung bases. High resolution CT scan showed diffuse thin-walled cystic air spaces throughout both lungs. A chest radiograph 5 yrs earlier had been normal.

Pulmonary function tests displayed near normal static and dynamic volumes (vital capacity (VC) 3.14 *l* (92% pred); forced expiratory volume in one second (FEV_1) 2.29 *l* (79% pred); total lung capacity (TLC) 5.09 *l* (90% pred); residual volume (RV) 2.10 *l* (97% pred). DLCO was considerably reduced (3.3 $mmol \cdot min^{-1} \cdot kPa^{-1}$; 38% pred), as was arterial oxygen tension (Pao_2 55 mmHg (7.3 kPa)); arterial carbon dioxide tension ($Paco_2$) was normal (38 mmHg (5.1 kPa)). Bronchoalveolar lavage cytology showed a normal pattern, apart from 20% red blood cells; the macrophages contained no haemosiderin. Transbronchial biopsy was inconclusive. Examination for bacteria, including mycobacteria, fungi and viruses was negative both in tissue specimens and lavage fluid. Open lung biopsy showed PLAM (fig. 1). Follical stimulating hormone (FSH) prolactin, leutinizing hormone (LH) and progesterone serum levels were consistent with the post menopausal status; the oestradiol level was slightly above the normal postmenopausal range.

Prednisone (30 $mg \cdot day^{-1}$) and domicilary oxygen therapy were initiated and the patient's condition was reviewed periodically. Over the ensuing 12 months, pulmonary function tests remained unchanged and dyspnoea did not improve. In June 1991, anti-oestrogen therapy with tamoxifen (10 mg *b.i.d.*) was started, and the prednisone reduced to 10 $mg \cdot day^{-1}$. Subsequently, pulmonary function, arterial oxygen tension and walking distance slightly

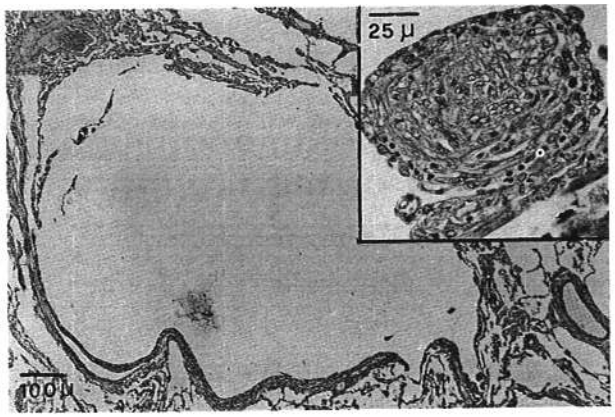


Fig. 1. – Case No. 1: cyst-like spaces are lined by thickened alveolar walls. Focal proliferations of smooth muscle cells are present (inset), partially protruding into a cystic cavity. (Haematoxylin and eosin stain; magnification 100×, scale bar 100 µm; inset 400×, scale bar 25 µm).

improved (figs. 2–4), and in March 1992, long-term oxygen therapy and prednisone could be withdrawn. In August 1992, VC (3.23 *l*; 94% pred), DLCO (3.9 mmol·min^{-1}·kPa^{-1}; 49% pred) and Pa_{O_2} (67 mmHg (8.9 kPa)) were still satisfactory and the patients was able to walk 340 m in 6 min, compared with 290 m in 6 min before treatment.

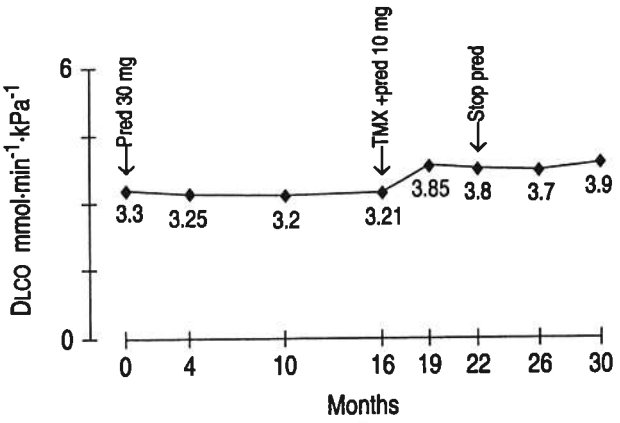


Fig. 2. – Case No. 1: diffusing capacity of the lungs for carbon monoxide (DLCO) during the follow-up period. Arrows represent onset/cessation of treatment. Pred: prednisone, TMX: tamoxifen.

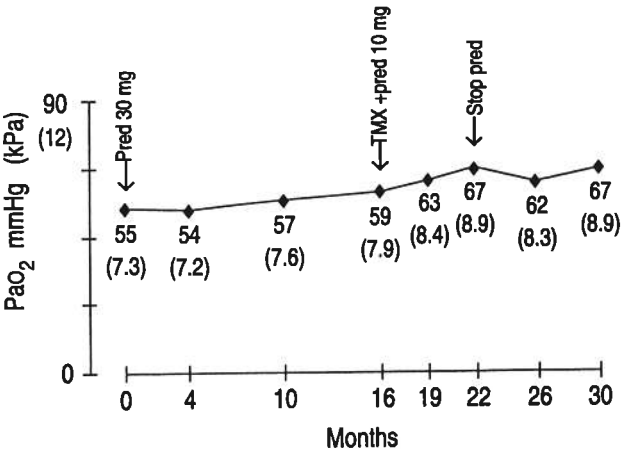


Fig. 3. – Case No. 1: arterial oxygen tension (Pa_{O_2}) during the follow-up period. Arrows represent onset/cessation of treatment. Pred: prednisone, TMX: tamoxifen.

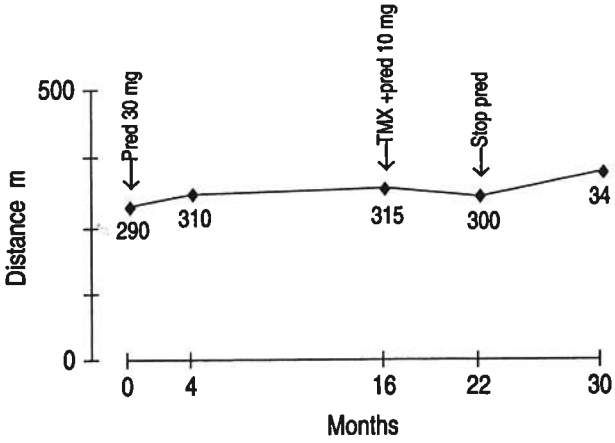


Fig. 4. – Case No. 1: 6 min walk test during the follow-up period. Arrows represent onset/cessation of treatment. Pred: prednisone, TMX: tamoxifen.

Case report No. 2

A 62 year old woman, with two children, complained of dyspnoea and right chest pain. Since the menopause, which had occurred 10 yrs previously she had been taking hormone replacement therapy to prevent osteoporosis. She had never smoked and had not previously had pulmonary symptoms. Her medical history included resection of a uterine myoma at the age of 32 yrs, and a cervical polypectomy at the age of 59 yrs. Physical examination was consistent with a right pleural effusion. This was confirmed by chest radiographs and CT scan, neither of which showed any significant parenchymal involvement. No previous radiographs were available. Chylous fluid was obtained by thoracocentesis. Because of repeated recurrences of the pleural effusion, a tetracycline pleurodesis was performed 3 months after the onset of symptoms. At the same time, an open lung biopsy was obtained. The histological appearances were those of PLAM (fig. 5).

The patient was treated with the anti-oestrogen agent Farlutal, 1 g daily for 1 month, followed by 1 g every other day. There was no recurrence of the pleural

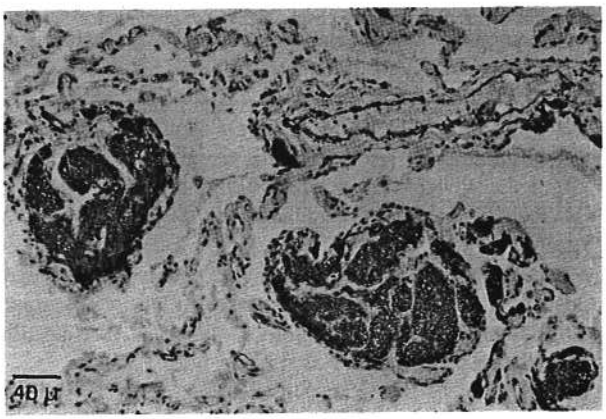


Fig. 5. – Case No. 2: immunostaining for smooth muscle actin reveals bundles of proliferating smooth muscle in thickened alveolar septa. (Immunoperoxidase - avidin biotin complex (ABC) method; nuclei counterstained with haemalum; magnification 250×, scale bar 40 µm).

effusion, but 6 months later an asymptomatic pericardial effusion was radiographically detected and found to be chylous. After a few days drainage, Farlutal was instilled into the pericardial space. Twelve months after thoracotomy, the patient remains substantially asymptomatic apart from exercise dyspnoea.

In both cases, oestrogen and progesterone receptors were studied by immunohistochemistry using specific antibodies, and also by *in situ* hybridization with an oligonucleotide probe specific for oestrogen receptor messenger ribonucleic acid (mRNA). All of these tests were negative, but they were performed on formalin-fixed paraffin-embedded tissues, which in general are not the most suitable material for such determinations.

Discussion

The aetiology and pathogenesis of PLAM are obscure. The pathological features in the lungs and lymph nodes are identical to those seen in tuberous sclerosis, but whereas the latter is an autosomally dominant familial disorder of infancy or early childhood that affects males and females equally, PLAM is unusual in infancy, typically affects the middle-aged, and is exclusively confined to women [1, 14]

A relationship with hormonal secretion is supported by the following considerations: the disease is largely confined to women in the reproductive years [1]; exacerbations have been documented during pregnancy [15, 16], the menses [17], with use of oral contraceptives [18], and after administration of exogenous oestrogens [19]; oophorectomy, progesterone and tamoxifen seem to have a beneficial effect on the disease [18, 20–23] and receptors for oestrogen and progesterone have been identified in lung biopsies from some patients [16, 19, 24, 25]. We failed to find hormonal receptors in lung tissue in either of our cases, but the tissue preservation was not ideal.

Hormonal manipulation of some type or other is generally employed for these patients [15, 18, 20, 22, 23), but the ideal form of treatment has yet to be identified. Our first case seemed to demonstrate some response to tamoxifen: functional respiratory parameters, such as DLCO, arterial blood oxygen tension and the 6 min walk test were slightly improved 14 months after this therapy (figs 2–4). Our second case also showed some response to hormonal therapy (Farlutal, 10 mg·day^{-1}), although the condition here appeared to be more aggressive. The slightly raised oestradiol blood levels may be responsible for the late onset of the disease in patient No. 1, and the 10 yr history of oestrogen replacement therapy may explain the post menopausal occurrence of the disease in patient No. 2. Hormonal status would, therefore, seem to play a role in the outcome of this condition in older as well as in premenopausal patients, and hormonal treatment would appear to be justified.

Nine cases of PLAM affecting postmenopausal patients were found in the literature, at least two of whom were receiving exogenous oestrogens as replacement therapy (table 1) [6–13]. These older women resemble younger patients with PLAM in that chylous effusions and pneumothoraces are found in both, but it is suggested that the disease runs a slower course after the menopause [5, 12]. Whilst it is tempting to view the menopause as exerting a beneficial effect on the progression of PLAM, this may be premature in view of the variable course seen in younger patients. The prognosis has generally been regarded as poor in such patients [1, 5], but this has recently been disputed [13]. A review of cases reported up to 1973 found that death from respiratory insufficiency usually occurred within 4 yrs of the onset of lung disease [5], and in the large series of CORRIN *et al.* [1] most patients died from respiratory failure within 10 yrs of diagnosis. However, in more recent series [13], 78% of the patients were still alive 8.5 yrs after onset.

Table 1. – Reported cases of lymphangioleiomyomatosis in elderly women

Ref.	Year	Age* yrs	Follow-up yrs
[6] [9]	1955/1966	42**	12
[7]	1963	70	>1
[8]	1964	69	>1.5
[9]	1966	61	>8
[10]	1973	65	5
[11]	1980	70	15
[12]	1985	72	12
[13]	1990	49	NS
[13]	1990	61	NS
Case No. 1	1994	59	3.5
Case No. 2	1994	62	1.5

*: age at presentation; **: oophorectomy 4 yrs earlier. NS: follow-up period not specified.

It would be of interest to know whether, in these older women, PLAM truly commenced after the menopause, or began before and only became symptomatic later. The literature is unhelpful on this point, but our first patient had a normal chest radiograph 3 yrs after the menopause and 5 yrs before the onset of symptoms, suggesting that the disease may indeed start after the menopause.

In summary, PLAM in older women appears to be similar to that described in younger women, with the possible exception that the clinical course may be more prolonged. Our observations suggest that, as in younger women, hormonal factors may play a role in the development of the disease after the menopause, and that hormonal treatment may be beneficial in these older women.

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