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Original article

High resolution computed tomography and pulmonary function tests in childhood systemic lupus erythematosus and juvenile rheumatoid arthritis

Background: *Alveolar and airway injury represent one of the most common features of rheumatological diseases and is believed to have a significant impact on the course of these diseases.*
Objective: *This work aimed at evaluating airway and alveolar involvement in children with systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA).*
Methods: *Thirty four children (21 with SLE and 13 with JRA) were assessed by pulmonary function tests (PFTs) namely spirometry and carbon monoxide diffusion capacity (DLCO) in comparison to 10 healthy controls, as well as by plain roentgenography and high resolution computed tomography (HRCT) of the chest.*
Results: *The studied patients had significantly lower mean PFT values as compared to controls. A restrictive pattern of PFTs was more common as it was detected in 62% of patients with SLE and 23% of those with JRA whereas an obstructive pattern was detected in 14% and 8% respectively. Significantly lower FEF $_{25-75\%}$ values were detected in symptomatic patients. Low values of DLCO (less than 80% of predicted) were recorded in 60% of the studied patients. Chest HRCT was abnormal in 68% of studied patients. In SLE, ground glass appearance and pleural irregularity were the most common findings whereas in JRA, bronchial wall thickening, mosaic appearance and air trapping were prominent. Abnormal findings were detected in 5/9 of asymptomatic patients.*
Conclusion*: airway and alveolar abnormalities are frequently encountered in children with SLE (95%) and JRA (85%) even if they are asymptomatic. HRCT and pulmonary function tests including diffusion studies are recommended as useful tools for the diagnosis and early detection of pulmonary involvement in these patients.*

Key words: JRA, SLE, HRCT, PFTs, DLCO.

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INTRODUCTION

The pleuropulmonary complications associated with collagen vascular diseases are frequently recorded [1]. The involvement may be subclinical, but its true extent may be masked by exercise limitation due to musculoskeletal features of the connective tissue disease[2]. Although most pulmonary complications appear in an established case of a collagen vascular disease, in some situations, the lung disease precedes the more typical manifestations[3].

Abnormalities of pulmonary functions have been found in children with collagen diseases even in the absence of clinical or radiographic evidence of pulmonary involvement. However, it is not known whether they represent an early sign of progressive lung disease which is not clinically evident or they are associated with disease activity[4]. The increasing incidence of lung involvement of most of collagen vascular diseases is primarily due to increased recognition aided by the use of spirometry, lung volume measurement, bronchoalveolar lavage and computed tomography which can detect abnormalities even in asymptomatic patients[5].

This work aimed at evaluation of the clinical and functional characteristics of the lung in children with SLE and JRA using pulmonary function tests (PFTs) and high resolution computed tomography (HRCT) of the chest. The relation of pulmonary involvement to the type and duration of disease was also assessed.

METHODS

The study was conducted in the Pediatric Allergy and Immunology, Pediatric Pulmonary Function, and Radiology Units of Ain Shams University, Cairo, Egypt during the period from October 2001 to October 2002.

Patients:

The study included 34 patients (21 with SLE and 13 with JRA). They were 7 males and 27 females with a mean age of (14.63± 3.28) years, and a mean disease duration of (4.73 ± 3.51) years. According to their diagnosis, patients were classified into:

Group of SLE:

It included 21 patients with SLE fulfilling the American Rheumatism Association (ARA) revised Criteria for diagnosis of SLE [6]. They were 2 males and 19 females with a mean age of 15.3±2.54 years, and mean disease duration of 4.76±3.66 years. Disease severity was assessed using the SLEDAI score[7]. All patients were under long-term oral prednisolone in a dose ranging from 0.5-2 mg/kg/day (maximum dose 60mg/m^2/day). Five patients were receiving monthly pulse cyclophosphamide therapy.

Group of JRA:

It included 13 patients with JRA fulfilling the ARA revised criteria for diagnosis of rheumatoid arthritis[8]. They were 5 males and 8 females, with a mean age of 13.57±4 years, and mean disease duration of 4.68±3.4 years. Eight of them were of the polyarticular-onset type, 3 had pauciarticular-onset JRA and 2 had systemic-onset JRA. All patients were receiving NSAIDs. In addition, seven were on oral prednisolone, and three were on oral methotrexate (10 mg/m^2/wk).

Ten clinically healthy children age and sex matched to the patients, were studied as a control group. They were 4 males and 6 females, with a mean age of 14.2±1.99 years.

Methods:

The patients were assessed clinically for pulmonary involvement. Symptoms such as dyspnea, cough, hemoptysis and recurrent attacks of chest infection were recorded. General and local signs of lung diseases such as clubbing, cyanosis, chest deformity and limited expansion, diminished air entry, or the presence of rhonchi or rales, were sought.

Routine laboratory investigations

Included complete blood picture by Coulter Counter (Coulter Instruments, Model T660, Fullerton, California, USA), ESR by the Westergren method, ANA and anti dsDNA by indirect immunofluorescent microscopy (IMMCO Diagnostics, USA), serum rheumatoid factor by latex agglutination (Avitex-RF; Omega Diagnostics, Alloa, UK) and complement 3 and 4 by turbidimetry (Turbiquant; Behring Diagnostics GmbH, Marburg, Germany).

Pulmonary function tests (PFTs) [9]

(Med-Graphics 1070 series 2E/105). The data obtained were:

- *Spirometry*

- FVC: forced vital capacity (liter/min).
- FEV1: forced respiratory volume in the first second (liter/min).
- FEV1%: FEV1/FVC
- MVV: maximum voluntary ventilation (liter/min).
- RV: residual volume (liter/min).
- SVC: slow vital capacity (liter/min).
- FEF25-75%: forced expiratory flow at 25-75% of FVC.

For every parameter, actual and predicted values for age, sex, height and weight were obtained and the percentages from predicted values were calculated. The results of spirometric pulmonary functions were categorized as:

- Normal if values lie between 80-120% of predicted.
- Obstructive if FEV1% is < 85%.
- Restrictive if FEV1% is > 85%.

- *Carbon Monoxide Diffusion capacity (DLCO):* Through a single breath test, DLCO was assessed for controls and for 13 patients with SLE and 10 with JRA. DLCO was considered abnormal if it was below 80% of the predicted value.

Exclusion criteria for PFTs were age below 5 years, presence of a cardiac problem, or a hemoglobin concentration below 8 gm/dl, all of which would affect the results.

Radiological assessment of patients by:

- Plain chest X-ray (CXR) postero-anterior view to evaluate lung fields.
- High-resolution computed tomography (HRCT) of the chest using General Electric Prospeed VX Scanner. While lying in supine position with arms above heads, patients were scanned at maximal inspiration during suspended respiration to promote separation of pulmonary parenchymal structures. Axial 1-2 mm thin sections were obtained every 10mm, using an FOV of 25-28, 140 KV, 170 MA, and 3 second scan time. Data are reconstructed with bone algorithm to preserve sharp edges of the fine details of the lung parenchyma. Scans were imaged at window width (WW) of 1200 and window level (WL) of -600[10].

Statistical methods:
Analysis of the results was done via SPSS computer software version 8 (Statistical Package of Social Science) employing mean and standard deviation as descriptive tools and student's T test, Mann-Whitney U test, Chi square test and Pearson's correlation for comparisons. Results were considered significant at a p value of <0.05.

RESULTS

Comparing the studied groups as regards demographic data revealed absence of any statistical significant difference between them except for the duration of illness, which was statistically higher in symptomatic patients with JRA compared to the asymptomatic ones (Table 1).

Abnormal spirometric PFTs were recorded in 58% of all studied patients (71% of SLE patients, and 31% of JRA patients). A high percentage of patients with SLE and JRA had restrictive pattern of PFTs (62% and 23% respectively) whereas an obstructive pattern was detected in 14% and 8% respectively.

The mean values of FVC, FEV1, MVV and DLCO were significantly lower in patients with SLE and JRA in comparison to controls (Table 2). Apart from a significantly lower mean FEV1 in SLE, comparable PFT results were obtained in both patients' groups. SLEDAI (mean ± SD = 11.4 ± 6.8) correlated negatively, though insignificantly, with $FEF_{25-75\%}$ and with DLCO (p>0.05). There existed a significant negative correlation between duration of illness and FEV1 in JRA (r -0.54, p<0.05)

Clinically manifest pulmonary problems were encountered in 77% of patients with JRA and in 71.4% of patients with SLE. The mean values of PFT results were largely comparable among symptomatic and asymptomatic patients of both groups (SLE and JRA) except for a significantly lower $FEF_{25-75\%}$ in symptomatic patients (Fig.1).

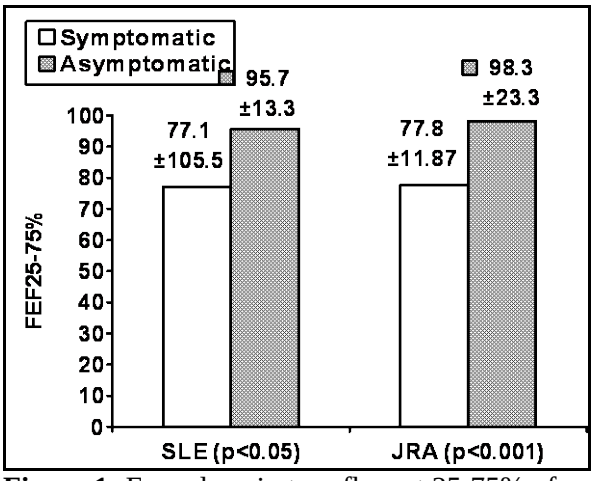

Figure 1: Forced expiratory flow at 25-75% of forced vital capacity (FEF25-75%) in symptomatic versus asymptomatic patients (values are given as mean±SD).

Abnormal HRCT findings were detected in 5/9 of the asymptomatic patients. In patients with SLE, the most common HRCT findings were ground glass appearance (Fig 2), mosaic appearance, pleural irregularity, and bronchial wall thickening. However, in JRA patients, bronchiolar wall thickening (Fig 3) was the most prominent finding followed by mosaic appearance (Fig 4) and air trapping (Table 3). Prominent atelectasis may also be seen in SLE as in Fig 5. Pulmonary nodules were detected in 3 SLE and 1 JRA patients. Pleural effusion was found in a patient with active JRA.

HRCT was able to detect a greater percentage of patients with pulmonary involvement in the studied groups compared to plain chest x-ray (Table 4). The only significant difference in the frequencies of abnormal findings between SLE and JRA was in spirometry; being higher in SLE.

Table (1): Statistical comparison between studied groups as regards some demographic data

	SLE patients (n=21)		**JRA patients (n=13)**	
	Symptomatic (n=15)	Asymptomatic (n=6)	Symptomatic (n=10)	Asymptomatic (n=3)
Age (years)	15.2 ±3.7	15.3 ±2.6	14.6 ±3.75	15.6 ±2.5
	t = 0.51	P= 0.60	t = 2.14	P= 0.054
Age of onset (years)	10.8 ±3.01	9.75 ±2.4	9.18 ±3.82	7.67 ±2.08
	t = 0.76	P= 0.46	t = 0.65	P= 0.53
Duration of illness (years)	4.43 ±3.7	5.58 ±3.7	5.4 ±3.4	2.1 ±1.4
	t = 0.64	P= 0.53	t = 2.84	P= 0.049??/

Table (2): Pulmonary function tests (PFTs) as % predicted in patients with JRA and SLE versus controls**.**

PFTs % of predicted	Control	JRA			SLE		
	Mean ± SD	Mean ± SD	t	P	Mean ± SD	t	P
FVC	94.7 ± 8.05	77.3 ± 90.4	4.79	0.00*	71.09 ± 15.05	4.6	0.00*
FEV_1#	99.1 ± 9.4	81.46 ± 8.8	4.63	0.00*	71.67 ± 16.26	4.9	0.00*
FEV_1%	91.7 ± 6.4	877.25 ± 2.7	2.12	0.57	88.3 ± 6.25	1.4	0.17
SVC	97.5 ± 12.5	91.18 ± 18.7	0.93	0.36	84.57 ± 16.12	2.2	0.04*
RV	80 ± 27.2	75.38 ± 35.9	0.04	0.96	85.81 ± 72.37	0.4	0.68
$FEF_{25-75\%}$	98 ± 23.9	97.15 ± 22.6	0.09	0.93	85.6 ± 29.5	1.2	0.26
MVV	118.9± 25.6	71.88 ± 15.7	4.27	0.00*	74.14 ± 12.39	3.9	0.003*
DLCO	87.9 ± 7.9	75.7 ± 26.06	1.24	0.18	68.2 ± 26.7	2.52	0.024*

* Significant

Borderline significantly low value in SLE compared to JRA (t=1.99, p = 0.05).

FVC: forced vital capacity (liter/min). FEV1: forced respiratory volume in the first second (liter/min). FEV1%: FEV1/FVC. SVC: slow vital capacity (liter/min). RV: residual volume (liter/min). $FEF_{25-75\%}$: forced expiratory flow at 25-75% of FVC. MVV: maximum voluntary ventilation (liter/min). DLCO: lung diffusion capacity for CO.

Table (3): High resolution computed tomography findings (HRCT) in relation to the presence or absence of clinically manifest pulmonary problems.

HRCT Findings	SLE patients (n=21)				JRA patients (n=13)			
	Symptomatic (n=15)		Asymptomatic (n=6)		Symptomatic (n=10)		Asymptomatic (n=3)	
	No.	%	No.	%	No.	%	No.	%
Ground glass appearance	5	33	2	33	-	-	-	-
Mosaic appearance	4	27	-	-	3	30	1	33
Consolidation	3	20	2	33	1	10	-	-
Pulmonary nodules	3	20	-	-	1	10	-	-
Interlobular septal thickening	2	13	-	-	-	-	-	-
Interstitial thickening	2	13	1	17	-	-	-	-
Bronchial wall thickening	4	27	-	-	3	30	2	67
Atelectatic bands	1	7	-	-	-	-	-	-
Air trapping	2	13	2	33	4	40	-	-
Cylindrical bronchiectasis	-	-	-	-	1	-	1	33
Pleural irregularity	4	27	2	33	-	-	-	-
Pleural effusion	-	-	-	-	1	10	-	-

Table (4): Percentage of abnormal HRCT, spirometric PFTs, DLCO, and plain chest roentgenogram findings in patients with SLE and JRA.

Variable	SLE patients (n=21)		JRA patients (n=13)		Total (n=34)	
	N	%	N	%	N	%
Spirometry	15	71*****	4	31	19	56
DLCO	9/13	69	6/10	60	15/23	65
CXR#	2	10	1	8	3	9
HRCT	15	71	9	69	23	68

* Frequency of patients with abnormal spirometry in SLE versus JRA: X^2=32, p=0.00.

Percent abnormal findings by CXR versus by spirometry, DLCO or HRCT both in SLE and JRA: P=0.00.

HRCT= High resolution computed tomography, PFTs: pulmonary function tests, DLCO: lung diffusion capacity for CO, CXR: chest x-ray.

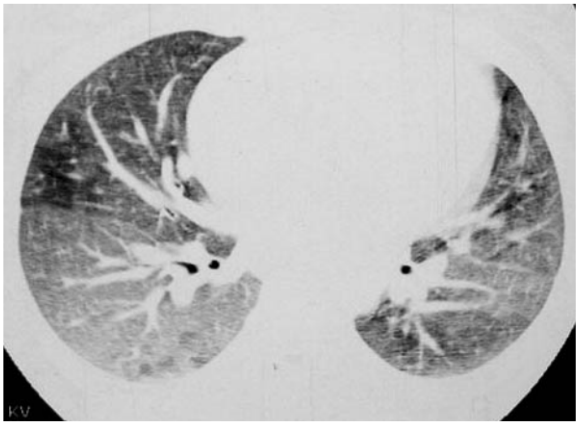

Figure (2): HRCT scan of a 16 years old female patient with SLE of 2 years duration. Bilateral diffuse hazy increased density (ground-glass appearance) is noticed.

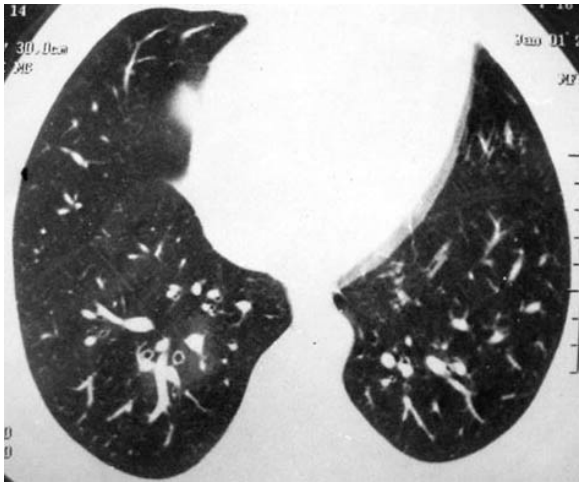

Figure (3): HRCT scan of a 12 years old male patient with JRA of 6 years duration. Bilateral bronchiolar wall thickening and ectasia are seen (more evident on the right side).

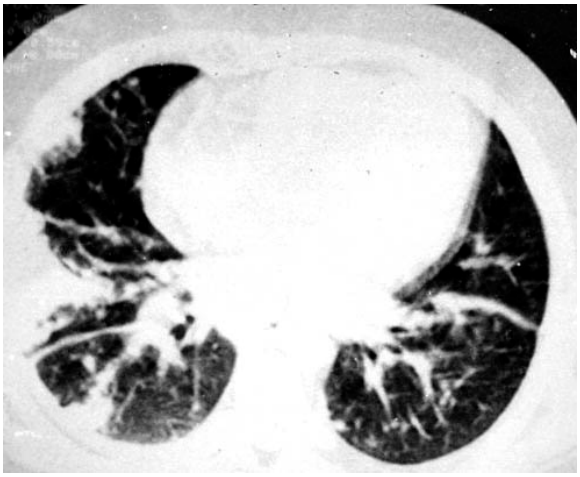

Figure (4): HRCT scan of a 10 years old female patient with JRA of 3 years duration showing a fairly triangular homogeneously dense area of consolidation seen at the right lateral basal segment. Similar smaller lesions are seen at the right anterior and posterior basal segments. Few variable sized bilateral subpleural nodules are also identified. Mild right sided pleural effusion extending into the right major fissure. Interstitial thickening and septal lines are also noted. Scattered patchy areas of decreased attenuation are noted (mosaic appearance). An arc-like atelectatic band is seen crossing the left anterior basal segment.

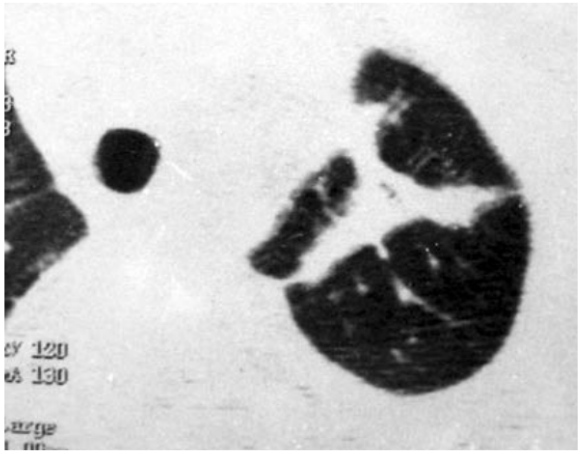

Figure (5): HRCT scan of a 12 years old female patient with SLE of 4 years duration showing left apical y-shaped plate-like atelectatic band extending to the costal and mediastinal pleura.

The overall pulmonary involvement, by all investigational measures, was 95% in SLE and 85% in JRA: 75% of the polyarticular-onset type, and 100% of the pauciarticular- and systemic-onset types.

DISCUSSION

The increasing incidence of lung involvement in most of collagen vascular diseases is primarily due to increased recognition by different diagnostic

tools, which can detect abnormalities even in asymptomatic patients. However, the pattern of involvement varies with each connective tissue disease [5].

This work revealed statistically significant lower values of PFTs (FVC, FEV_1 and MVV) in the studied patients compared to the control group ($P<0.05$). This was more prominent in SLE than in JRA (76% and 30% respectively showed abnormal PFTs). In SLE, a higher SLEDAI tended to be associated with lower PFTs, namely $FEF_{25-75\%}$ and DLCO. However, in JRA, impaired PFTs was more commonly linked to a longer duration of illness. Varying percentages of abnormal PFTs were recorded by several investigators [11-13]. The variation could be attributed to different clinical characters of the studied groups as the duration of illness, disease severity, and whether they have symptomatic chest problems.

A restrictive pattern of PFTs was recorded in 62% of the studied SLE patients, and in 23% of those with JRA. This was supportive to the results of earlier studies [14,15] . The restrictive pattern of PFTs is either the result of parenchymal impairment due to interstitial connective tissue involvement, or is due to weakness of the respiratory muscles [9] caused by phrenic nerve conduction abnormalities with secondary weakness of the diaphragm as explained by Trapani and associates [15]. These pathologies are expected to occur more frequently in SLE.

In the current study obstructive pattern of PFT was detected in 14% of SLE and 8% in JRA patients. DuBois and Wells [2] explained the obstructive pattern of PFT in patients with rheumatological diseases by external compression of bronchioles by hyperplastic lymphoid follicles "follicular bronchiolitis" or destruction of the bronchiolar wall and its replacement by fibrous tissue "bronchiolitis obliterans".

Diffusion studies showed significantly lower mean values in the studied patients compared to controls and the values were reduced in 69% of patients with SLE and 50% of those with JRA. This was in agreement with the results of previous investigators [15-19]. Reduced DLCO could be attributed to loss of functioning alveolar –capillary bed with decreased lung volume or to microvascular changes [11]. Some investigators correlated the reduced DLCO to increase secretion of some cytokines e.g. connective tissue growth factor [20] or surfactant D [21].

In the present study, 26% of patients were chest-wise clinically free. McDonagh and associates [22] attributed the delay in appearance of chest symptoms in JRA-patients to their limited exercise level by arthritis. Five out of the 9 asymptomatic patients (55.5%) showed abnormal HRCT (ground-glass appearance, consolidation, air-trapping, and bronchial wall thickening) despite having normal chest roentgenograms and PFTs. Previous investigators also recorded abnormal HRCT in patients with no signs or symptoms of pulmonary disease [1, 22-24]. This observation highlights the importance of screening patients with connective tissue diseases for pulmonary abnormalities regardless the absence of clinically manifest pulmonary disease.

Pulmonary involvement was frequent both in SLE and JRA (95% and 85% respectively) and its detection was best with HRCT (68% of all the studied patients) followed by DLCO and spirometry (65% and 56%). Chest roentgenograms were abnormal in only 9% of the studied patients. The higher percentage of pathologic findings at HRCT in patients with normal chest radiographs could be explained by the fact that pathologic HRCT findings are too discrete to be seen on chest radiographs**.** Perez and associates [1] found that HRCT depicted features of small airway disease in 20 of the studied 33 patients with RA with normal PFTs, and concluded that HRCT is a more sensitive mean of detecting small airway disease than PFTs. They added that this could be explained by the likelihood of patchy basal interstitial disease which does not significantly impair overall pulmonary function.

Previous reports on the role of tomography in the imaging of systemic collagen vascular diseases indicated that neither the nature nor the distribution of tomography findings in this group of disorders is reliably specific for a particular disease [12]. In the current study, HRCT showed a range of abnormalities among the studied patients. The most frequently detected HRCT abnormality in patients with SLE was the ground glass appearance (33%) which is suggestive of active alveolitis. Salaffi and coworkers [24] emphasized the relationship between the cellularity of lower respiratory tract as assessed by BAL, and the ground glass pattern of HRCT scan. Bankier and associates [23] reported that ground-glass attenuation most commonly reflects an active inflammation and is thus a reversible process, or may also result from changes that follow the acute phase of lung injury in the form of very fine intralobular fibrosis that lies below the limits of resolution of the CT scanner, and is therefore depicted as an amorphous increase in lung attenuation. They found that the most common abnormal HRCT findings are interlobular septal

thickening and intralobular interstitial thickening (33% for each finding). Fenlon and associates [12] and Sant and associates [25] found HRCT abnormalities suggestive of interstitial lung disease in 32% and 38% of their patients respectively. Concerning JRA, the most common abnormal HRCT finding was bronchial wall thickening (38%), followed by air trapping and mosaic appearance (34% for each finding). In a study on adult onset RA, air trapping was the most common HRCT finding (32% of patients) [1].

In the present study, pulmonary nodules were detected, on HRCT, in 4 patients (3 with SLE and 1 with rheumatoid factor positive JRA). Worth mentioning is that the recognition of small nodules is rather difficult, being easily missed between HRCT sections, and when present, are difficult to distinguish from blood vessels. Seaton [26] noted that nodules occasionally appear in patients without rheumatoid disease. There seems to be an association between the presence of subcutaneous nodules and the positivity of rheumatoid factor in JRA.

Pleural abnormalities are less common than previously suggested and were elicited in 7 patients: 6 (28%) with SLE (pleural thickening), and one (8%) with systemic-onset JRA (effusion). Effusions usually occur with disease flares as is the case with our JRA patient whereas pleural irregularities represent the consequence of poor control of such flares.

In conclusion, lung involvement is a frequent finding in patients with SLE and JRA even if they are asymptomatic. This tended to correlate with disease severity in SLE and with disease duration in JRA. HRCT of the chest and PFTs give better insight onto the degree of pulmonary abnormalities, and are recommended as useful tools for the early detection of subclinical pleuropulmonary involvement in these patients.

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