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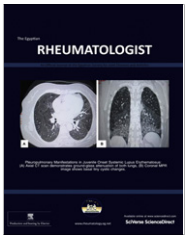

ORIGINAL ARTICLE

Pleuropulmonary manifestations in juvenile onset systemic lupus erythematosus: Assessment by pulmonary function tests and multidetector computed tomography

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Abstract *Introduction:* Pulmonary involvement is a common finding in adults with systemic lupus erythematosus (SLE) also it is one of the most important systems that can be affected in Juvenile onset SLE (JOSLE). Early detection and evaluation of the extent and severity of pulmonary involvement are quite critical for disease prognosis and patients management.

Aim of the work: To determine the frequency and type of pleuropulmonary involvement in JOSLE using pulmonary function tests (PFTs) and multidetector CT (MDCT).

Patients and methods: Twenty five patients with JOSLE were evaluated for the detection of pleuropulmonary affection in them. The evaluation included clinical, functional & radiological

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examination using MDCT as a recent & accurate modality for chest imaging. Based on clinical evaluation, patients were divided into two groups; group A (No = 16) and group B (No = 9), consisting of those asymptomatic and symptomatic as regard pleuropulmonary symptoms, respectively.

Results: This study revealed that PFT abnormalities were detected in 60% of all studied JOSLE patients while MDCT abnormalities were detected in 52% of them. 37.5% of the asymptomatic patients had abnormal PFTs & 31.25% of them had abnormal findings on MDCT. There was statistically significant difference between patients groups regarding SLEDAI, percentages of abnormal PFTs, abnormalities in plain X-ray and MDCT. With the exception of forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25-75\%}$), the study revealed statistically significant lower values of mean ± SD of all measured PFTs in group B compared to group A. The most frequent MDCT findings in all studied patients were pleural effusion and pleural thickening in 16% of all findings, also ground glass opacities found in 16% of all abnormalities suggesting early interstitial lung disease.

Conclusion: Clinical assessment and PFTs revealed a significant percentage of pleuropulmonary involvement in JOSLE patients. MDCT can be helpful in diagnosing the pulmonary involvement in asymptomatic JOSLE patients with normal chest X-ray and uncertain PFT.

1. Introduction

Systemic lupus erythematosus (SLE) is a rare complex autoimmune disease with a multisystem involvement [1]. It characterized by inflammatory changes in connective tissues, blood vessels, and serosal surfaces [2]. SLE may affect all components of the respiratory system; it can affect the pleura, lung, and respiratory muscles, all contributing to respiratory dysfunction [3].

Involvement of the respiratory system in SLE is relatively common; between 40% and 57% of patients with SLE may have symptoms of dyspnea and poor exercise tolerance [4]. These symptoms may arise from primary pulmonary dysfunction, a complication secondary to infection, or from a disease process in another system as renal failure leading to pulmonary edema [4]. The pleuropulmonary manifestations of SLE range in severity from the minor pleuritic pain of serositis to the life threatening consequences of pulmonary haemorrhage. Many of the abnormalities have non-specific presentations and require extensive work up to determine the aetiologies [5].

Finding the true prevalence of lung involvement with SLE is complicated by the high rates of pulmonary infections [6]. Pleuritis occurs in 17–60% of patients at some point in the course of the disease [7]. Lung involvement occurring in 80% of SLE patients at autopsy and chart review from past reports is now thought to be largely a result of infection and not directly SLE-induced [8].

Although pulmonary involvement is relatively frequent in adult patients; it has been rarely reported in children with SLE. It may be an initial and/or life-threatening complication of jeuvenile SLE [9,10], but neither clinical findings nor roentgenogram were specific [11].

The most commonly used noninvasive methods for the study of interstitial lung disease are pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT) [12]. However, different HRCT series have demonstrated a higher rate of ILD features (about one third of SLE patients), suggesting that subclinical lung disease is common [13].

The aim of this study was to determine the frequency and type of pleuropulmonary involvement in juvenile onset SLE (JOSLE) using PFTs and multidetector CT (MDCT).

2. Patients and methods

2.1. Patients

Twenty five patients with juvenile onset systemic lupus erythematosus (JOSLE) were included in this study. All fulfilled the 1997 updated American College of Rheumatology criteria for SLE [14]. All the patients had the disease at or before the age of 16 years. However at inclusion in the study, their ages ranged from (10–18 years) and the disease duration ranged from (3.3–8.4 years).

They were recruited from inpatient and outpatient clinics of Rheumatology & Rehabilitation, Chest, and Pediatric departments of Zagazig University Hospitals from October 2008 to August 2010. Patients were unable to undergo CT technique and those with pulmonary manifestations secondary to advanced cardiac disease or renal failure were excluded from the study. All patients received prednisone; 13 were taking azathioprine, 6 patients were receiving cyclophosphamide and seven were receiving hydroxychloroquine. An informed written consent was obtained from patients' guardians.

All patients were subjected to full assessment including history taking with stress on any symptoms of pleuropulmonary involvement as cough, expectoration, chest pain and wheeze, dyspnea and hemoptysis. Clinical examination was done with stress on local chest examination. Based on pleuropulmonary manifestations, patients were divided into two groups; group A (No = 16) and group B (No = 9), consisting of those asymptomatic and symptomatic patients respectively. Assessment of disease activity was done through SLE Disease Activity Index (SLEDAI) described by Bombardier et al. [15].

2.2. Pulmonary function tests

They were performed using (ZAN 100 Flow Handy II) pulmonary function apparatus. Pulmonary function testing was done according to Grippi and Tino [16]. Observed values were compared with those predicted for age, sex, and height for each individual.

The following parameters were assessed; forced vital capacity (FVC) and FVC% of predicted. Forced expiratory volume

in 1 s as FEV_1 (liter/min) and FEV_1% of predicted. Then FEV_1/FVC was measured. Maximum voluntary ventilation (MVV) (liter/min) & MVV% of predicated. Lastly forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25-75\%}$) was calculated.

Every parameter obtained by spirometric pulmonary function testing was expressed as a percentage (%) from predicted values, and depending on the results patients were categorized as follow; normal pulmonary functions 80-100% of predicated, obstructive if $FEV_1/FVC < 70\%$, restrictive if $FVC < 80\%$ of predicted and $FEV_1/FVC > 70\%$, combined obstructive and restrictive if $FVC < 80\%$ of predicted and $FEV_1/FVC < 70\%$ while small airway dysfunction when $FEF_{25-75\%}$ is less than 65% of predicted.

2.3. Arterial blood gases analysis (ABG)

Hypoxemia was diagnosed when PaO_2 is less than 70 mm Hg & Hypocarbia was diagnosed when $PaCO_2$ is less than 33 mm Hg [17].

2.4. Laboratory investigations

Routine laboratory tests: Complete blood count (CBC), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) was done with the indirect immunoflorescence technique using (Hep-2 substrate, IMMCO Diagnostics, Inc., USA, complement C3 (ProSpec-Dade Behring), anti-dsDNA Ab was also determined by EIA (the Binding Site, Birmingham, U.K).

Sputum & induced sputum examination by Gram stain and Ziehl Nielsen stain. Sputum induction was performed according to Mandell et al. [18] by inhalation of nebulized hypertonic saline (20 mL of 3% hypertonic saline for 30 min).

2.5. Radiological examination

2.5.1. Plain chest X-ray (CXR) Postero–anterior & lateral views.

2.5.2. Multidetector CT (MDCT) examination and evaluation

Chest scanning was done using 64 multidetectors CT scanner (GE lightspeed-VCT). All patients underwent cranio-caudal scanning in a supine position and at end-inspiratory suspension during a single breath hold, thin section scans were obtained. Acquisition parameters of tube voltage, tube current and slice thickness were 120 kV potential (kVp), 130–150 mAs and 1 mm respectively.

I.V. contrast was given to the clinically suspect case of having pulmonary embolism after laboratory estimation of blood urea and creatinine by injecting 100 mm of non ionic contrast using automatic injector at a rate of 3–4 ml/s and scanning began 20–25 s after start of injection.

The axial raw data acquired was transferred to the advantage windows work station (Advantage Window, Volume share 4) where multiplanar reconstruction (MPR) software was used to reconstruct coronal and sagittal images at mediastinal window setting.

Statistics: The collected data were statistically analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA), comparison between group means was done using student's *t*-test while chi-squared test was used for qualitative data. The significance level was considered at $P < 0.05$.

3. Results

3.1. Data of all studied juvenile onset SLE patients

This study included 25 patients with juvenile onset SLE, 21 females and 4 males, their mean age was 14.3 ± 3.13 years, ranged from 10 to 18 years and mean disease duration was 5.6 ± 1.62 years, ranged from 3.3 to 8.4 years. The mean of SLEDAI of all studied patients was 12.04 ± 4.18. Among all studied patients, frequency of chest symptoms presented in 9 patients (group B) in form of 7 symptoms of dyspnea, 5 of expectoration, another 4 symptoms with chest pain while cough and chest wheeze each was detected three times, and hemoptysis presented once only. Abnormal PFTs were detected in 15 (60%) of total JOSLE patients while abnormalities in plain X-ray were in 7 (28%) patients however 13 (52%) out of the 25 studied patients had abnormal MDCT findings.

3.2. Comparison between asymptomatic and symptomatic patients

Table 1 illustrates demographic, clinical and radiological features of both groups of patients. There was none significant difference between group A (asymptomatic) and group B (symptomatic) as regard age, sex and disease duration. However there was significant difference between both of them as regard mean of SLEDAI ($P < 0.001$), percentage of abnormal PFTs ($P = 0.002$) and abnormalities in plain X-ray ($P = 0.002$) and MDCT ($P < 0.01$). Abnormal MDCT detected in 31.25% of the asymptomatic patients.

Table 1 Demographic, clinical and radiological features of both groups of JOSLE patients.

Variables	Group A No. = 16	Group B No. = 9	*P*
Age (years) (mean ± SD)	14.0 ± 3.2	15.0 ± 2.91	0.45
Sex (female/male) No	13/3	8/1	1.0
Disease duration (years)	5.21 ± 1.4	6.3 ± 1.76	0.09
SLEDAI (mean ± SD)	10.62 ± 3.87	14.65 ± 3.74	0.02*
Abnormal PFTs (No,%)	6 (37.5%)	9 (100%)	0.002*
Abnormal plain X-ray (No,%)	1 (6.25%)	6 (66.6%)	0.002*
Abnormal MDCT (No,%)	5 (31.25%)	8 (88.9%)	0.01*

JOSLE = juvenile onset SLE, Group A = asymptomatic patients, Group B = symptomatic patients, SLEDAI = SLE Disease Activity Index.
* Significant when compared Group A versus B.

3.3. Interpretation of pulmonary function tests and ventilatory dysfunction among all studied patients

There was a statistically significant difference between symptomatic and asymptomatic patients regarding mean ± SD of FVC% ($P < 0.001$), FEV_1% ($P < 0.001$), FEV_1/FVC ($P < 0.01$) and MVV% of predicted values ($P < 0.01$) (Table 2.).

Table 3 shows that the most frequent ventilatory dysfunction in the studied JOSLE patients was restrictive pattern in 24% of them and the least was the small airway dysfunction in 8% of patients only. There was statistically significant difference between both patients' groups regarding total ventilatory dysfunction ($P = 0.02$).

3.4. Arterial blood gases analysis (ABG) in both patients' groups

All patients in group A (asymptomatic) had normal ABG while in group B (symptomatic), 2 patients only had normal ABG (22.2%), 3 patients had hypoxemia (33.35%) and four had hypocarbia (44.4%). There was highly significant difference between symptomatic and asymptomatic groups as regards results of ABG analysis ($P < 0.001$).

3.5. Findings of plain X-ray and multidetector CT among all studied patients

As regard abnormalities in plain X-ray, *one* patient only in groups A had pleural thickening, while 6 patients in groups B had abnormalities in the form of consoliditions, nodular areas and pleural effusion.

Multidetector CT examination of JOSLE patients with and without symptoms demonstrated in Table 4 where the most frequent MDCT findings in all studied patients were pleural effusion and pleural thickening in 16% of all findings, also ground glass opacities found in 16% of all abnormalities suggesting early interstitial lung disease. The least frequent findings were septal lines, honeycoombing and pulmonary artery filling defect, each was detected in 4% only (Figs. 1 and 2).

There was highly significant difference between symptomatic and asymptomatic patients regarding total abnormal CT findings being higher in symptomatic group, $P < 0.001$.

3.6. Final diagnosis of pleuropulmonary manifestations in JOSLE patients

It was found that the most frequent pleuropulmonary manifestations were pleural effusion and thickening in 16% of JOSLE patients, also interstitial lung disease was detected in 16% of studied patients. Community acquired pneumonia was detected in 12% of them. Bronchiectasis was found in one patient also acute pulmonary embolism was diagnosed in one patient only where anticardiolipin antibodies was positive in this patient. The overall frequency of pleuropulmonary affection (both symptomatic and asymptomatic) was 52% in all studied JOSLE patients.

4. Discussion

The pleuropulmonary complications associated with the collagen vascular diseases are frequent occurrences; all the elements of the respiratory system may be affected either separately or in combination [19]. Early detection and evaluation of the extent and severity of pulmonary involvement is quite critical for collagen vascular disease prognosis and patient management [20].

This study revealed a statistically significant difference between symptomatic & asymptomatic patients regarding SLE-

Table 2 Mean pulmonary function tests in both groups of JOSLE patients.

Pulmonary function tests	Group A No. = 16	Group B No. = 9	*P*
FVC%	77.6 ± 7.4	61.4 ± 9.4	0.001*
FEV_1%	76.9 ± 6.6	60.3 ± 8.6	0.001*
FEV_1/ FVC%	76.6 ± 8.3	65.5 ± 10.2	0.01*
$FEF_{25–75\%}$	75.5 ± 5.1	60.1 ± 14.1	0.12
MVV%	78.3 ± 12.4	66.7 ± 6.2	0.01*

JOSLE = juvenile onset SLE, Group A = asymptomatic patients, Group B = symptomatic patients, FVC% = Forced vital capacity of predicted, FEV_1% = Forced expiratory volume in 1 s of predicted, MVV% = Maximum voluntary ventilation of predicated, $FEF_{25–75\%}$ = forced expiratory flow at 25–75% of forced vital capacity. Group A = asymptomatic patients, Group B = symptomatic patients.
* Significant when compared Group A versus B.

Table 3 Frequency of ventilatory dysfunction among all studied patients.

Ventilator dysfunction	Group A No. = 16		Group B No. = 9		Total No. = 25		*P*
	No	%	No	%	No	%	
Obstructive dysfunction	1	6.25	2	22.2	3	12	0.5
Restrictive dysfunction	2	12.5	4	44.4	6	24	0.14
Combined obstructive and restrictive	2	12.5	2	22.2	4	16	0.60
Small airway dysfunction	1	6.25	1	11.1	2	8	1.0
Total	6	37.5	9	100	15	60	0.02*

Group A = asymptomatic patients, Group B = symptomatic patients.
* Significant when compared Group A versus B.

Table 4 Comparison between patients' groups as regards findings of multidetector CT.

Findings	Group A No.= 16		Group B No. = 9		Total No. = 25		*P*
	No	%	No	%	No	%	
Ground glass	1	6.25	3	33.3	4	16	0.11
Consolidation	0	0	3	33.3	3	12	0.03*
Nodular areas of high attenuation	0	0	2	22.2	2	8	0.12
Septal lines	1	6.25	0	0	1	4	0.36
No septal lines	1	6.25	2	22.2	3	12	0.53
Honeycoombing	0	0	1	11.1	1	4	0.36
Pleural effusion and thickening	2	12.5	2	22.2	4	16	0.60
Pulmonary artery filling defect	0	0	1	11.1	1	4	0.36

Group A = asymptomatic patients, Group B = symptomatic patients.
* Significant when compared Group A versus B.

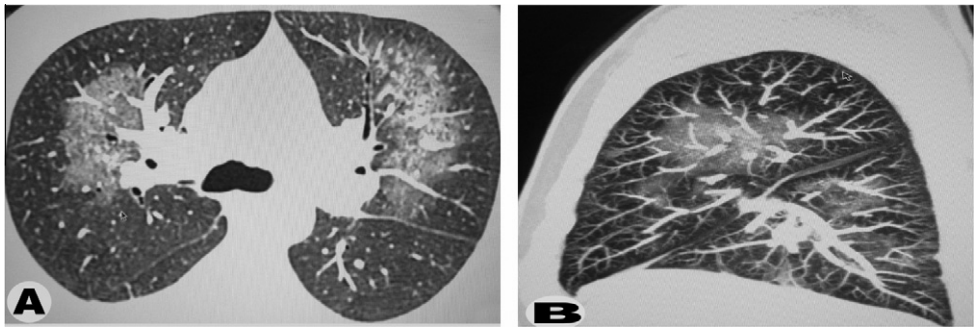

Figure 1 Female patient 16 years old suffered from dry cough and dyspnea, her PFTs shows a restrictive pattern, (A) axial CT scan shows reticular perihilar opacities in both lungs, (B) Sagittal MPR image shows the craniocaudal extent of the reticular opacities.

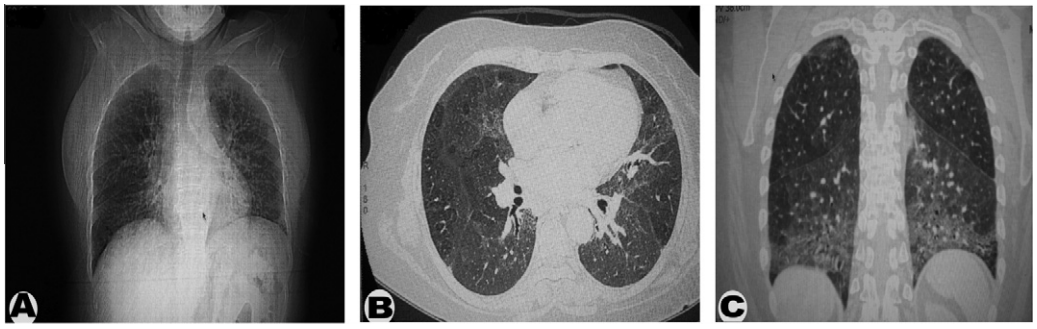

Figure 2 Female patient 14 years old suffered from chest pain and grade II dyspnea, her PFTs showed a restrictive pattern, (A) plain chest shows accentuated lung markings, (B) axial CT scan of demonstrates ground-glass attenuation of both lungs, (C) coronal MPR image shows basal tiny cystic changes.

DAI, frequency of abnormal PFTs and abnormal MDCT. In 2001, Al-Abbad et al. stated that various percentages of abnormal PFTs were recorded by several investigators; the variation could be attributed to different clinical data of the studied groups as regard age of onset, duration of illness and whether they have symptomatic chest problems [21].

Authors explained that, in SLE patients without clinical evidence of respiratory involvement, pulmonary function abnormalities have been reported in a number of studies of childhood onset SLE, which suggests the presence of subclinical disease [22]. They have found that PFT results were impaired in 37% of the patients & they concluded that lung function was moderately impaired while the frequency of pulmonary parenchymal involvement was low in patients with childhood-onset SLE. Grippi & Tino stated that ventilatory pulmonary function tests are effort dependent and those patients frequently have poor respiratory effort, anemia and physical unfitness [19]. Several studies [23,13] reported abnormal HRCT in asymptomatic SLE patients detected in 70% and 72% respectively of those patients. These studies concluded that screening of patients with connective tissue disease for pulmonary abnormalities is very important even in asymptomatic patients.

This study revealed that restrictive ventilatory dysfunction was much frequent than obstructive ventilatory dysfunction. The least observed ventilatory dysfunction was small airway

dysfunction in only 8% of patients. There was statistically significant difference between symptomatic and asymptomatic patients regarding overall pulmonary function abnormalities. This is in agreement with Kakati et al. [24] who observed that 28.95% of patients with SLE had abnormal PFT results and the most frequent ventilatory dysfunction was restrictive pattern in 26.3% of patients. Obstructive dysfunction in our patients can be attributed to the final diagnosis in those patients of bronchiectasis, acute pulmonary embolism and pneumonia with excessive airway secretions or bronchospasm. Small airway dysfunction can be attributed to early interstitial lung disease in those patients.

Restrictive dysfunction can be attributed to the final diagnosis of pleural effusion and pleural thickening and interstitial lung disease. Combined obstructive and restrictive dysfunction can also be a manifestation of ILD and bronchiectasis. Researchers explained that the restrictive pattern of pulmonary function can be attributed to diaphragmatic myopathy and this may occur in 25% of patients with SLE [19]. One study performed on 64 children with juvenile SLE for detection of pleuropulmonary manifestations in them. Infectious pneumonia was found in 38%, pleuritis in 33%, pulmonary vasculitis in 11% and acute lupus pneumonitis, chronic interstitial pneumonia and pulmonary embolism, each one in 5.5% of patients [25].

In the present study we used MDCT examination of the thorax as a rapid and accurate technique. MDCT scanners now use multiple beams, so that 4–64 images are created simultaneously and at a much faster rate than when a single detector is used [26].

The most frequent MDCT findings in the studied JOSLE patients were pleural effusion and pleural thickening in 16% of all findings and ground glass opacities suggestive of early interstitial lung disease in another 16%. Lalani et al. mentioned that pleural effusions are the most common manifestation of SLE in the respiratory system and are bilateral in approximately 50% of patients [4].

Evidence of pulmonary consolidation during MDCT examination of JOSLE patients was present in 12% of patients. This is compatible with the final diagnosis of community acquired pneumonia in the same patients under immunosuppression. Also, nodular areas of high attenuation in 8% of patients, septal lines in 4% and non septal lines in 12% of patients, all are suggestive of irreversible pulmonary fibrosis and may be sequel of infectious pneumonia or acute lupus pneumonitis. Cosgrove and Schwarz emphasized that infectious pneumonia represents the most common cause of pulmonary disease in SLE patients [19]. Researchers concluded that common HRCT findings are interstitial thickening or thickened interlobular septa, parenchymal bands and ground glass opacification and most of these features suggest ILD [24].

In the present study, honeycoombing was detected on mutidetector CT examination of JOSLE in 4%, this is compatible with the final diagnosis of bronchiectasis in the same patient. This is in agreement with Kakati et al. who reported bronchiectasis in 2.8% of SLE patients on HRCT thoracic examination [24].

One of the observed findings of JOSLE patients is pulmonary artery filling defect in 4% on multidetector CT examination. This is compatible with the final diagnosis of acute pulmonary embolism in the same patient. Acute pulmonary embolism was diagnosed on the basis of history of acute dyspnea together with the finding of tachypnea, hypoxemia and hypocarbia on ABG analysis; this was confirmed on MDCT examination with dye. One study stated that the occurrence of pulmonary thromboembolic disease correlates with the presence in the serum of antiphospholipid antibodies [19].

In conclusion clinical assessment and PFTs revealed a significant percentage of pleuropulmonary involvement in JOSLE patients. MDCT can be helpful in diagnosing the pulmonary involvement in asymptomatic JOSLE patients with normal chest X-ray and uncertain PFT. Assessment of diffusion capacity of carbon monoxide is recommended for further studying of pluropulmonary involvement in SLE. A wider study on a bigger number of patients may investigate the correlations between the detected abnormalities of PFTs and MDCT, and the disease manifestations and drugs used by the involved patients.

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