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SYSTEMIC LUPUS ERYTHEMATOSUS;

PULMONARY MANIFESTATIONS, A CLINICAL STUDY AT A UNIVERSITY HOSPITAL, SAUDI ARABIA WITH SPECIAL REFERENCE TO HIGH RESOLUTION COMPUTED TOMOGRAPHY (HRCT) FINDINGS

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ABSTRACT: Systemic lupus erythematosus (SLE), is a multifactorial, complex etiological disorder, characterized by inflammation and involvement of multiple organ systems including lungs. **Objective:** 1-To evaluate whether high resolution computed tomography (HRCT) helps in the diagnosis of pulmonary manifestations of SLE. 2-To study the pattern and extent of lung involvement using HRCT. **Design:** A Prospective cross - sectional clinical study. **Period:** Four years, July 2012 to June 2016. **Setting:** King Khalid University Hospital (KKUH) King Saud University (KSU), Rheumatology division Department of Medicine. **Methods:** This study included 113 patients attending outpatients or admitted as inpatients having respiratory symptoms and diagnosed as SLE according to American College of Rheumatology (ACR) classification criteria. Chest X- ray, pulmonary function tests, and HRCT chest were done. Investigations to detect other organ involvement were done. Pregnant females and patients having other connective tissue or occupational diseases were excluded. **Results:** Of the total 113 patients 102 were female and 11 males. Age of patients was 37.1 ±13.0 years. The HRCT abnormalities were pleural effusion, pleural thickening, atelectasis, ground glass opacities including non-specific interstitial pneumonitis (NSIP) and usual interstitial pneumonitis (UIP), pulmonary arterial hypertension, pulmonary embolism and hilar lymphadenopathy. **Conclusion:** Various pulmonary manifestations are present in a significant number of symptomatic SLE patients and a variety of HRCT patterns can be seen to diagnose and treat them.

Key words: High Resolution Computed Tomography, Pulmonary, Systemic lupus Erythematosus,

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INTRODUCTION

Systemic lupus erythematosus (SLE), is a disease with complex, multifactorial etiology and effects most of the body organs. In Saudi Arabia its prevalence is 19.28 per 100,000 population.[1] Women of child bearing age are predominantly affected. Pulmonary involvement was first described in a 24 years old lady with bilateral lungs consolidation and haemoptysis associated with skin rash, lupus nephritis and anemia.[2] Lungs and pleura may be directly effected or indirectly due to other organ involvement. Pleural manifestations are reported in 30 % to 60 % of SLE patients including pleural effusion. Other lung complications include ground glass opacities, pneumonitis, pulmonary haemorrhage, bronchiolitis obliterans, atelectasis, pulmonary vascular disease, pulmonary hypertension, pulmonary embolism, especially when associated with anti- phospholipid syndrome (APS). Diaphragmatic elevation due to shrinking lung syndrome.[3]

At present thoracic radiological studies, especially HRCT recognize in conjunction with clinical assessment, various diagnostic patterns of SLE lung disease. With HRCT, delineation of the lung parenchyma down to the secondary lobule level is possible.[4] The purpose of this study was to evaluate HRCT chest, individual and combination of various patterns of findings in SLE patients.

PATIENTS AND METHODS

In this prospective study, we evaluated the

findings of HRCT chest in 113 patients presenting with respiratory symptoms like cough, shortness of breath or haemoptysis, seen in clinics or admitted in King Khalid University Hospital during four year period 2012 to 2016. Patients with other causes of lung disease like occupational lung disease, cardiac lung involvement, and pregnant ladies were excluded from the study.

Systemic lupus erythematosus was defined by the 1997 revised ACR classification criteria. A detailed history taking, physical examination and laboratory tests including immunological work up, chest x -rays and pulmonary function tests were done. Study was approved by internal review board (IRB).

High resolution computed tomography (HRCT) were performed on CT General Electric prospered VER 20.4.00 with scan protocols, supine scan routine, 3-5 section were performed on the lung apices, mid as well as lower zones and additional scans in the area of focal abnormalities as seen in the plain x- ray, 120Kv and 200 Ma, slice thickness I mm; on performing HRCT of the lung to detect diffuse parenchymal lesions or interstitial disease. Signs of Pulmonary nodules, linear opacities, increased lung density (Ground glass opacities or Consolidation), Honey combing, lymphadenopathy, pleural thickening and pleural effusion were evaluated.

Statistical analysis: Descriptive statistics (means, standard deviation, and percentages) were used to describe the quantitative and categorical study variables. Chi- square statistics and the Fisher's exact test were used for categorical data. A two-sided $p<0.05$ was considered statistically significant. SPSS version 18 (SPSS inc. Chicago, IL, USA) was used for all analysis.

RESULTS

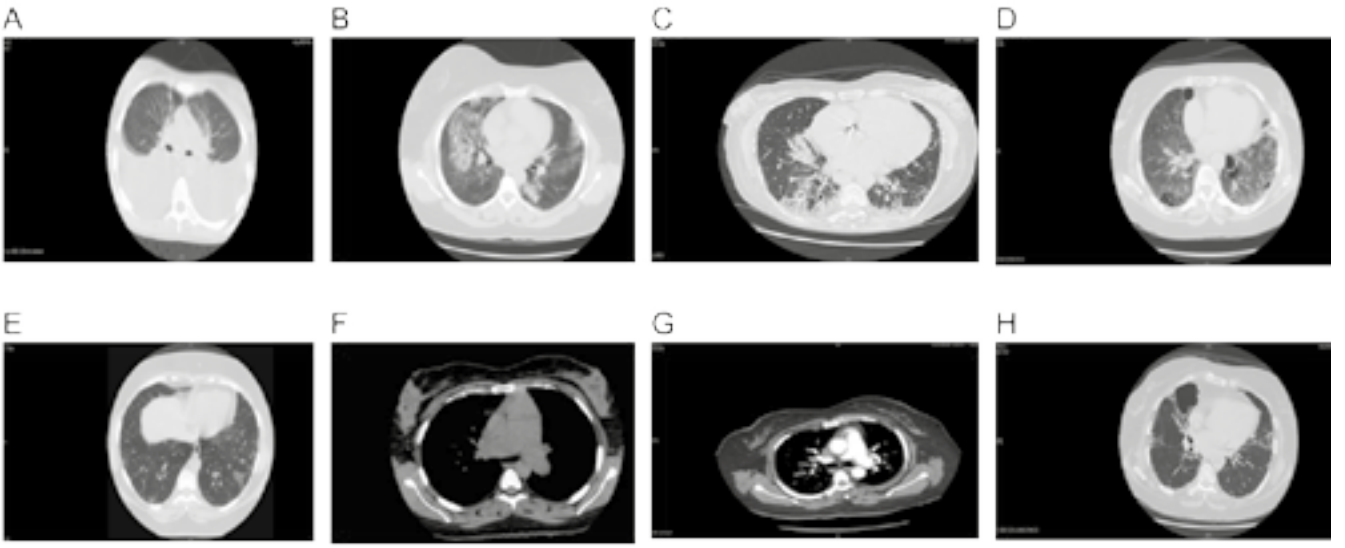
One hundred and thirteen (113) patients were included in this study, the mean age at diagnosis was 38±13.0 years predominantly females 90.3 %. Disease duration was 100.9 ± 98.5 months. All were antinuclear antibodies (ANA) positive, 93 (82.3%) double stranded DNA (ds DNA) positive. However anti- Smith antibodies (anti-Sm) was positive in 43 (31.1%) patients. Other demographic and serological features are shown in (Table-I).

	N=113
Age, yr	37.1±13.0
Female	102 (90.3)
Smoker	10 (8.8)
Disease duration, months	100.9±98.5
Serology	
ANA Positive	113(100)
DsDNA positive	93 (82.3)
Anti-Sm	43 (38.1)
AcL Ab	36 (31.9)
Lac	33 (29.2)
B2GP1	29 (25.7)
SSA	39 (34.5)
SSB	38 (33.6)
Rheumatoid factor	38 (33.6)
CCP	9 (8.0)
Histone	6 (5.3)
RNP	19 (16.8)
C3	79 (69.9)
C4	65 (57.5)
CRP	76 (67.3)
Anti-Jo1	9 (8.0)

Table-I. Demographic and serological characteristics of study subjects
Data presented as n (%) or mean±SD

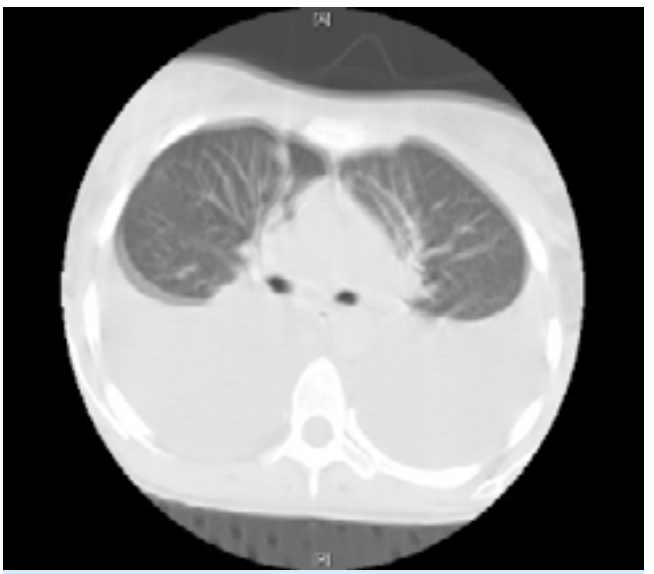
High Resolution Computed Tomograhic (HRCT) Findings Multiple features were present in most of the patients. Most common high resolution computed tomographic finding was Pleural effusion in 56 (49.6%) (Figure panel A) showing massive bilateral pleural effusion. Atelectasis and pleural thickening in 39 (34.5 %). Most serious complications as pulmonary hemorrhage (Figure panel B) in 16 (14.2%). Ground Glass opacities (GGO) like nonspecific interstitial pneumonitis (NSIP Figure Panel C), in 34 (30.1%), usual interstitial pneumonitis (UIP Figure Panel D), in 16 (14.2%), Organizing pneumonia (OP Figure panel E), 17 (15.0%), pulmonary arterial hypertension (PAH Figure panel F) in 23 (20.4%) and pulmonary embolism (PE Figure panel G) in 31 (27.4%) of patients respectively. Other findings on HRCT like hilar lymphadenopathy, honeycombing, cystic, fibrotic changes (Figure panel H), and others are summarized in Table-II.

Figure showing various patterns of Images



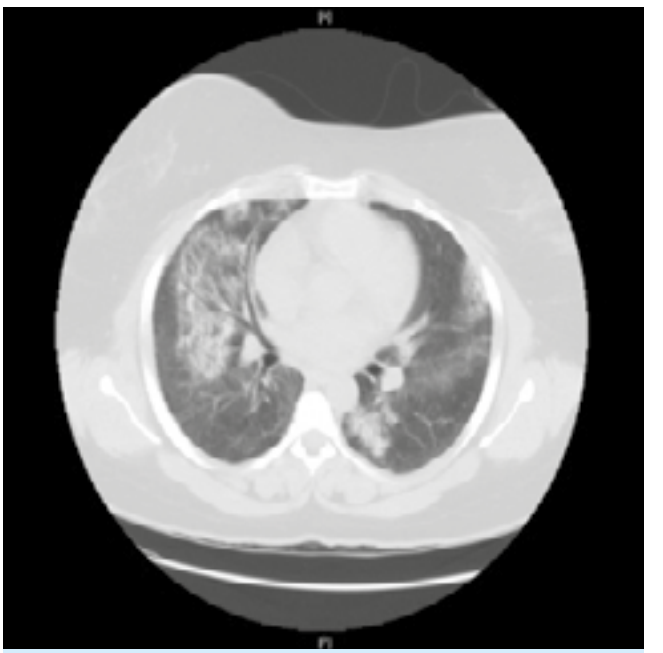
A. Bilateral massive pleural effusion.
B. Pulmonary hemorrhage.
C. Nonspecific interstitial pneumonitis (NSIP).
D. Usual interstitial pneumonitis (UIP).
E. Organizing pneumonia (OP).
F. Pulmonary arterial hypertension (PAH)
G. Bilateral pulmonary embolism (PE).
H. Fibrotic, pleural thickening and cystic changes.

Each image on separate page is shown below



Panel A. 19 Years old lady having SLE presented with shortness of breath. HRCT showing bilateral massive pleural effusion.

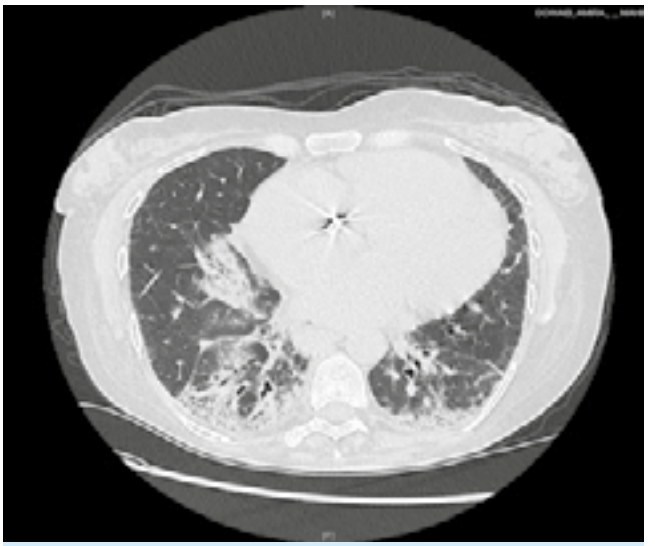
Anti-Phospholipid Syndrome (APS) is a hype coagulable state, correlation between pulmonary embolism were significantly high in SLE patients who were anti-Cardiolipin antibodies, lupus anticoagulant (LAC) and Beta2 glycoprotein 1 (B2GP1) anti -bodies positive (Table-III), with significant odds ratio (OR), 95% confidence interval (CI), and p-value <0.0001.



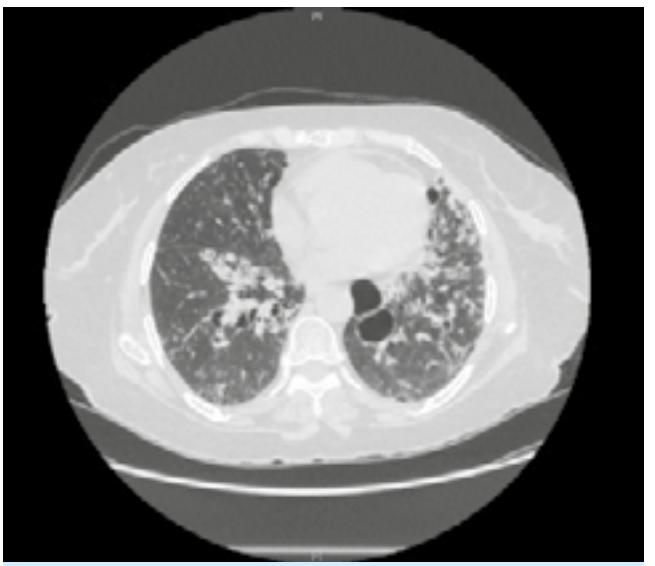
Panel B. 38 years old lady known case of SLE, presented with short ness of breath, fever, haemoptysis and chest pain. HRCT showing bilateral infiltrates with pacification, suggestive of pulmonary haemorrhage

DISCUSSION

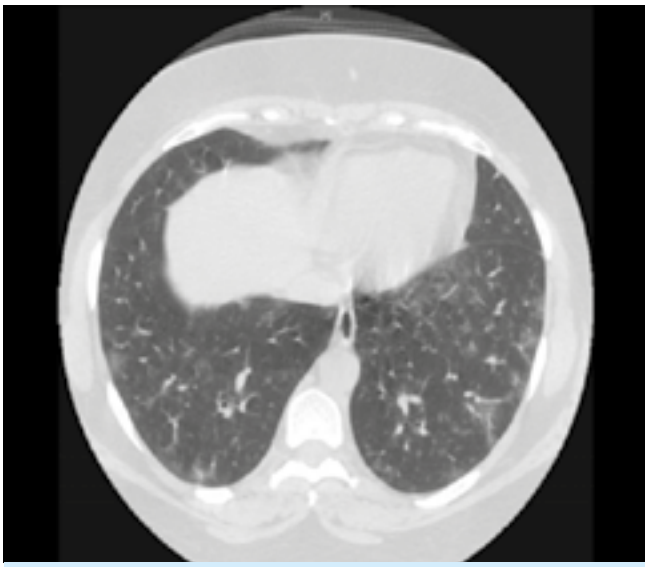
In this study all SLE patients, having repiratory symptoms like shortness of breath, cough, with or without sputum, chest pain, fever, hemoptysis



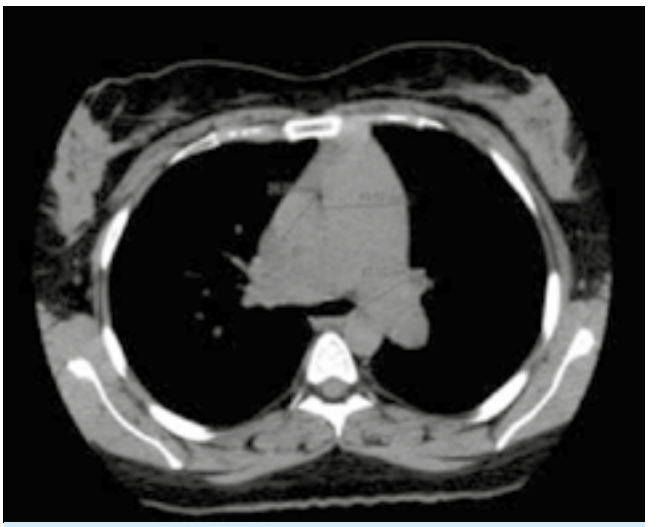
Panel C. 53 old lady known case of SLE, presenetd with dysnoea and basal crackles. Predominant abnormalities of diffuse ground glass appearance. Peripheraly based reticular opacities suggestive of NSIP



Panel D. 65 years old lady presented with cough and shortness of breath. Honeycomb formation, traction bronchiectasis and ground glass opacities predominantly seen in both lower lobes in addition to some cystic changes consistent with the diagnosis of UIP.



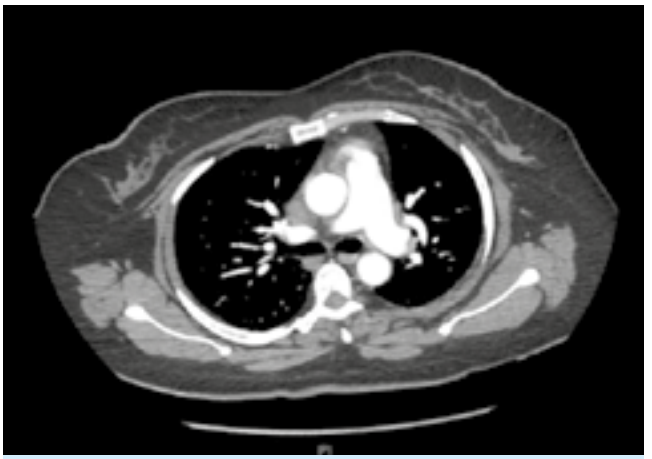
Panel E. 48 Years old lady known patient of SLE presented with dry cough There is evidence of fluffy ill defined nodular airspace consolidation multi focal in nature seen in both lung fields. Predominantly in middle and lower lobes with peribronchial and subpleural distribution, picture suggestive of organizing pneumonia(OP).



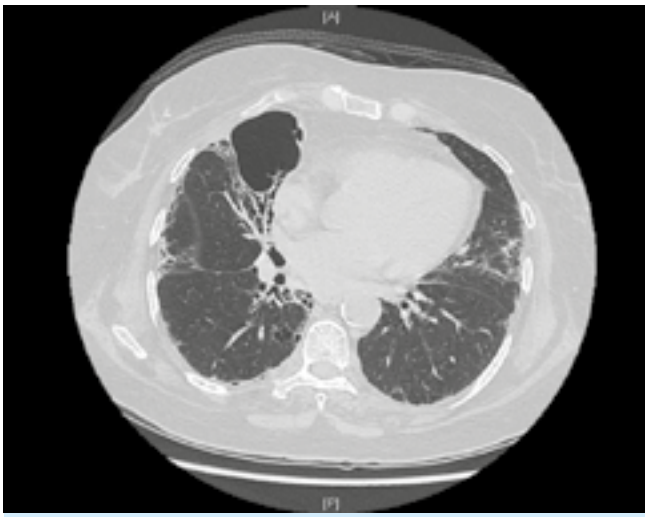
Panel F. 28 years old lady known patient of SLE, showing markedly enlarged pulmonary arterial trunk suggesting underlying severe pulmonary arterial hypertension. Cardiomegaly noted.

and others were included. Lung involvement had been investigated in SLE patients previously using various techniques. Pleural, parenchymal, vascular and interstitial abnormalities correlate with disease activity and is reported in various studies.[5,6]

HRCT is a sensitive and reasonably specific method to diagnose lung involvement in SLE. But unfortunately about all available studies using this tool, were retrospective and all patients were not having only SLE. Rather having other associations like scleroderma, rheumatoid arthritis, polymyositis and infections.[7,8,9]



Panel G. Filling defects are seen in lobar branch and segmental/ sub segmental branches of the right lower lobe suggestive of pulmonary embolism. The pulmonary trunk diameter is also prominent reaching up to 3.6cm, suggestive of pulmonary arterial hypertension.



Panel H. 65 years old lady known case of SLE presented with long standing cough and shortness of breath. HRCT showing Bullae in right middle lobe with pleural thickening and fibrotic changes.

HRCT findings	N=113
GGO-NSIP	34 (30.1)
GGO-UIP	16 (14.2)
Honeycombing	31 (27.4)
Acute pneumonitis	13 (11.5)
Organizing pneumonia	17 (15.0)
Pleural effusion	56 (49.6)
Pleural thickening	39 (34.5)
Infection	14 (12.4)
Atelectasis	39 (34.5)
Shrinking lung	15 (13.3)
Pulmonary hemorrhage	16 (14.2)
Enlarged PA	23 (20.4)
Pulmonary embolism	31 (27.4)
Hilar lymphadenopathy	24 (21.2)

Table-II. HRCT scan findings
Data presented as n (%)

	OR	95% CI	p-value
DsDNA	8.156	1.039 – 64.052	0.020
Anti-Sm	3.694	1.553 – 8.788	0.002
AcL Ab	11.524	4.384 – 30.292	<0.0001
LAc	20.125	7.097 – 57.065	<0.0001
B2GP1	15.778	5.643 – 44.114	<0.0001
SSA	1.309	0.551 – 3.108	0.542
SSB	1.466	0.611 – 3.516	0.390
Rheumatoid factor	0.783	0.318 – 1.932	0.595
CCP	1.442	0.336 – 6.185	0.696
Histone	1.188	0.180 – 7.843	1.000
RNP	1.905	0.673 – 5.390	0.220
C3	1.110	0.432 – 2.849	0.829
C4	0.872	0.373 – 2.039	0.751
CRP	1.061	0.426 – 2.642	0.899
Anti-Jo1	0.824	0.161 – 4.221	1.000

Table-III. Correlation between serology and finding of pulmonary embolism on HRCT among patients with SLE
Data presented as OR and 95% CI. P-value 0.05 considered as significant.

Bilateral pleural effusion is present in about 56 % of patients in our study which correlates with other studies in which it is reported in 40% to 57 % of patients with SLE.[10] However in these studies it is small to moderate, whereas in our study as the patients selected were symptomatic, even massive pleural effusion was present in some patients (Figure panel A).

In some autopsy series it was present in 98% of patients.[11] Although an isolated pleural effusion is a nonspecific radiographic finding, its presence may suggest SLE when clinical picture suggestive of an underlying autoimmune disease. Computed tomographic or ultrasound guided thoracocentesis may aid in differentiating between pleural effusion from SLE and pleural effusion from other causes like infections leading

to sepsis requiring intensive care especially when prompt treatment with antibiotics or with steroids and immunosuppressive drugs is required.[12]

Acute lupus pneumonitis and pulmonary hemorrhage are important and serious complications of SLE characterized radiologically by diffuse or patchy consolidation and ground glass appearance is present in 14.2 % of SLE patients, which is higher in contrast to other studies where frequency ranges from 2 % to 5.4 %.[13] It might be due to inclusion of studied patients with respiratory symptoms while other studies selected both symptomatic and asymptomatic patients.

Several HRCT findings SLE associated interstitial lung disease (ILD) are seen. Fibrotic or non-fibrotic appearance of NSIP (30.1%) is more common than UIP (14.2%) or OP (15.0 %) with decreased lung attenuation in SLE in contrast to Rheumatoid arthritis, where UIP is more common.[14] SLE associated NSIP shows minimal response to treatment. In one study of symptomatic SLE patients HRCT results showed ILD in 33 % of cases[15] while in some other studies real incidence of ILD is still not well defined.[16,17]

Pulmonary thromboembolism and pulmonary arterial hypertension may be present in isolated SLE patients but SLE when associated with APS, these complications and diaphragmatic dysfunction leading to shrinking lung syndrome rise significantly (SLE alone 5 % versus SLE and APS 14.8 %).[18,19] However all these cases were having no respiratory symptoms. In our study of symptomatic SLE patients with pulmonary embolism and pulmonary arterial hypertension also had significant correlation with ACL antibodies, lupus anti-coagulant (LAC) and B2GP1 anibodies, odds ratio (OR), confidence interval (CI), shown in Table-III, with p-value <0.0001. A special care for primary APS or associated with SLE patients having complications like pulmonary embolism, deep venous thrombosis, thromboembolic cerebrovascular injuries, females having history of recurrent abortions, using long term anticoagulation is needed.[20]

Currently proven management of these patients is antithrombotic therapy such as heparin and warfarin which is not effective in all patients and in near future new approaches are warranted.

The present study has several limitations such as pathologic confirmation was not available.

Correlation between HRCT findings and histopathologic findings would clarify the pathogenesis of the pulmonary manifestations in SLE with and without APS. Additional prospective studies with large number of patients may be necessary for exclusive results.

CONCLUSION

Multi slice pulmonary HRCT with vascular reconstruction, and multiplanar capability is important and useful tool in demonstrating the thoracic manifestations of systemic lupus erythematosus in symptomatic and even asymptomatic patients. Multiple patterns of lung involvement from pleural effusion to interstitial lung disease (ILD) and parenchymal lung abnormalities can be detected.

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2	Dr. Khalid Parvez	Fascilitate, Data collection, Analysis and Critically Revising the draft work.	
3	Dr. Faisal Naseeb	Fascilitate, Data collection, Analysis and Critically Revising the draft work.	
4	Dr. Umair Afzal	Fascilitate, Data collection, Analysis and Critically Revising the draft work.	
5	Dr. Bashiruddin	Review of all HRCTs and interpretation of findings	
6	Dr. Joseph Hope Cal	Review of all HRCTs and interpretation of findings. Fascilitate statistical analysis of data .	
7	Dr. Sajjad Hussain	Review of all HRCTs and interpretation of radiological findings.	