Shrinking lung syndrome in systemic lupus erythematosus patients with dyspnea

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Abstract
Aim of the work: To identify the frequency of shrinking lung syndrome (SLS) in systemic lupus erythematosus (SLE) with dyspnea and study the clinical characteristics and differences in disease activity and damage.

Patients and methods: The study included 47 SLE patients complaining of dyspnea. SLS was considered in those with exertional dyspnea, restrictive pulmonary function tests (PFTs) and elevated copula of the diaphragm. Full history taking, thorough clinical examination, laboratory and relevant radiological investigations were performed for all the patients. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) indices were compared. High resolution CT chest was performed for patients with radiological findings consistent with SLS.

Results: The mean age of the patients was 29.43 ± 7.45 years, mean disease duration 5.18 ± 3.62 years. The SLS was present in 8 patients (17.02%). There was bilateral elevation of the diaphragm copulae in 25% of SLS patients and two had associated basal atelectatic bands. The serum uric acid was significantly higher in those with SLS while the 24 h urine protein was significantly lower and C4 normalized. The levels of SLEDAI and SLICC tended to be lower in those with SLS, yet there was no significant difference from those without. The demographic features, clinical and laboratory manifestations, disease activity and damage scores, PFTs and radiological findings of the SLE patients are presented.

Conclusion: In SLE patients with dyspnea, SLS should be looked for as it is present in a high proportion of cases.

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1. Introduction

Systemic lupus erythematosus is an autoimmune systemic disease that commonly affects the respiratory system [1]. In spite of being frequent, the diagnosis may be difficult because of the diversity of anatomical and clinical presenta-
tions. Proper diagnosis is important as new immunosuppressive drugs have considerably improved the prognosis [2]. At some time during their course, most patients with SLE show signs of involvement of the lung, its vasculature, the pleura, and/or the diaphragm [3]. Pleurisy, coughing, and/or dyspnea are often the first clues either to lung involvement or to SLE itself [4].

The respiratory system is commonly compromised in SLE. The most prevalent presentation includes pleuritis. Other frequent manifestations include interstitial lung disease (ILD), acute lupus pneumonitis, diffuse alveolar hemorrhage, pulmonary arterial hypertension, acute reversible hypoxemia and shrinking lung syndrome (SLS). As survival in lupus patients has improved over years, avoiding pulmonary damage emerges as a crucial aim [5]. Respiratory complications of SLE are relatively common as the initial manifestation and >50% have pulmonary involvement at some stage of disease progression [6,7].

In SLE patients, dyspnea is common, frequently disabling and associated with a history of lupus involvement of the lung [4]. As it is a complex systemic disease, patients can manifest dyspnea for primary causes due to SLE itself or secondary to concomitant complications [8].

Shrinking lung syndrome is a rare respiratory complication associated with SLE. Patients present with dyspnea alone or associated with chest pain, lung volume reduction with no parenchymal abnormalities and a restrictive ventilatory defect on pulmonary function tests. The pathogenesis, treatment, and prognosis of SLS remain controversial [1,9]. It has also been reported as a rare complication of systemic autoimmune diseases including SLE, Sjögren’s syndrome and polymyositis. Shrinking lung syndrome should be suspected in any patient with an autoimmune disease presenting with unexplained dyspnea [10]. It is characterized by the dysfunction of respiratory muscles, especially the diaphragm, resulting in dyspnea [6]. Respiratory function tests demonstrate severe restrictive ventilatory impairment, Chest X-ray demonstrates elevated hemi diaphragms and computed tomography (CT) shows no evidence of interstitial fibrosis, significant plural disease or pulmonary emboli [11,12].

Shrinking lung syndrome may cause significant morbidity and occasionally mortality. Its cause remains controversial and could be attributed to diaphragmatic weakness or to chest wall restriction. No definitive therapy exists; however, corticosteroids lessen symptoms and improve pulmonary function in some patients [13–15]. Other hypotheses include diaphragmatic paralysis secondary to phrenic nerve injury [10,16], diffuse diaphragm fibrosis [17] and limited chest wall expansion [18]. Imaging reveals the absence of any significant parenchymal disease [19]. Pleuritic inflammation and pain may have an important role in the pathogenesis of SLS [10]. A possible mechanism linking pleural inflammation and diaphragm dysfunction may be via a reflex inhibition of diaphragmatic activation [20]. SLS is a cause of pulmonary damage [21] and corticosteroids are the most common method of treatment with a generally good prognosis [11].

The aim of the present study was to detect the frequency of SLS in SLE patients with dyspnea and study their clinical, laboratory and radiological characteristics and differences in disease activity and damage.

2. Patients and methods

The study included 47 SLE patients fulfilling the updated ACR revised criteria for the classification of SLE [22]. The patients were attending the Rheumatology and Internal medicine outpatient Clinics of the Cairo University Hospitals. The patients were grouped according to the presence or absence of shrinking lung syndrome (SLS). All patients had symptomatic pulmonary manifestation in the form of dyspnea. Shrinking lung syndrome was considered in those with exertional dyspnea, restrictive pattern of the pulmonary function tests and elevated copula of the diaphragm on one or both sides. Full history taking, thorough clinical examination, laboratory and relevant radiological investigations were performed for all the patients. High resolution CT chest was performed for patients with radiological findings consistent with SLS. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [23] while assessment of organ damage was made using the Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) index [24]. The study was approved by the local ethics committee and it conforms to the standards currently applied in the Cairo University Teaching Hospitals. All patients gave their informed consent prior to their inclusion in the study.

Statistics: Analysis of data was performed with a statistical package for the social sciences (SPSS) version 15. Data were presented as mean ± standard deviation and percentage, median (min.–max.). Mann–Whitney test was used for the analysis of two non-parametric quantitative data. Correlation was performed by the Spearman correlation coefficient. p value was considered significant if <0.05.

3. Results

The 47 female SLE patients had a mean age of 29.43 ± 7.45 years [27(18–50)] and disease duration of 5.18 ± 3.62 years [5 (0.25–17)]. Shrinking lung syndrome (SLS) was present in 8 patients (17.02%). The demographic, clinical and laboratory features, disease activity and damage scores of the SLE patients with and without SLS are shown in Table 1. All patients were receiving corticosteroids at a mean dose of 17.22 ± 11.09 mg/day. Twenty-one patients were also receiving azathioprine, 24 hydroxychloroquine, 9 cyclophosphamide and 3 mycophenolate mofitil. Those with SLS and 2 without were receiving theophylline tablets (150 mg/day) for their respiratory manifestations. The mean steroid dose received by the patients with and without SLS was insignificantly different (23.33 ± 14.72 and 16.25 ± 10.33 mg/day respectively, p 0.3).

Dyspnea was present in all the studied SLE patients. In addition to SLS, other causes of dyspnea included pleurisy in 41, airway obstruction in 2, mild interstitial lung disease with minimal plural effusion in 3, upper airway disease in 2 and respiratory muscle disease in 5. Two patients were asthmatic, while none had chest infection, pulmonary thromboembolism, pneumonitis or any concomitant complication that may cause dyspnea. Plain X-ray and CT of SLS patients are shown in Figs. 1 and 2. The pulmonary function test results of the 8 patients with SLS were as follows: Forced Vital Capacity (FVC): 3.01 ± 0.43 L with a percentage predicted of 77.49 ± 7.1;
FEV: Forced Expiratory Volume in 1 s (FEV1): 2.34 ± 0.39 L with a percentage predicted of 78.97 ± 9.51 and the FEV1/FVC 97.78 ± 10.28%.

The HRCT of the 8 SLS patients was free of any parenchymal disease. There was bilateral elevation of the diaphragm copulae in 2 (25%) of SLS patients while the rest had elevation of the right copula. Two patients had associated basal atelectatic bands; otherwise the lung fields were clear. In SLE patients without SLS there was associated pulmonary parenchymal disease seen on radiology in the form of minimal pleural effusion and mildILD in 3.

4. Discussion

Although respiratory manifestations of SLE are frequent, SLS represents a rare complication and its pathogenesis and therapy remain controversial, however it must be considered in a patient with autoimmune disease and dyspnea. [25–27].

In the present study, SLS was present in 17.02% of SLE cases. In 2 SLS patients, the copula was bilaterally elevated.

Figure 1  Plain X-ray chest (PA view) of a female SLE patient with SLS showing bilateral elevated copula with right basal atelectatic bands.
The appearance of SLS is considered a very rare clinical condition classically described in SLE patients [28] and is seldom seen in other diseases [29]. Despite being rare, SLS must be considered when SLE patients present by dyspnea without heart insufficiency, anemia or diseases of the lung parenchyma [30]. A case report with SLS showed bilateral involvement with reduced lung volumes [16]. In a Japanese SLE patient with SLS, bilateral elevated diaphragms, clear lung fields with a restrictive defect of PFT were present. Relation to lupus flare-up was suggested by the elevated ESR, leucopenia and elevated anti-DNA titer [31]. In a report on three female SLE cases with SLS, dyspnea and chest pain were present with bilateral elevation of the diaphragm in two and a severe restrictive defect of the PFTs. However, the onset of pulmonary manifestations occurred in the absence of a lupus flare [32]. In SLE, the prevalence of SLS has been reported to be as low as (1.77%) [21] and as high as 23%. It is noteworthy that the published data on this condition are small in amount and it is seldom seen in clinical practice [13]. A study on SLE patients reported respiratory symptoms in 63% with 10% meeting the definition for SLS [33] being 9.1% in another study [34]. In 87.23% of the SLE patients, dyspnea was due to pleurisy. The SLE clinical manifestations were comparable between those with and without SLS. The lung fields were clear except for two SLS patients with an atelectatic band. Other case reports on SLS found that these patients also presented with arthritis, autoimmune hepatitis and polyserositis and their chest x ray showed elevated diaphragms and atelectasis at both lung bases. The CT imaging revealed profound low lung volumes with compressive atelectasis and no evidence of ILD [25,35,36]. In a previous study, SLS was present in a considerable subset of SLE patients (13.5%) in which serositis was present in 50% [37]. The current patients all had dyspnea which could explain the increased frequency of SLS compared to the earlier work that also included SLE cases without dyspnea. In SLE patients with dyspnea or chest pain, SLS should be looked for and PFTs are highly suggestive [37]. It has been stated that respiratory symptoms, abnormal lung function, and SLS are common in SLE. Clinicians should consider evaluation of SLS among symptomatic patients with long-standing disease and a history of pleuritis [33].

In the present study, the 24 h urine protein and alkaline phosphatase were significantly lower and the C4 level significantly normalized in SLE patients with SLS. Normal kidney function tests have been reported in SLS patients [38]. These favorable laboratory results support the lower disease activity and damage found in this subset of SLE patients. This may further throw light on the reported good prognosis of SLS cases and the favorable outcome [11]. Long-term prognosis is good although respiratory failure can occur in some cases [10]. The serum uric acid was significantly higher in SLE patients with SLS. There is no obvious explanation other than the use of theophylline by all SLS patients and 2 other SLE cases. Theophylline is known to increase the serum uric acid level. It has been reported that theophylline increased the plasma concentrations of purine bases including uric acid without a decreased urinary excretion in normal subjects [39]. In the present study, the anti-ds DNA was comparable between those with and without SLS. It has been reported that respiratory dysfunction appears to be independent of the clinical course, duration and lupus antibodies (ANA and anti-DNA) [35].

Restoring a near-normal lung function is an achievable goal in SLS [40]. However, it may cause severe functional pulmonary abnormalities and must be treated promptly and aggressively in order to, at least, stabilize PFTs [1]. Prognosis is generally good and most patients improve on increasing the dose of steroids aimed at the subclinical respiratory myositis-like process [35].

In conclusion, in SLE patients with dyspnea, SLS should be looked for as it is present in a high proportion of cases. A longitudinal study on a larger scale of patients is recommended to confirm the findings and properly assess the outcome of this subset and response to treatment strategies.

Conflict of interest

The authors have no conflict of interest.

References

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