Shrinking Lung Syndrome: A Pulmonary Manifestation of Systemic Lupus Erythematosus
Diurnal Findings and Nocturnal Events

Elsa Naval, MD[*]
Christian Domingo, MD, FCCP[*]
Jordi Gratacós, MD[†]
Montserrat Bosque, MD[‡]
Manel Luján, MD[*]
Albert Marín, MD[*]

[*]*S. Pneumologia,* [†]*S. de Reumatologia,* [‡]*S. de Pediatria, Corporació Parc Taulí, Institut Universitari Parc Tauli-FPT Universitat Autonoma de Bellaterra, Barcelona, Spain*

KEY WORDS: shrinking lung syndrome, systemic lupus erythematosus, nocturnal events

ABSTRACT

Objectives: To describe the diurnal and nocturnal findings of 4 adults (3 women) and one child with systemic lupus erythematosus and shrinking lung syndrome.

Design: A prospective observational study.

Setting: A 750 teaching-bed-hospital with a reference population of 350,000 people.

Interventions: Clinical history, blood analysis, imaging test, pulmonary function tests, maximal inspiratory and expiratory pressures, arterial blood gases, and sleep studies.

Measurements and Results: Patients were referred to the pneumology service for dyspnea. Two adults who showed severe arthritis in their hands had been previously diagnosed of rheumatoid arthritis. No visceral involvement was found other than lung disease. Biological results showed normal muscle enzyme values. Chest x-ray and CT scan revealed small lungs without parenchymal or pleural involvement. Pulmonary function tests indicated the presence of restrictive disease with normal carbon monoxide transfer. The alveolar-arterial gradient was within normal limits. Maximal inspiratory pressure was slightly low and maximal expiratory pressure was within normal limits. Sleep studies ruled out nocturnal hypoventilation and mild sleep-apnea syndrome was observed in 2 previous heavy snorers. During the follow-up period (10 to 46 months) none of the patients deteriorated.

Conclusions: Shrinking lung syndrome affects a small proportion of patients with lupus and may also occur in children. It should be suspected in patients

with lupus who present exertional dyspnea without apparent cause. The condition does not seem to affect sleep physiology, the clinical features tend towards stabilization regardless of the treatment prescribed. The origin of the syndrome seems to be a self-limited myositis of the diaphragm.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory disease of unknown origin. It occurs most frequently in women at fertile ages, though it has also been reported in males, children, and the elderly. Any organ or system may be affected: the skin, musculoskeletal system, kidney, nervous system, digestive tract, cardiocirculatory system or lungs.[1]

Fifty percent of SLE patients present pleuropulmonary manifestations. Pleuritis is the most frequent disorder, occurring in approximately 45% of cases. Other forms of pulmonary impairment are lupus pneumonitis (acute or chronic), pulmonary hemorrhage, obliterating bronchiolitis with organized pneumonia, pulmonary vascular disease in the form of pulmonary thromboembolism and plexogenic pulmonary hypertension, interstitial pulmonary impairment (more frequent in other connective tissue disorders such as rheumatoid arthritis or systemic sclerosis), and finally impairment of the respiratory muscles, especially of the diaphragm, which may lead to a respiratory disorder without visceral lung involvement. This condition is known as shrinking lung syndrome (SLS).[1] To date, the experience on the evolution of these patients is controversial and there is no information about nocturnal respiratory behavior.

The aim of this study is to describe the diurnal and nocturnal behavior of 4 adults and one child with SLS and SLE.

MATERIAL AND METHODS

Population

Four adult patients (3 women and 1 man), aged between 51 and 76, referred to the Pneumology Service for exertional dyspnea and one pediatric patient referred to the Pediatric Service at our hospital for fever and pleural effusion.

Methodology

The following examinations were performed in all patients during their first visit to the Pneumology Service: clinical history, with special attention to length of evolution of the SLE and its form of presentation; physical examination; blood analysis including erythrocyte sedimentation rate, hemogram, general blood biochemistry (antinuclear antibodies, muscle enzymes, C-reactive protein, Rheumatoid factor); imaging tests (x-rays of chest, hands and feet and chest computed tomography scan [CT scan]) and pulmonary function tests (PFTs). Pulmonary function tests were carried out in our pulmonary function laboratory, which is equipped with automated PFT equipment (MedGraphics system 1070 Series 2E/1085) for pulmonary volume, diffusion, spirometry testing and an automated pletysmographic cabin for pulmonary volume and airway resistance testing**.** Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were also determined using a manometer (Sibelmed manometer 163, Sibel S.A., Barcelona, Spain) Arterial blood gases were measured with a radial puncture using local anesthesia, while the patient was breathing room air (Radiometer ABL 500).

In the adults, respiratory polysomnographies were performed with a Nocturnal Simplified Polygraph (Sibel home 300, Sibel S.A., Barcelona, Spain), which records nasal/oral airflow (nasal cannula and thermistor), chest wall impedance, oxygen saturation, car-

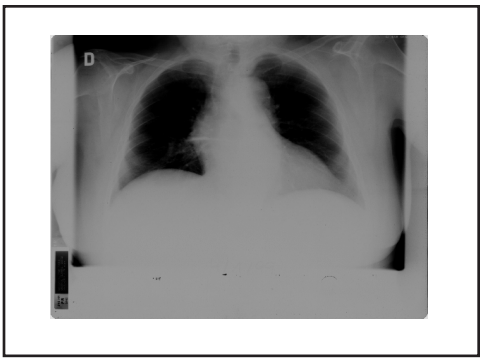

Figure 1. Chest x-ray of patient 1. Observe the decreased number of intercostal spaces as well as the absence of pleural and parenchymal lung disease.

diac frequency, snoring, and body position.[2] For the adults, the studies were performed in the sleep laboratory of our hospital. In the pediatric patient, a nocturnal domiciliary pulse-oximetry (Pulsox 3-Minolta) was performed. Mediterranean population reference values were used.[3] For the pediatric patient, the reference values of the Spanish Society of Lung Disease (SEPAR)[4] and Polgar values were used.[5] For MIP and MEP, Wilson's predicted values were used.[6] During follow-up all the complementary examinations were repeated. Patients were controlled on an outpatient basis at our hospital's pneumology and rheumatology services.

RESULTS

In the past fourteen years, 126 cases of SLE have been diagnosed at our hospital. Only 5 cases of SLS have been detected: 4 adults and one child (age range, 10 to 76).

Clinical History

All patients met the American Rheumatism Association (ARA) criteria for SLE. Two cases presented striking articular impairment with high degree of deformation and little erosion (Figure 1); they were classified as an overlap syndrome with SLE and rheumatoid arthritis (also called "Rupus"). In 4 patients, SLS presented as dyspnea on effort, 10, 12, and 20 years after SLE diagnosis. In one of the cases, a patient with a prior diagnosis of seronegative RA, SLE, presented as SLS.

Dyspnea was the predominant respiratory symptom and the reason for consultation. The dyspnea did not progress during follow-up (in one patient the dyspnea was difficult to evaluate due to the extent of her articular limitations).

Biology

In addition to the alterations typical of SLE, all patients had normal antinuclear antibody titers, rheumatoid factor was negative, and normal levels of muscle enzymes (CK and aldolases) at the time of diagnosis were obtained. During follow-up no increase in CK or aldolase values was observed. Renal function remained unimpaired in all cases.

Pulmonary Function

Patients presented a restrictive ventilatory alteration without alteration in carbon monoxide transfer (normal KCO), stable MEP, but low MIP. Arterial blood gases showed a normal or slightly increased alveolar-arterial oxygen gradient.

Individual values are shown in Table 1. The mean values of the PFTs in the adults showed a restrictive ventilatory alteration: FEV1/FVC: 74 ± 2%; FEV1: 1482 mL ± 262 mL (64 ± 8%); FVC: 2010 mL ± 434 mL (63 ± 4%); TLC: 3665 mL ± 1143 mL (68 ± 6%); RV: 1417 ± 516 mL (71 ± 9%). CO transfer study showed: DLCO: 60 ± 10 %; DLCO mL/min/mmHg: 13.3 ± 1.6 ; KCO (DLCO/AV): 91 ± 13 %; KCO (DLCO/AV)mL/min/mmHg: 4.7 ± 0.8; MEP %: 95.5 ± 21.7; MIP %: 82.25 ± 10%. The values of the pediatric patient are the following: FEV1/FVC: 97%; FEV1: 1340 mL (56%); FVC: 1380 mL (71%); MIP 74 cmH2O; MEP: 81 cmH2O.

Table 1. Pulmonary Function Test*

		Patient 1	Patient 2	Patient 3	Patient 4
FEV_1/FVC	(%)	77	74	71	74
FEV_1	(%)	76	64	60	57
	(mL)	1290	1520	1840	1280
FVC	(%)	68	66	61	58
	(mL)	1670	2050	2610	1710
TLC	(%)	65	72	75	62
	(mL)	2920	3400	5350	2990
VC	(%)	61	75	70	61
	(mL)	1580	2400	3180	1890
RV	(%)	71	62	85	69
	(mL)	1340	1060	2170	1100
DLCO	(%)	73	64	51	52
DLCO (mL/min/mmHg)		14.10	14.67	13.38	11.10
KCO	(%)	108	82	78	98
KCO (mL/min/mmHg)		5.56	4.64	3.68	5.28
MIP	(%)	97 *	75	77	80
MEP	(%)	128	82	86	86

*Data given in a percentage form (%) are percent of predicted normal values. FEV_1 indicates forced expiratory volume in the first second; FVC, forced vital capacity; TLC, total lung capacity; VC, vital capacity; RV, residual volume; DLCO, diffusion lung capacity; KCO, DLCO/VA (alveolar volume), MIP, maximal inspiratory pressure; and MEP, maximal expiratory pressure. *During the following of MIP value decreased 48%.

Respiratory Polysomnography

Two adults, who had a history of snoring before the beginning of the disease showed a mild sleep apnea syndrome (SAS) but none referred diurnal hypersomnia. In the other 2 cases, respiratory polysomnography was completely normal. In the pediatric patient, the nocturnal pulse-oximetry was normal (Mean Sp02: 96.8%; Time spent Sp02<90%: 0,0%; 4% average dips/hour: 0.5). The sleep studies also ruled out episodes of hypoventilation (see Table 2). The polygraphic studies were repeated after a year and no significant changes were observed.

Imaging Results

Chest x-ray in this condition shows a characteristic elevation of the diaphragm, with reduction of the number of intercostal spaces (between 5 and 7) and, as a result, a reduction in lung size. Chest x-ray did not reveal interstitial infiltrates but in 2 patients there was bibasilar atelectasis associated with the elevated diaphragm. CT scan confirmed the absence of any interstitial disease.

Treatment

At the time of diagnosis the patients were receiving treatment with oral corticoids (dose 4 to 20 mg/day). One patient was also administered delayed theophylline at 10 mg/Kg/weight at the onset of symptoms without any clinical improvement.

Follow-up

Length of follow-up varied between 18 and 46 months. None of the subjects presented progression of dyspnea, analytical changes in the immunological study, radiological images, or in the nocturnal studies. The only change observed in the respiratory function study was a reduction of the MIP in one case, at 3 months and 2 years after diagnosis of the SLS.

Table 2. Polysomnograhic Studies*

	Patient 1	Patient 2	Patient 3	Patient 4
BMI (Kg/m2)	29	25	26	27
AHÍ	2	1	14	24
Initial SpO2 (%)	96	97	97	98
Mean SpO2 (%)	94	96	96	97
Sp02< 90 (%)	0	0	0	0

*BMI indicates body mass index; AHI, apnea/hypopnea index; and Sp02, oxygen saturation measured by the pulse-oximeter.

DISCUSSION

The connective tissue diseases cause multisystemic alterations, and their impact on the lung is particularly important. The type of pulmonary impairment in SLE varies widely. Possibly the least common manifestation is the SLS, which in fact is exclusive to SLE.[1] The clinical presentation of SLS tends to be subacute dyspnea, without any other accompanying respiratory manifestations. Chest x-ray reveals reduced lung volumes (with at most 7 intercostal spaces) without evidence of occupation of the pulmonary fields or pleural impairment. Spirometry indicates a restrictive ventilatory defect that is confirmed by reduced lung volumes. Diffusing capacity is not impaired. The absence of interstitial pulmonary impairment is confirmed by the observation of normal pulmonary parenchyma on chest CT scan. The biological anomalies typical of SLE are seen; interestingly, muscle enzymes are normal.

All patients met the ARA criteria for SLE. Case 4, a woman in whom seronegative RA had been diagnosed several years before, was referred to our service for dyspnea. Clinically, she had articular deformation in both wrists, though hand x-rays ruled out the presence of the erosive changes characteristic of RA. The dyspnea was attributed to SLS and the previous diagnosis of RA was rectified.

Four of our cases were referred for dyspnea, the most frequent symptom of SLS.[1] In common with other reports, the results of radiological, biological, and functional studies in our series showed reductions in FVC and MIP in the absence of pulmonary parenchymal pathology. These findings indicate an impairment of the respiratory muscles. Though it is true that the MIP and MEP measurements reflect alterations of the respiratory muscles as a whole and do not distinguish between muscle groups, the diaphragm is the primary respiratory muscle. The elevation of both hemidiaphragms and the compression of the lungs (which on occasion produces bibasilar laminar atelectasis, as in 2 of our cases) also confirms the involvement of the diaphragm and might be responsible for the slightly increased alveolar-arterial oxygen gradient and slightly decreased KCO occasionally found due V/Q mismatch.

Unlike previous reports of SLS, we studied the respiratory behavior of our patients during sleep. In 2 cases, a mild SAS was detected although the absence of diurnal hypersomnia when the respiratory polysomnography was performed and the fact that patients had a history of snoring before the diagnosis of SLS made us think that their sleep physiologic status did not change before and after the SL. So we considered unlikely the possibility that the SLS was the trigger of a SAS**.** In the remaining 2 cases, we did not observe any phenomena suggestive or compatible with SAS. In the pediatric patient, the absence of sugges-

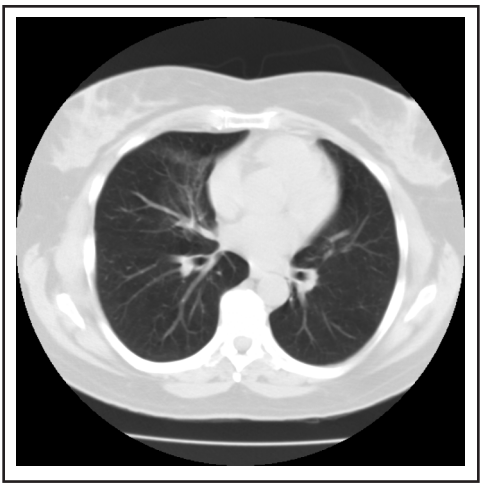

Figure 2. The CT scan, of patient number 3, rules out the presence of interstitial disease.

tive clinical data of SAS and the absence of typical oxygen desaturations[7] during sleep also ruled out the diagnosis of SAS. This point is important, as it rules out any alteration of the pharyngeal muscles, which might have favored airway obstruction during sleep. We conclude that the clinical effect of the muscle impairment seems to be restricted to the diaphragm and is not particularly severe at night given that it does not cause hypoventilation.

The clinical evolution of SLS shows a clear tendency towards stabilization. No central changes were observed during follow-up. The existing treatment of the patients was maintained (oral corticosteroids in most cases) and in one case theophylline was added without appearing to modify the course of the illness. The experiences reported by different authors vary, but our follow-up period is among the longest in the literature and we believe that most of these patients stabilize once diagnosis is made.

SLS has been reported almost exclusively in adults, possibly because the incidence of SLE is far higher in adults than in children. Our 10-year old patient developed a respiratory alteration compatible with SLS 3 months after improving his clinical situation and disappearance of the pleural effusion. The patient was treated with corticosteroids at an initial dose of 0.5 mg/Kg weight/day; the dose was progressively reduced over a 6-month period, at the end of which the patient was asymptomatic. After eighteen months the patient continued to present a functional respiratory alteration compatible with a pulmonary restriction (Forced Spìrometry: FVC: 2.20 L- 56%; FEV1. 2.0L- 62%; FEV1/FVC: 91%). It is well known that functional evaluation in children presents the added problem that pulmonary development and its assessment via a functional study depends on a range of aspects, among them the prediction equations used. We first used the SEPAR equations[4] and then corroborated the results with the Polgar equations[5]; we did not find notable changes in the clinical interpretation of the spirometry results. The patient's absolute values for FVC and FEV1 improved slightly (820 mL and 660 mL respectively), but this was due mainly to the lung growth that accompanies development. The subject's height increased from 143 cm to 156 during the follow-up period. The spirometry, MIP, and MEP values, obtained at the end of follow-up (after 18 months and obviously after the end of corticoid treatment), were still compatible with SLS. We conclude therefore that the patient presented SLS (the history of a pleural effusion with total resolution as

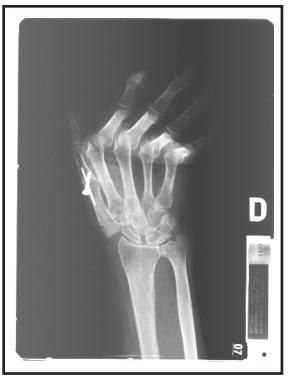

Figure 3. The x-ray of the right hand of patient 3 shows an important deformation of her metacarpophalangic joints with lack of bone erosion, which is typical in rheumatoid arthritis.

shown on the chest CT scan does not account for the presence of a pulmonary restriction) associated with SLE.

Interestingly, SLS presents in patients with SLE with little or no visceral impairment. SLS is then often the condition that leads patients to seek medical attention. Furthermore, SLS has only been reported in SLE patients, and has not been observed in other connective tissue diseases; so SLS seems to occur in particularly benign forms of SLE, in which there is little visceral involvement. In addition, a clinical picture suggestive of SLS should alert the clinician to the possibility of SLE because the condition has only been described in the context of lupus.

The etiopathogenesis of the process is controversial. Gibson et al[8] and Martens et al[9] reported a reduction in transdiaphragmatic pressure (measured by esophageal and gastric balloon), suggesting diaphragm weakness. These authors attributed the muscle weakness to the SLE. At one point, it was suggested that corticosteroids treatment might be the cause of the myopathy, but this possibility was ruled out because some patients presented SLS before the beginning of treatment. However, Laroche et al[10] reported normal transdiaphragmatic pressure (measured by the "sniff" maneuver) in some of their patients and conclude that the weakness of the respiratory muscles is not the cause of the syndrome. Moreover, these authors suggested the possibility of phrenic nerve impairment as the cause of the syndrome although the majority of studies of nerve conduction have found no phrenic nerve lesions.[8,9] Although we did not attempt to study phrenic nerve involvement, we observed, in our series, elevated diaphragms in both hemithorax and a respiratory function compatible with muscular involvement. The possibility that both phrenic nerves were affected at the same time seemed unlikely. Moreover a phrenic nerve palsy would impair respiratory function much more than observed. A polygraphic nocturnal study that ruled out the involvement (at least to a clinically relevant degree) of the pharyngeal muscles, as the cause of the nocturnal obstructive phenomena typical of SAS, was also performed**.** The impairment, therefore, appears to be restricted to the respiratory muscles, basically the diaphragm muscle. It is interesting that all our cases presented normal muscle enzyme values, but we believe that this is due to the fact that the patients presented clinical respiratory disorders after the outbreak of myositis, during which increases in CK and aldolase values would have been detected.

To conclude, we believe that SLS affects a small proportion of SLE patients but may be under diagnosed in daily clinical practice. It should be suspected in lupus patients who present exertional dyspnea without an apparent cause, with x-ray findings of pulmonary restriction and normal pulmonary parenchyma. The condition does not seem to affect sleep physiology and in our experience tends to stabilize, however, is not influenced by treatment. Therefore, it seems advisable to avoid measures that may cause iatrogenia, such as adding oral corticoids or increasing the dose. Although not definitely demonstrated, the hypothesis that this syndrome might be due to a myositis probably limited to the diaphragm muscle is attractive. Finally, physicians must keep in mind that the condition may also occur in children.

REFERENCES

1. Murin S, Wiedemann HP, Matthay RA. Pulmonary manifestations of Systemic Lupus Erythematosus. *Clinics Chest Med.* 1998;19:641-665.
2. Ballester E, Solans M, Vila X, et al. Evaluation of a portable respiratory record-

ing device for detecting apnoeas and hypopnoeas in subjects from a general population. *Eur Respir J.* 2000;16:123-127.

3. Roca J, Sanchis J, Agustí-Vidal A, et al. Spirometric reference values for a Mediterranean population. *Bull Eur Physiopathol Respir*. 1986;22:217-224.

4. Sanchís J, Casán P, Castillo J, et al. Espirometría Forzada. In:. *Recomendaciones SEPAR*. Barcelona, Spain, Doyma, ed: 1998;1-18.

5. Polgar G, Weng TR. The functional development of the respiratory system from the period of gestation to adulthood. Am Rev Respir Dis 1979;120: 625-695.

6. Wilson SH, Cooke NT, Edwards RHT, et al. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax*. 1984;39:535-538.

7. Douglas NJ, Thomas S, Jan MA. Clinical value of polisomnograhy. *Lancet.* 1992;339:347-350.

8. Gibson CJ, Edmons JP, Hughes GR. Diaphragm function and lung involvement in systemic lupus erythemtosus. *Am J Med.* 1977;63:926-932.

9. Martens J, Demedts M, Vanmeenen MT, et al. Respiratory muscle dysfunction in systemic lupus erythematosus. *Chest*. 1983;84:170-175

10. Laroche CM, Mulvey DA, Hawkins PN, et al. Diaphragm strength in the shrinking lung syndrome of systemic lupus erytematosus. *Q J Med.* 1989;71:429-439.