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Pulmonary manifestations in systemic lupus erythematosus: Association with disease activity

OMER S.B. ALAMOUDI AND SUZAN M. ATTAR

Department of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

ABSTRACT

Background and objective: **Although systemic lupus erythematosus (SLE) is the most common connective tissue disease affecting the lung, few studies have assessed risk factors that predict pulmonary manifestations. The objectives of the present study were to determine the prevalence of lung manifestations in SLE patients from Western Saudi Arabia by analysing results from high-resolution computed tomography (HRCT) scans and to identify independent risk factors for lung involvement.**

Methods: **This was a 10-year retrospective study involving 184 SLE patients. We examined all HRCT lung abnormalities and determined whether findings were associated with the presence of lupus nephritis (LN), SLE disease activity (as defined by SLE Disease Activity Index 2000 item scores ≥4 for any and all items) or levels of complement and anti-double-stranded DNA (anti-dsDNA).**

Results: **We identified 61 patients (33%) with pulmonary involvement, and 52 (85%) of these subjects showed HRCT abnormalities. The most common HRCT findings were pleural effusion, consolidation and atelectasis (58%, 42% and 42%, respectively). There was a significant association between abnormal HRCT results and hypocomplementemia, high levels of anti-dsDNA and disease activity ($P < 0.05$), particularly with regard to pleuropericardial effusion and consolidation. Pulmonary abnormalities were significantly higher within the first five years after SLE diagnosis ($P < 0.001$). However, neither disease duration nor LN was associated with increased risk.**

Conclusions: **Lung manifestations were frequent in SLE patients from Saudi Arabia, with pleural effusion, consolidation and atelectasis being the most common. Low complement levels, high anti-dsDNA levels and disease activity were significantly associated with abnormal HRCT findings (all $P < 0.001$).**

SUMMARY AT A GLANCE

Researchers in diverse geographical regions have begun to investigate variables that contribute to pulmonary involvement in SLE. Here, we conducted the first study in Saudi Arabia to identify specific risk factors that predict pulmonary manifestations in SLE, observing a significant association between lung involvement and disease activity.

Key words: high-resolution computed tomography, lung, pulmonary involvement, risk factors, systemic lupus erythematosus.

Abbreviations: ARDS, adult respiratory distress syndrome; CI, confidence interval; COP, cryptogenic organizing pneumonia; DAH, diffuse alveolar haemorrhage; HRCT, high-resolution computed tomography; KAUH, King Abdulaziz University Hospital; KSA, Kingdom of Saudi Arabia; LN, lupus nephritis; LP, lupus pneumonitis; PE, pulmonary embolism; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; TB, pulmonary tuberculosis; WHO, World Health Organization.

INTRODUCTION

Systemic lupus erythematosus (SLE) is the most common connective tissue disease affecting the lung.[1] However, the reported prevalence of pulmonary involvement in SLE varies from 14% to 100%, depending on the criteria used to define lung abnormalities.[2] Previous studies in the Middle East have suggested the rate of pulmonary involvement to range from 4.9% to 30%,[3–9] with the most common pulmonary abnormality reported to be pleural effusion. It occurs in 50% of the patients and is typically associated with pericardial effusion.[10]

Despite the potentially high prevalence of these lung complications in SLE, few studies have assessed the risk factors that predict pulmonary manifestations or associated their development with disease activity.[11] So far, Fenlon *et al.*[2] demonstrated no relationship between the extent of high-resolution computed tomography (HRCT)-identified chest abnormalities and SLE activity, whereas Bankier *et al.*[11] found a significant correlation between

Correspondence: Omer S. B. Alamoudi, Department of Medicine, King Abdulaziz University Hospital, P.O. Box 80215, Jeddah 21589, Saudi Arabia. Email: dramoudi@yahoo.com

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abnormal HRCT scans and SLE duration. Additionally, it was reported that SLE duration was the only risk factor associated with the development of pulmonary manifestations.[12]

Nevertheless, no previous studies have specifically assessed the prevalence or independent risk factors for SLE-associated lung abnormalities in the Middle East. Therefore, in the present study, we have retrospectively investigated the prevalence of pulmonary manifestations in SLE using clinical, radiological and HRCT technology in order to determine risk factors for developing lung abnormalities and assess their relationship with disease activity.

METHODS

Patients and study design

This was a hospital-based study conducted at King Abdulaziz University Hospital (KAUH) located in the Western region of the Kingdom of Saudi Arabia (KSA). Data were collected retrospectively from 1 January 2003 to 31 December 2012. All patients included in the study were diagnosed and classified according to the American College of Rheumatology criteria.[13] Patients <15 years old and those with mixed connective tissue diseases were excluded from the study. Also, this investigation was conducted in accordance with the Declaration of Helsinki and was approved by the Biomedical Ethics Research Committee of the Faculty of Medicine at KAUH.

Data collection

The following demographic data were extracted from patient files: age, gender, nationality, smoking history and disease duration (<1, >1–5, >5–10 and >10 years). SLE Disease Activity Index 2000 (SLEDAI-2K) scores were used to measure disease activity. This index represents a weighted point system in which nine distinct organ systems are differentially scored, with renal and central nervous system involvement given higher point values. Briefly, 24 self-explanatory items related to different manifestations occurring within the 10 days preceding the assessment were given weighted scores from 1 to 8, yielding a total maximum score of 105. Results ranged from 0 to 105 points, and the SLE patients were divided into two groups: inactive patients with a low SLEDAI-2K score (<4 for any and all items) and active subjects with a higher score (≥4 for any and all items).[14,15] Notably, as part of the SLEDAI-2K score, complement levels, antibodies against double-stranded DNA (anti-dsDNA) and pleurisy were considered. In this regard, pleurisy was specifically assessed based on the following definition: pleuritic chest pain with pleural rub or effusion, or pleural thickening. Anti-dsDNA antibodies were always measured using the same enzyme-linked immunosorbent assay upon diagnosis of the pulmonary manifestation. Results were classified according to the manufacturer's instructions: 'negative' for 0–200 IU/mL (0–92.6 World Health Organization (WHO) units/mL), 'equivocal' for 201–300 IU/mL (92.7–138.9 WHO units/mL), 'moderately positive' for 301–800 IU/mL (139–370.4 WHO units/mL) and 'strongly positive' if the level was >801 IU/mL (>370.5 WHO units/mL).[16] In addition, complements 3 and 4 (C3 and C4) were measured by nephelometry (normal values 0.75–1.65 and 0.2–0.6 mg/L, respectively).[17] The following chest symptoms were recorded: cough, shortness of breath, haemoptysis, fever, musculoskeletal pain and pleuritic chest pain. Two senior radiologists independently reviewed chest X-ray and HRCT scans, with each diagnosis reached by consensus. Furthermore, the presence of the following pulmonary manifestations were recorded[18,19]: pleural thickening/effusion, pericardial effusion, pneumonia, pneumonitis, interstitial lung disease, bronchiectasis, diaphragmatic dysfunction, pulmonary embolism (PE), adult respiratory distress syndrome (ARDS), diffuse alveolar haemorrhage (DAH), cryptogenic organizing pneumonia (COP) and pulmonary oedema.

Statistical analysis

All data analyses were performed using statistical package for social sciences (SPSS, SPSS Inc., Chicago, IL, USA; version 16). Means with standard deviations were calculated for quantitative data. Categorical variables are reported as proportions, which were compared using the chi-square test to determine relative risk with 95% confidence intervals (CI). Also, we assumed normal distribution based on Levene's test for homogeneity of variance. The Student's *t*-test was employed to compare disease duration and the presence or absence of HRCT chest abnormalities. Results were considered significant if the *P*-value was greater than 0.05 ($P < 0.05$).

RESULTS

Patient characteristics

A total of 184 SLE patients were reviewed, and their characteristics are presented in Table 1. Approximately one third of these patients (33%) displayed pulmonary manifestations, yielding an overall prevalence of 33.2% (95% CI: 26.35–39.95). Mean age of the study subjects was 32 ± 13.2 years, and 159 patients were female (86%; female to male ratio was approximately 8:1). Among those with pulmonary manifestations, there were 34 non-Saudi patients (56%) and 27 Saudi patients (44%). Moreover, most of the SLE patients (66%) without pulmonary involvement presented with lupus nephritis (LN). We observed a significant association between high levels of anti-dsDNA, low levels of complement (C3 and C4) and the presence of pulmonary involvement of SLE ($P < 0.001$ for all; Table 1). Additionally, we found that the overall death rate between the populations with and without pulmonary involvement was not significantly different ($P = 0.325$; Table 1), with the only variable showing a significant relationship with survival being 'active disease' (i.e. 75% of the patients who died displayed active disease).

Data concerning symptoms, chest X-rays and HRCT scans are presented in Table 2. In patients

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Table 1 Demographic and clinical characteristics of all SLE patients in this study (n = 184)

Variable	*N*	Pulmonary involvement n = 61	No pulmonary involvement n = 123	*P*-value
Age (mean ± SD, years)	NA	32 ± 13.2	32 ± 11	0.277
Gender (%)				
Male	25	28	72	0.324
Female	159	44	66	NA
Disease duration (mean ± SD, years)	NA	5.13 ± 3.14	11.07 ± 4.93	<0.001
Active disease (%)	87	52	48	<0.001
Lupus nephritis (%)	74	34	66	0.17
Active smoking (%)	11	18	82	0.23
Death (%)	20	35	65	0.325
Low complement level (%)†				
C3	57	67	33	<0.001
C4	87	52	48	<0.001
C3 and C4 combined	50	64	36	<0.001
Anti-dsDNA (%)†				
Negative	79	9	91	<0.001
Equivocal	25	52	48	0.031
Moderately positive	34	42	68	0.48
Strongly positive	46	61	39	<0.001

The demographic and clinical characteristics for all SLE patients are presented by pulmonary involvement. The data were analysed using the chi-square test to determine *P*-values.

† Cut-off values for these parameters are described in the Methods section.

NA, not applicable; SLE, systemic lupus erythematosus; SD, standard deviation; dsDNA, double-stranded DNA.

showing lung complications, 72% displayed symptoms, which most frequently consisted of pleuritic chest pain (50%), shortness of breath (49%) and cough (34%). Furthermore, 77% of these patients showed abnormal chest X-rays, which indicated pleural effusion, consolidation and atelectasis (55%, 34% and 27% of subjects, respectively). Nevertheless, HRCT chest scans revealed a higher incidence (85%) of these abnormalities as compared with chest X-ray results.

Finally, diagnoses of patients presenting pulmonary manifestations based on clinical and HRCT findings are summarized in Table 3. Nine (15%) of the subjects had chest pain with a normal HRCT scan. Among these patients, one was suspected to have pulmonary arterial hypertension from echocardiogram, which was not a definitive diagnosis, and eight (13%) displayed pleuritic chest pain in the absence of pleural effusion. A total of seven patients (12%) died during the study period, with six patients (9.8%) resulting from acute pneumonitis complicated by ARDS and one suffering pulmonary haemorrhage.

Finally, we were able to link HRCT findings from patients having pulmonary involvement to disease activity, the presence of LN, as well as complement (C3 and C4) and anti-dsDNA levels (Table 4). Notably, we found that hypocomplementemia, strongly positive anti-dsDNA levels and disease activity were all associated with pulmonary abnormalities in HRCT scans. In contrast, neither LN nor SLE disease duration were associated with the development of the pulmonary abnormalities. In addition, there was no relationship between chest symptoms and abnormal HRCT findings (Table 5).

DISCUSSION

In the present study, we have determined the prevalence of pulmonary manifestations in SLE to be 33.2% in the Western region of KSA, with pleural effusion identified as the most common abnormality. In addition, we observed significant associations between the development of pulmonary manifestations in SLE and disease activity, hypocomplementemia and high levels of anti-dsDNA.

Our results are in accordance with previous findings by Swigris *et al.*,[20] who reported that the entire pulmonary system or any of its compartments can be independently or simultaneously affected in SLE, including airways, lung parenchyma, vasculature, pleura and respiratory musculature. However, in the literature, the most common pulmonary involvement appears to be pleural effusion, which affects 50% of patients during their lifetime and 93% upon autopsy.[21] Moreover, 50% of the patients display bilateral presentation. Indeed, these previous findings are almost identical to observations from our study, in which 49% of patients had pleural effusion (60% bilateral).

The prevalence of pneumonia was higher in our study than in a previously analysed French cohort (36% vs 28%, respectively).[22] However, in both studies, pneumonia was found to be associated with active disease. Therefore, due to the high incidence of pneumonia in SLE patients, it might be appropriate to rule out this complication in those presenting with chest infiltrate prior to delivering aggressive immunosuppressive therapy. Moreover, lupus pneumonitis (LP) showed a higher incidence (20%) in the present study compared with previous investigations, which

Table 2 Summary of clinical, X-ray and HRCT findings in SLE patients showing pulmonary manifestation ($n = 61$)

Investigated parameters	% Patients†
Symptoms	72
Pleuritic chest pain	50
Dyspnoea	49
Cough	34
Fever	29
Haemoptysis	5
Musculoskeletal chest pain	2
Chest X-ray	77
Pleural effusion	55
Consolidation	34
Atelectasis	26
Bronchial wall thickening	17
Pulmonary infiltrate	17
Bronchiactasis	6
Elevation of the hemidiaphragm	6
Pulmonary cavity	2
Pulmonary oedema	2
Pleural thickening	2
HRCT	85
Pleural effusion	58
Air space consolidation	42
Atelectasis	42
Lymphadenopathy	23
Interlobular septal thickening	19
Ground glass opacity	17
Bronchiectasis	12

Among SLE patients with pulmonary manifestation ($n = 61$), the percentage of subjects presenting various clinical, X-ray and HRCT findings are shown.

† Multiple abnormalities were present in each patient.

HRCT, high-resolution computed tomography; SLE, systemic lupus erythematosus.

Table 3 Final clinical diagnosis in SLE patients ($n = 61$) based on clinical, HRCT and echocardiography results

Final clinical diagnosis	% Patients†
Pleural effusion	49
Pneumonia	36
Pleuritic chest pain	29
Pulmonary hypertension	23
Lupus pneumonitis	20
Bronchiectasis	11
Tuberculosis	8
Pulmonary embolism	7
Adult respiratory distress syndrome	4
Cryptogenic organizing pneumonia	2
Diffuse alveolar haemorrhage	2
Pulmonary oedema	2

Among the 61 SLE patients showing pulmonary involvement, final diagnoses and diagnosis criteria are presented. The percentage of patients receiving each diagnosis is also indicated.

† Multiple abnormalities were present in each patient.

HRCT, high-resolution computed tomography; SLE, systemic lupus erythematosus.

reported rates ranging from 1% to 12%, mostly occurring 5 years after SLE onset.[23] Thus, in our patients, LP could be related to longer disease duration or, to a lesser extent, a high incidence of non-compliance with therapy. In this regard, implementing patient education programmes in Saudi Arabia aimed at promoting earlier detection/management of SLE, and therapeutic compliance could be beneficial.

DAH is a rare SLE complication and is often fatal. In fact, a study from the Cleveland Clinic reported that while the frequency of DAH was found to range from 2% to 5.4%, it resulted in a mortality rate of 92%.[24] Indeed, in the present study, we identified one patient who died from this severe complication. In addition, another less-severe pulmonary manifestation is bronchiectasis, which was identified in 21% of our SLE patients by HRCT.[2] Although this complication typically presents with recurrent exacerbations that require antibiotic therapy, it appears to be clinically irrelevant in SLE.[20,25] Here, we observed a lower frequency of bronchiectasis (12%) than previously reported, with only 3% requiring hospitalization and antibiotic treatment.

It is known that the incidence of pulmonary tuberculosis (TB) in SLE patients is higher than that of the general population. In this regard, a Spanish study found that the incidence of TB was sixfold higher in SLE patients compared with the general population,[26] whereas in China a 5–15-fold higher risk was reported.[27,28] Thus, it seems that the rate of TB in SLE patients might depend heavily on the local incidence of TB and/or the use of immunosuppressive therapies.[27] For instance, in India a 10–60-fold higher risk was reported for SLE patients when compared with the general population, but India also displays a very high TB burden (up to 40% with latent infection).[29–31] Notably, our investigation indicated a prevalence of 8% in SLE patients in KSA, and this finding is also likely to be linked with the incidence of pulmonary TB observed in the Saudi population, which has been reported to be up to 10%.[32] However, it must be noted that the rate of TB in Saudi Arabia is highly dependent on the population being analysed, as immigrants to KSA make up a large proportion of the TB patients.[33] Therefore, efforts aimed at reducing the incidence of TB in KSA should diminish the exposure of SLE patients to TB, improving their overall prognosis.

There are conflicting reports regarding the relationship between pulmonary involvement on HRCT scans and duration or activity of SLE.[12] In 1995, Bankier *et al.*[11] evaluated HRCT chest scans in a prospective study of 48 patients with no pulmonary symptoms, observing abnormalities in 38% of the participants. A significant correlation between the extent of pulmonary involvement and disease duration was identified (mean: 2.4 years). Moreover, Fenlon *et al.*[2] studied 34 SLE patients with no pulmonary symptoms, of which 70% displayed abnormal HRCT scans. However, they found no association between HRCT results and disease activity, findings that were confirmed by Sant *et al.*[34] Despite these previous results, pulmonary involvement was significantly associated with disease activity, hypocomplementemia and high anti-dsDNA levels in our study population (all $P < 0.001$).[12] It is

Table 4 Risk factors associated with abnormal HRCT findings in SLE patients showing abnormal HRCT scans ($n = 52$)

Variable	*n*	Abnormal HRCT scan (%)	χ2	*P*-value	RR	95% CI
Disease activity						
Active	87	46	25.4	<0.001*	3.7	(2.08–6.62)
Not active	97	12				
Complement						
Low C3	57	56	31.6	<0.001*	3.56	(2.24–5.66)
Low C4	87	45	22.3	<0.001*	3.34	(1.91–5.83)
Low C3 and C4	50	58	29.9	<0.001*	3.38	(2.17–5.24)
Anti-dsDNA						
Positive	34	35	1.08	0.31	1.32	(0.78–2.24)
Strongly positive	46	52	17.299	<0.001*	2.57	(1.67–3.95)

The percent of patients showing abnormal HRCT scans from each predictor subset are indicated. The data were also analysed using the chi-square (χ^2) test.

* Significant positive association: $P < 0.05$.

CI, confidence interval; dsDNA, double-stranded DNA; HRCT, high-resolution computed tomography; RR, relative risk; SLE, systemic lupus erythematosus.

Table 5 Pulmonary abnormalities in 61 SLE patients and relation to clinical and biochemical variables

Pulmonary abnormalities in SLE patients	*n*†	Active disease (%)	Low C3 (%)	Low C4 (%)	Strongly positive anti-dsDNA (%)
Pleural effusion	30	87*	73*	87*	57*
Pneumonia	22	86*	63*	72*	50*
Atelectasis	21	81	62	81*	58
Lymphadenopathy	12	66	50	75	42
Septal thickening	11	55	33	58	25
Ground glass opacity	9	44*	33	55	22
Bronchiectasis	7	71	57	57	43
Pulmonary hypertension by echo	14	75*	36	57	43

Among the 61 SLE patients showing pulmonary involvement, the number of patients presenting each of the pulmonary abnormalities is indicated. Within each pulmonary abnormality group, the per cent of patients displaying the indicated clinical and biochemical variables is shown. relation to variables.

* Significant positive association: $P < 0.05$.

† Multiple abnormalities were present in each patient.

SLE, systemic lupus erythematosus; dsDNA, double-stranded DNA.

possible that this difference might be attributed to the use of the SLEDAI score in our patients, which was not used in previous studies.

LN is a serious complication of SLE that occurs in more than 60% of patients.[3–6] In our study, LN was associated with a higher incidence of atelectasis, which could be related to increased risk of infection in the form of pneumonia or bronchitis in patients with LN. Similar findings were demonstrated in a cohort of 470 British patients with SLE, of which 15% had pneumonia requiring hospitalization.[35] The mortality rate in SLE patients is three times higher than in the general population, which can be related to either the disease itself or treatment complications.[36] However, a recent study of 9547 SLE patients has indicated that the mortality rate has dropped from 12.6% to 3.46%.[37] Nevertheless, the mortality rate identified in our study was up to 12% and was found to be more significant in those having over 50 years of age ($P < 0.001$), female gender ($P < 0.0001$) or DAH ($P = 0.02$). Therefore, further analysis of unique factors that might contribute to higher mortality in SLE patients in Saudi Arabia is warranted and could lead to improved overall clinical management of SLE.

This investigation presented a few limitations. Indeed, being a retrospective study, it is possible that some patient information could have been missed despite careful efforts by the authors to record all pertinent details. In this regard, it must also be noted that some data related to specific diagnoses were collected from patients' files. Therefore, we cannot rule out diagnostic errors for closely related conditions (e.g., pneumonia vs LP). In addition, the fact that data were collected from a single centre may have introduced bias. Moreover, although the sample size was adequate in the present study, this cohort likely consisted of subjects with genetically diverse backgrounds (i.e. over half non-Saudi). Thus, further research is warranted to prospectively evaluate

pulmonary manifestations in SLE using increased numbers of patients and a multicentre design.

In conclusion, this is the first study to assess the frequency of pulmonary involvement and disease activity in SLE using HRCT scans and SLEDAI-2K scores. Furthermore, this study represents the first investigation in KSA aimed at identifying specific risk factors that predict pulmonary manifestations in SLE, which is important considering that genetic background and environmental factors are widely known to differentially influence disease states. Pulmonary involvement was found to be frequent in SLE patients, with the most common abnormality being pleural effusion. Low complement levels, high levels of anti-dsDNA and disease activity were found to be significantly associated with abnormal HRCT findings. Also, the presence of pleural effusion, pneumonia and ground glass attenuation were significantly associated with disease activity ($P < 0.001$). Taken together, our findings have the potential to enhance preventive care in SLE patients both nationally and internationally.

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