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Shrinking Lung Syndrome

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Take-Home Messages:

1. Shrinking lung syndrome is a rare pulmonary manifestation of systemic lupus erythematosus.
2. Natural history is not known because almost all the patients receive steroids and some also receive immunosuppressive drug
3. Although clinical and pulmonary function tests are frequent, only a minority of patients fully recover

Key words: shrinking lung syndrome, systemic lupus erythematosus, outcomes, immunosuppressive drugs, corticosteroids

Abstract

Introduction - Shrinking lung syndrome (SLS) is a rare respiratory manifestation of systemic lupus erythematosus (SLE), characterized by dyspnea, chest pain, elevated hemidiaphragm and a restrictive pattern on pulmonary function tests. Here, we report 15 new observations of SLS during SLE and provide a systematic literature review. We studied the clinical, biological, functional and morphologic characteristics, the treatments used and their efficacy.

Methods – The inclusion criteria were all patients with SLE defined by the American College of Rheumatology criteria [1], associated with a restrictive pattern on pulmonary function tests. The exclusion criteria were all differential diagnoses of restrictive patterns, including obesity and pulmonary fibrosis. The patients were recruited from local databases through chest physicians, rheumatologists and internists. The data for the literature review were extracted from the Medline database using “shrinking lung syndrome” and “lupus” as key words.

Results – All 15 new cases were women with a median age at SLS onset of 27 years old (range 17-67). All of them complained of dyspnea and all but one of chest pain. The antibodies were similar to those found in SLE, although the anti-SS-A was positive in 10 of 13 cases. Thoracic imaging showed elevated hemidiaphragm (12/15) and/or basal atelectasia (8/15). All of the patients had an isolated restrictive pattern on PFT, with a median decrease > 50% of lung volume. All of the patients were treated, using corticosteroids (11/15), immunosuppressive drugs (8/15), beta-mimetics (2/15), physiotherapy (3/15) and/or colchicine (1/15). Improvement was described in 9 of 12 patients and stability in 3 of 12. We extracted 155 cases of SLE-associated SLS from the Medline database. The clinical, biological and functional parameters were similar to our cases. Clinical improvement was described in 48 of 52 cases (94%) and PFT improvement in 36 of 47 cases. Worsening occurred in 4 cases.

Conclusion – SLS is a rare SLE manifestation. Pain and parietal inflammation seem to play important pathogenic roles. Steroids and antalgics are the most commonly used therapies with good responses. There is no proof of efficacy with immunosuppressive drugs for this entity. Rituximab can be discussed after failure of corticosteroids, as well as antalgics, theophylline and beta-mimetics.

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Introduction

Systemic lupus erythematosus (SLE) is a rare auto-immune disease principally affecting young women. It is characterized by several features, including arthritis, cutaneous and renal involvement, serositis, central nervous system disorders and hematologic abnormalities, associated with the presence of auto-antibodies targeting double-stranded DNA [2].

Respiratory involvement in SLE is common, affecting 60 to 80% of patients [3–5]. It consists mostly of pleuritis, alveolar hemorrhage, pulmonary embolism, pulmonary hypertension, acute pneumonitis, chronic interstitial lung disease, and less frequently, shrinking lung syndrome (SLS).

SLS is a rare although debilitating condition, involving up to 1% of SLE patients [6,7]. It was first described in 1965 by Hoffbrand and Beck, as a constellation of respiratory symptoms including dyspnea and pleuritic chest pain, associated with reduced lung volumes as demonstrated by elevated hemidiaphragms on chest radiography and a restrictive defect on pulmonary function tests (PFTs). SLS has been described in the spectrum of SLE, and it has been very rarely associated with other connective tissue diseases [8–12]. Differential diagnoses include restrictive respiratory defect due to pulmonary fibrosis, obesity, diaphragmatic palsy, and central nervous system disorders.

There are no definite criteria for the diagnosis of SLS, and it usually relies on the association of reduced lung volumes and restrictive defects on PFTs, together with the exclusion of other causes.

The physiopathology of SLS is not well understood, nor are its treatment response and long-term outcomes.

Here, we report 15 new patients with SLE-associated SLS, and we provide an exhaustive review of all cases of this rare association reported in the French and English literature, focusing on clinical, biological and radiological presentation, treatment response and long-term outcome.

Patients and Methods

Patient selection and follow-up

We conducted a retrospective, multicenter study to identify and describe new cases of SLE-associated SLS. Identification of cases was achieved by interviewing French internal medicine physicians, chest physicians and rheumatologists.

Data were extracted retrospectively from medical records.

Patients were included in the study if they had

1. SLE defined by the American College of Rheumatology criteria [1]; and
2. A restrictive defect on PFT with total lung capacity (TLC) < 80% or forced vital capacity (FVC) < 80%.

They were excluded if there was an alternative cause of a restrictive pattern on PFT, including pulmonary fibrosis or obesity with body mass index (BMI) > 40 kg/m².

Demographic, clinical, biological and radiographic data were collected. Functional data, including FVC, TLC, forced expiratory volume in 1 second (FEV1), carbon monoxide diffusing capacity (DLCO) and carbon monoxide transfer coefficient (KCO) were analyzed.

All treatments received were noted, as well as the evolution of symptoms and PFT and imaging data.

Literature review

We searched through the National Library of Medicine's MEDLINE database for relevant literature using the key words shrinking lung syndrome. Sixty references were returned in the English, French, Portuguese (n=1) and Spanish (n=1) literature. We selected 155 patients from 58 articles published between 1965 and 2014 in the English and French literature.

Only patients with definite SLE were finally included in the study.

The demographic and clinical characteristics, diagnostic modalities, and biological and functional results were collected, as well as the treatments received and outcomes.

Results

Reported cases

Patient characteristics

The clinical, biological and radiological findings of the new cases are reported in Table 1 and are summarized in Table 2.

The patients were 15 women and no men, with a median age of 27 years old at the time of SLS diagnosis (range 17 to 67). No SLS was diagnosed before SLE. In 3 cases, SLS was diagnosed at the same time than SLE, and in 12 cases, it was diagnosed after SLE diagnosis (median delay, 36 months; range, 2-456 months).

Patients had respiratory symptoms in 15 of 15 cases (100%), including dyspnea (n = 15/15, 100%), pleuritic chest pain (n = 14/15, 93%) and coughing (n = 2/15, 13%).

Extra-thoracic manifestations of SLE included arthralgia (n=14/15, 93%), cutaneous involvement (n=7/15, 47%), alopecia (n=3/15, 20%), pericardial effusion (n=4/15, 27%), fever (n=2/11, 18%) and glomerulonephritis (n= 2/15, 13%). No patients had neurological involvement.

All of the patients had positive tests for antinuclear antibodies (ANA). Eleven of 12 patients were positive for anti-DNA antibodies (92%), 10 of 13 for anti-SSA (77%), 5 of 13 for anti-SSB (38%), 6 of 13 for anti-RNP (46%), and 2 of 13 for anti-Sm (15%).

Radiographic or CT scans were abnormal in all but one patient, and they showed reduced lung volumes with elevated hemidiaphragm in 12 of 15 patients (80%), basal atelectasis in 8 of 15 (53%) patients, pleural thickening in 4 of 15 patients (27%), and pleural effusion in 2 of 15 patients (13%).

As required in the inclusion criteria, all of the patients had restrictive patterns on PFT. The median FVC was 1.55 L (42% of theoretical measurement) (range 0.79-2.78 L [19-66%]), and the median TLC was 2.80 L (61%) (range 1.91-4.35 L [34-73%]). The median DLCO was 39% (range 23-57%), and the median KCO was 83% (range 54-120%). No patients had associated obstructive patterns.

Four patients underwent electro-neuro-myography of the diaphragm. The results were normal for these four patients.

Maximal inspiratory pressure and maximal expiratory pressure were assessed in 8 patients and showed impaired values in 5 of 8 patients (62.5%) and normal values in 3 of 8 patients (37.5%).

Four patients underwent echography studies of the diaphragm, which showed impaired movement of the diaphragm in all cases.

Treatments and outcomes

All of the patients were treated after diagnosis of SLS. Three patients were lost to follow-up so that treatment efficacy could not be assessed for them. For one patient, the treatment modalities were not detailed in the medical records.

The treatments included corticosteroids in 11 of 15 patients (73%). Six patients received more than (or equal to) 0.5 mg/kg/day of prednisone equivalent, and 5 received less than 0.5 mg/kg/day. Three patients received corticosteroids alone, but outcome was assessed only for one of them: there were clinical, imaging and PFT improvements.

Eight patients also received at least one immunosuppressive drug, including mycophenolate mofetil (MMF) (n=4), cyclophosphamide (n=2), methotrexate (n=2) and rituximab (n=2). SLS was the only indication for immunosuppressive drugs in 6 patients. One patient received cyclophosphamide and then MMF to treat a class IV glomerulonephritis. One patient received MMF to treat class III glomerulonephritis. Immunosuppressive drugs were associated with corticosteroids in all but one

patient who received methotrexate alone. They were used in 5 patients as a first-line therapy and in 3 patients as rescue therapy or as a steroid-sparing agent. Cyclophosphamide was used in one case after corticosteroid failure and was not successful. Methotrexate was used as a corticosteroid-sparing drug in one patient, who remained stable. Methotrexate was also used alone in one patient who was clinically impaired. Rituximab was used after low-dose steroids and beta-mimetics failure in one patient and was successful. Rituximab was also used to treat a class III glomerulonephritis and SLS in one patient and was successful.

Physiotherapy and antalgic drugs were used in 3 patients (associated with 1 mg/kg/day of prednisone [n=1], alone (n=1) or associated with steroids, beta-mimetics and rituximab [n=1]). All of these patients showed clinical and PFT improvements. One patient received beta-mimetics in association with corticosteroids and improved.

Colchicine was used alone without steroids in one patient, leading to mild clinical improvement of pain but not of dyspnea, as well as stability of PFT.

Clinical outcome was assessed in 12 patients, showing improvement in 9 of 12 patients (75%) and stability in 3 of 12 (25%). PFT outcome was assessed in 10 patients, with improvement in 7 of 10 patients (70%), stability in 2 of 10 (20%) and mild impairment in 1 of 10 (10%). Radiographic evolution was assessed in 5 patients and revealed improvement in 3 of 5 patients (60%) and stability in 2 of 5 (40%). The patient in whom PFT showed mild impairment was treated with methotrexate alone.

Literature review

We extracted data for 164 patients from 58 articles published between 1964 and 2014 in the English and French literature.

In 9 reported cases, SLS was associated with non-SLE disease, and these cases were further excluded from the analysis. In these cases, SLS was associated with mixed connective tissue disease in 2

patients [12], primary Sjögren's syndrome in 2 patients [8,10], undifferentiated connective tissue disease in 2 cases [9,12], rheumatoid arthritis in 2 cases [9] and systemic sclerosis in 1 case [11].

Demographic and clinical characteristics

The demographic and clinical characteristics of the literature review patients are summarized in Table 2.

Diagnosis was made by the authors on the variable association of clinical, biological, radiographic and functional signs, according to the initial description of Hoffbrand and Beck. Diagnosis of SLS was made at the time of SLE diagnosis in 9 of 95 cases (9.5%). In all of the other cases, SLS was discovered after SLE, and the mean delay between diagnosis of SLE and occurrence of SLS was 66.7 months (range 0-374 months).

The median age of the patients was 32 years old (range: 11-69 years) at SLS diagnosis. The sex ratio showed a large female predominance (122/20). The ethnic group was known in 27% of cases (n=42). Caucasian (n=11) and North African people (n=28) were predominant, followed by Asian (n=2) and African-American (n=1) people. Smoking status was reported in 11 cases (7%): 2 of 11 patients (18%) were current smokers at the time of SLS diagnosis.

Respiratory symptoms were present in 155 of 155 cases (100%), and there were complaints of dyspnea (n = 133/133, 100%), pleuritic chest pain (n = 73/91, 80%) and coughing (n = 13/75, 17%).

Extra-thoracic manifestations of SLE included arthralgia (n=78/88, 89%), cutaneous involvement (n=46/89, 52%), glomerulonephritis (n= 45/91, 49%), fever (n=29/69, 42%), pericardial effusion (n=13/67, 19%), alopecia (n=12/67, 18%), and neurological involvement (n=15/76, 20%).

Biological characteristics

Biological results were reported in 88 cases (57%). Blood inflammatory syndrome was present in 10 of 10 cases. Blood cell counts and electrolytes, creatinine, and liver enzyme levels were normal,

except in cases with extra-respiratory localization (elevated creatinine level, proteinuria). Creatine kinase (CK) was normal in 21 of 21 cases. Complement proteins were normal in 10 of 19 cases (53%), or they showed a low level of C3 (n=1/19, 5%), C4 (n=3/19, 15%) or both C3 and C4 (n=5/19, 27%).

Antinuclear antibodies were present in all cases. Anti-DNA antibodies were present in 42 of 56 cases (75%) and anti-ENA in 30 of 60 patients (50%), including anti-SS-A (n=23/60, 38%), anti-SS-B (n=7/60, 12%), anti-RNP (n=9/60, 15%), and anti-Sm (n=8/56, 14%). Antiphospholipid antibodies were found in 9 of 14 patients (64%).

Radiological findings

Thoracic imaging (chest X ray or CT scan) was reported in 139 cases and was abnormal in almost all of the cases (n=136/139, 98%). The most frequent finding was elevated hemidiaphragm with reduced lung volume (n = 133/139, 96%), which could affect one or both sides of the diaphragm. Basal atelectasis was reported in 47 of 139 cases (34%). Pleural effusions and pleural thickening were found in 19 and (14%) and 15 of 139 cases (11%), respectively.

Respiratory function

Respiratory function showed a restrictive defect in all cases (n=138/138) without obstructive defects. The mean forced vital capacity reported was 1.93 L (52% of theoretical measurement), the mean total lung capacity was 2.85 L (52%), the mean DLCO was 49%, and the mean DLCO corrected by vital capacity was 95%. The mean arterial oxygen and carbon dioxide partial pressures were 77 mm Hg and 39 mm Hg, respectively. All 23 of the echocardiographic studies were normal. Maximal inspiratory and expiratory pressures were decreased in, respectively, 39 of 50 (78%) and 38 of 47 (81%) cases. Among 12 phrenic nerve stimulations, 9 were normal (75%), and 3 showed mild signs of neuropathy (25%).

Treatments and outcomes

All of the patients were treated, although the treatment modalities were only reported in 108 cases. Treatment was introduced because of SLS in 92% of cases (n=44/48). The treatments included intravenous or oral corticosteroids (n=104/108, 96.0%), azathioprine (n=33/108, 30.6%), cyclophosphamide (n=20/108, 18.5%), beta 2-mimetics (n=9/108, 8.3%), theophylline (n=8/108, 7.4%), MMF (n=7/108, 6.5%), and rituximab (n=7/108, 6.5%).

Patients who were given corticosteroids received 0.5 to 1 mg/kg/day in 70% of cases (n=34/48) and less than 0.5 mg/kg/day in 30% (n=14/48). Fifty-three patients received corticosteroids alone. Outcomes were known for 34 of them: 31 of 34 (91%) were improved by corticosteroids on clinical evaluation, 10 of 13 on PFT evaluation, and 2 of 3 on chest radiography; 3 of 34 were stable, and 3 of 34 worsened.

Immunosuppressive drugs were used in 55 of 108 patients (51%). As first-line therapy, they were always associated with corticosteroids. Cyclophosphamide and methotrexate were each used after corticosteroid failure and were not successful in this condition. When used as a corticosteroid-sparing drug, azathioprine was a success. One patient was improved by MMF as a corticoid-sparing drug, and it was used because of azathioprine intolerance. Rituximab was used in 7 cases: improvement was reported as a first-line therapy associated with corticosteroids (n=1) and after corticosteroid and/or cyclophosphamide failure (n=6).

Theophylline was used as an adjuvant drug, associated with corticosteroids. Two patients were improved with theophylline alone after corticosteroid failure. Beta-mimetics were used alone (n=1) or associated with corticosteroids (n=8), with only 1 failure.

Outcomes were known in 52 cases (33.5%). Death occurred in 4 cases (5.5%): 1 patient died from infectious pneumonia, 1 died from an unexplained deterioration (this patient had a poor adherence to treatment), and 2 died from of unknown causes. One patient, who was treated with corticosteroids, cyclophosphamide and then rituximab, was stable. Finally, clinical improvement was

observed in 94% of cases (n=48/52), associated with functional improvement in 77% of cases (n=36/47) and radiological improvement in 57% of cases (n=8/14).

DISCUSSION

SLS is frequently associated with SLE

We reported 15 new cases of SLE-associated SLS and provided a review of the previously reported cases. SLS is a pulmonary manifestation of unknown cause, characterized by restrictive pulmonary capacity without interstitial lung disease, pleural effusion or phrenic nerve palsy. SLS is usually associated with SLE, and it has been rarely described in other disorders, including systemic sclerosis [11], primary Sjögren's syndrome [8,10], rheumatoid arthritis [9], and undifferentiated connective tissue disorders [9,12].

Respiratory manifestations in SLE are common, but SLS is rare. The prevalence of SLE-associated SLS was estimated at 0.6% in a large study including 626 SLE patients [6]. SLS usually occurs several months to years after the diagnosis of SLE, varying from 4 months to 24 years [13,14]. SLS is rarely the initial feature of SLE [15,16], representing 9 of 95 cases (9.5%) in our literature review. The occurrence in young women, well characterized for SLE, was also found for SLE-associated SLS (mean age of 34.1 years old, and a sex ratio of 6.2 women to 1 man).

SLS presentation and diagnosis

In the original characterization of this syndrome in 1965, Hoffbrand and Beck noted the following features: unexplained dyspnea, small lung volume and restrictive lung physiology with or without diaphragmatic elevation, in the absence of interstitial, alveolar or vascular pulmonary disease. The most frequent symptoms are dyspnea, which is constant, and pleuritic chest pain, which concerned 65% of patients in Toya's 2009 systematic review and 80% in our work. Chest radiography shows elevated hemidiaphragms with reduced lung volumes. Chest CT scan is useful for differential diagnosis and can show pleural thickening, mild pleural effusions and basal atelectasis due to poor

chest expansion. Pulmonary function tests reveal a restrictive defect with a conserved DLCO corrected for alveolar volume level (KCO). Interestingly, biologic inflammation with elevated C-reactive protein has been reported, which is unusual in SLE [17].

SLS physiopathology

In the first description of this syndrome, Hoffbrand and Beck implicated microatelectasis, caused by excessive surface tension related to the loss of surfactant. Other hypotheses have been developed, involving each part of the respiratory system. Respiratory muscle weakness has not been confirmed by magnetic stimulation of the phrenic nerves [18,19] and CK levels, which are usually normal. Steroid-induced myopathy has been suggested, but SLS can occur in patients who have not received any steroids. Diaphragm fibrosis and phrenic nerve palsy have been hypothesized [20,21], but phrenic nerve conduction is normal most of the time. Pleural adhesions have been described on pathologic examinations [5,22]. Because pleuritic chest pain is a prominent feature of SLS, it has been hypothesized that pleural effusion or inflammation could promote diaphragm splinting and reduced diaphragmatic mobility. Finally, Henderson et al. proposed that pleural inflammation could inhibit deep inspiration by neural reflexes, resulting in chronic lung hypo-inflation, consequently leading to parenchymal remodeling with changes in elasticity, proving responsible for decreased lung compliance. Due to a positive feedback loop, impaired compliance could induce hypo-inflation and so on [12].

Risk factors for developing SLS

Longstanding disease duration, positivity for anti-RNP and a history of pleuritis have been reported to be associated with the occurrence of SLS [3]. In our work, anti-RNP antibodies were also positive in 6 of 13 patients (46%), and a history of pleuritis was described in 5 of 14 patients (36%). A link between SLS and the presence of anti-Ro/SS-A antibodies was hypothesized in 1999 [8]. Then, Ishii et al. described four cases of SLS in SLE patients with positive anti-Ro/SS-A antibodies. In 2009, Souza Neves et al. published 7 cases of SLS, of which 6 were anti-Ro/SS-A positive and had pleurisy [23]. In

the same manner, we found in our series a high level of positive anti-Ro/SS-A. However, 61% of the cases of SLE-associated SLS in the literature review were anti-Ro/SS-A-negative [24]. Moreover, no correlation was found between SLS and SLE activity [5].

SLS treatment

There have been no controlled trial studies, and there is no consensual treatment for SLS. All 15 of our cases were treated. Steroids were used in most cases at low and high doses. Cyclophosphamide, used as first-line therapy or after steroid failure, did not show efficacy. The patient who received methotrexate alone showed mild PFT improvement. Beta-mimetics were useful in one of the two patients who were given beta-mimetics, but the drug was associated with corticosteroids. Patients without steroids did not improve. Finally, rituximab was successful after failure with low-dose steroids, beta-mimetics and physiotherapy.

All of the cases in the literature were treated. In our review, the first-line treatment included corticosteroids, with or without immunosuppressive agents. Oral prednisone from 20 mg to 1 mg/kg per day, sometimes preceded by short-term pulses of methylprednisolone, was largely effective alone. With retrospective results, there was no prognostic difference between patients receiving associated immunosuppressive drugs or not. When used after corticosteroid failure, immunosuppressive agents (including cyclophosphamide, methotrexate and azathioprine) were not successful. When used as a corticosteroid-sparing drug, azathioprine was successful.

Theophylline is known to increase diaphragmatic strength. Van Veen et al. showed a 31% improvement in total lung capacity after 1 week of theophylline therapy in one patient [25]. Furthermore, beta-agonists have been shown to decrease diaphragmatic fatigue through their positive inotropic effects [25,26]. Tavoni et al. used combined low doses of corticosteroids with beta-agonists and theophylline with great efficacy for clinical symptoms, even after one year of follow-up [8].

More recently, rituximab has been used successfully alone [27,28] or with cyclophosphamide and beta-agonists [29,30]. No other immunosuppressive drugs have been successfully used after corticosteroid failure.

Using all of these therapies, subjective improvement is obtained in most cases. Objective improvement, as demonstrated by increased values on pulmonary function tests or respiratory pressures, has been noted in more than 75% of cases. Symptomatic improvement can be observed within 48 hours, although it usually requires several weeks to months [31,32].

Antalgic agents have not been evaluated. Although the last pathogenic hypothesis involved the inhibition of respiratory muscles by pain, it should be considered a simple and useful first-line approach to treat SLS patients, associated with low doses of corticosteroids.

Outcomes

Long-term prognosis is good, with improvement [14,26] in most cases, and stabilization or only minor deterioration of lung function more rarely. Nine of 12 new cases clinically improved, and 3 were stable. PFT improvement was present in 7 of 10 patients, but none of them normalized. Chest imaging improved in 3 of 5 patients and was stable in 2 of 5 patients. In our literature review, clinical improvement was observed in 94% of cases, functional improvement in 77% of cases and radiological improvement in 57% of cases. In their prospective study [33], Martens et al. found no evidence of disease progression in 7 patients over 38.5 patient-years of follow-up [13]. However, in a review of 35 cases of SLS, Langenskiöld et al. found that only 20% recuperated to their normal lung function [29].

CONCLUSION

Shrinking lung syndrome is a rare respiratory manifestation of SLE that can occur at any time. Its diagnosis relies on the association of a restrictive pattern on PFT without another explanation, such as obesity or lung fibrosis. Patients present with dyspnea, pleuritic chest pain, and elevated

hemidiaphragm, often associated with basal atelectasis on chest imaging. The pathogenic mechanisms, if unclear, probably involve a positive feedback loop, in which pleural inflammation inhibits deep inspiration by neural reflexes, resulting in chronic lung hypo-inflation, consequently leading to decreased lung compliance. Treatment of SLS relies on steroids, analgesics and physiotherapy. After failure of these drugs, theophylline and beta-mimetics have shown efficacy in some patients. Finally, rituximab might be useful after all of these drugs if there is no improvement. Other immunosuppressive agents seem to be useless and should not be given in SLS, based on retrospective data. The prognosis is good in almost all patients, with improvement in a few weeks.

Table legends

Table 1: Clinical, biological, radiographic, and functional characteristics, treatments and outcomes of reported cases

Table 2: Demographic and clinical characteristics of patients reported and analyzed from the literature review

Table 1

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female
Age (years)	21	23	50	17	30	26	67	21	36	51	62	23	40	26	27
History of pleurisy	0	1	0	0	0	0	1	0	0	1	1	0	0	1	0
Chest pain	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Dyspnea	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Crackling	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0
Auto-antibodies	ANA, DNA, SSA, RNP	ANA, DNA, SSA	ANA	ANA, SSA, RNP	ANA, DNA	ANA, SSA, SSB	ANA, DNA, SSA, SSB	ANA, DNA, SSA, SSB	ANA, DNA, SSA, RNP	ANA, DNA, SSA, RNP	ANA, DNA, SSA, SSB	ANA, DNA, SSA	ANA, DNA, RNP	ANA, DNA, RNP	ANA, DNA, SSA, SSB
Chest imaging	Elev. Diaph., Atelectasis	Atelectasis, Pleural Thickening	Elev. Diaph., Atelectasis	Normal	Normal	Elev. Diaph., Atelectasis	Elev. Diaph., Atelectasis, Pleurisy	Elev. Diaph., Atelectasis, Pleurisy	Elev. Diaph., Atelectasis	Elev. Diaph., Pleurisy, Pleural Thickening	Elev. Diaph., Atelectasis, Pleural Thickening	Elev. Diaph.	Pleural Thickening, Reticulations	Pleural Thickening, Reticulations	Elev. Diaph.
FVC	37%	< 30%	2.78		1.61 (38%)	1.58 (47%)	66%	42%	42%	1.72 (61%)		0.79 (19%)	2.63 (73%)	1.38 (41%)	1.53 (45%)
TLC	46%	49%	4.35		2.80 (46%)		61%	65%	62%	2.77 (61%)	46%	1.91 (34%)	3.91 (73%)	3.03 (68%)	3.16 (68%)
DLCO	39%	NI	57%	Low	25%	45%	31%		43%	51%	25%		38%	34%	44%
KCO	118%	NI	74%	N	83%		97%		120%	95%	59%		54%		
Treatment	CS 60 mg/d + Physiotherapy	CS (1 mg/kg/d) + CyP then MMF	Physiotherapy	CS (< 0.5 mg/kg/d) + MTX	CS + CyP then MMF	MTX	Unknown	CS 1 mg/kg/d	CS 1 mg/kg/d	CS < 0.5 mg/kg/d	CS 20 mg/d + B2M + Rituximab + Physiotherapy	Colchicine	CS + MMF	CS + AZA + MMF + RTX	CS + AZA + B2M
Clinical outcome	Improvement	Improvement	Improvement	Stability	Stability	Stability				Improvement	Improvement (after rituximab)	Improvement	Improvement	Improvement	Improvement
PFT outcome	Improvement	Improvement			Stability	Mild impairment				Improvement	Improvement	Stability	Improvement	Improvement	Improvement
Imaging outcome						Stability				Improvement	Improvement	Stability	Improvement		

CS: Corticosteroids, MMF: Mycophenolate mofetil, CyP: Cyclophosphamide, MTX: Methotrexate, AZA: Azathioprine, RTX: Rituximab, B2M: Beta 2-mimetics, Elev. Diaph.: Elevated Diaphragm

Table 2

	Observations	Review
Sex ratio (F/M)	15/0	122/20
Median age (range), *years*	27 (17-67)	32 (11-69)
Mean time between SLE and SLS diagnosis (range), *months*	36 (2-456)	66 (0-374)
Clinical features	15/15 (100%)	155/155 (100%)
Dyspnea	15/15 (100%)	133/133 (100%)
Chest pain	14/15 (93%)	73/91 (80%)
Cough	2/15 (13%)	13/75 (17%)
Fever	2/11 (18%)	29/69 (42%)
Extra-thoracic features		
Joint involvement	14/15 (93%)	78/88 (89%)
Cutaneous involvement	7/15 (47%)	46/89 (52%)
Renal involvement	2/15 (3%)	45/91 (49%)

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