Pulmonary manifestations in children with systemic lupus erythematosus

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Abstract

Background Symptomatic pulmonary involvement in systemic lupus erythematosus (SLE) is commonly reported in children. However, few studies have assessed risk factors that predict pulmonary involvement in SLE.Methods This was a seven-year retrospective study involving 111 SLE patients. The demographic, clinical and laboratory data of the patients were collected. Logistic regression analysis was performed to identify different clinical characteristics and laboratory parameters associated with presence of high resolution computerized tomography(HRCT) chest abnormalities.Results Of the 111 patients with SLE, we identified 18 patients (16.2%) with pulmonary involvement. The most common HRCT findings were ground glass opacity, interlobular septal thickening, bilateral diffuse infiltrates and pleurisy/pleural effusion (55.6%, 50%, 50%, and 44.4%, respectively). The variables independently associated with pulmonary involvement were anti- ribonucleoprotein (RNP) antibody (OR:7.9; 95% CI: 1.1–54.6) and anti-neutrophil cytoplasmic antibodies (ANCA, OR: 73.6; 95% CI: 2.9-1894.7).Conclusions Lung involvement was frequent in SLE patients from Southeast China. Anti-RNP antibody and ANCA were significantly associated with abnormal HRCT findings.

Background

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder of unknown etiology in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes. Adult SLE and childhood SLE have similar clinical features, but children are known to have a more severe disease course. SLE is the most common connective tissue disease affecting the lung, with a similar proportion between adults and children. In children with SLE, it has been reported that pulmonary involvement occurred in 7.6–75% of the patients[1 – 3]. The types of pulmonary manifestations reported involve any portion of the pulmonary organ system including the pleura, diaphragm, parenchyma, and vasculature.

Due to the potentially high prevalence of lung complications in SLE, assessing the risk factors that predict pulmonary manifestations is of great importance. It was reported that SLE duration, low complement levels, high anti-dsDNA levels and disease activity were the risk factor associated with the development of pulmonary manifestations in adult patients[4, 5]. Nevertheless, no studies have assessed the risk factors that predict pulmonary manifestations in children with SLE.

Therefore, in this study, we retrospectively investigated the prevalence of pulmonary manifestations in childhood SLE in order to determine risk factors for developing lung abnormalities.

Method

Patients and study design

This was a hospital-based study conducted at Children's Hospital of Soochow University located in the Southeast region of China. We performed a retrospective review of the records of patients diagnosed with

SLE from 1 January 2012 to 31 December 2016. They were followed consecutively either as inpatients or outpatients until December 2019. We enrolled patients aged < 18 years who were diagnosed with SLE under the Criteria of the American Rheumatism Association for a diagnosis of SLE[6]. Patients with mixed connective tissue diseases were excluded from the study. This investigation was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Research Committee of Children's Hospital of Soochow University.

Data collection

The demographic and clinical data of patients with SLE including patients' age at onset, gender, disease duration (calculated from symptoms onset to the end of the study), follow-up duration, different clinical features at presentation. Laboratory data collected included hematological and immunological parameters consisting of the lowest levels of complement components 3 and 4 (C3 and C4) (low C3: <90 mg/dl; low C4:<20 mg/dl), anti-double stranded (ds) DNA antibody, anti- Smith (Sm) antibody, anti-neutrophil cytoplasmic antibodies (ANCA), anti-ribonucleoprotein (RNP) antibody, anti-SSA antibody and anti-SSB antibody.

Two senior radiologists independently reviewed HRCT scans, with each diagnosis reached by consensus. Furthermore, the presence of the following pulmonary HRCT manifestations was recorded as previously described[7, 8]: pleurisy/pleural effusion, pneumonitis, interstitial lung disease, bronchiectasis, diffuse alveolar hemorrhage and pulmonary edema. Respiratory involvement was considered primary when it was directly related to SLE activity, and infections, drug toxicity, and neoplasia had been excluded.

Statistical analysis

We used n (%) for categorical variables and median (quartiles) for continuous variables with non-normal distribution or mean and standard deviation (SD) for those with normal distribution. We assessed differences in categorical variables with the χ^2 test or Fisher exact test. We calculated 95% confidence interval (95% CI) for differences in medians with an exact test. Logistic regression analysis was performed to identify different clinical characteristics and laboratory parameters associated with presence of HRCT chest abnormalities. SPSS (version 22.0) software was used for all statistical analysis.

Results

A total of 111 SLE patients were included in our study. Of these, 73.0% were female and 27.0% were male; median age at SLE diagnosis was 136 (range 108 ~ 156) months. Median period of follow-up was 36 months (range, 1–84 months). The presenting symptoms at diagnosis are summarized in Table 1. Cutaneous lesions (71.2%), fever (56.8%), nephritis (56.8%) and hematological involvement (51.4%) were the major clinical manifestations. Of the 111 SLE patients, pulmonary involvement was found in 18 (16.2%) patients, yielding an overall prevalence of 16.2% (95% CI: 9.3–23.2).

Table 1
Demographic and clinical characteristics of systemic lupus erythematosus (SLE) patients in this study (n = 111)

	Patients n (%)
Demographic characteristics	
Female/male	1:0.37
Age at SLE diagnosis, median (range), m	136 (108–156)
Clinical characteristics, n (%)	
Fever	63 (56.8)
Cutaneous	79 (71.2)
Arthritis	22 (19.8)
Mucosal lesion	20 (18.0)
Nephritis	63 (56.8)
Pulmonary involvement	18 (16.2)
Pericarditis	18 (16.2)
Gastrointestinal involvement, except hepatitis	14 (12.6)
Hepatitis	14 (12.6)
Hematologic abnormalities	57 (51.4)
Neuropsychiatric manifestations	11 (9.9)

Data concerning HRCT scans of the SLE patients with pulmonary involvement are presented in Table 2. Ground glass opacity was found in 10 (55.6%) patients, interlobular septal thickening in 9 (50.0%) patients, bilateral diffuse infiltrates in 9 (50.0%) patients, pleurisy/pleural effusion in 8 (44.4%) patients, fibrotic streak in 6 (33.3%) patients and patchy infiltrates in 5 (27.8%) patients (Fig. 2). Most of the abnormalities were distributed bilaterally (94.4%), in the lower lobes (82.3%) or subpleural regions (61.1%).

Table 2
Summary of HRCT findings in SLE patients showing pulmonary involvement

HRCT findings	N (%) *
Abnormalities	
Ground glass opacity	10 (55.6)
Interlobular septal thickening	9 (50.0)
Bilateral diffuse infiltrates	9 (50.0)
Pleurisy/pleural effusion	8 (44.4)
Fibrotic streak	6 (33.3)
Patchy infiltrates	5 (27.8)
Distribution of abnormalities	
Bilateral	17 (94.4)
Lower lobes	14 (82.3)
Subpleural regions	11 (61.1)
Patchy random distributed	4 (22.2)
*Multiple abnormalities were present in each patient.	

In the univariate analysis, SLE patients with pulmonary involvement were more likely to presented with pericarditis and neuropsychiatric manifestations (both $P < 0.05$). We also observed a significant association between the presence of anti-Sm antibody, ANCA, Anti-RNP and the presence of pulmonary involvement of SLE (all $P < 0.001$; Table 3). In the multivariate analysis, the variables independently associated with pulmonary involvement were and ANCA and anti-RNP antibody. The odds of pulmonary involvement among infants with positive anti-RNP antibody were significantly greater than among those with negative anti-RNP antibody (OR:7.9; 95% CI: 1.1–54.6), as were the odds of pulmonary involvement among infants with positive ANCA compared with those with negative ANCA (OR: 73.6; 95% CI: 2.9-1894.7).

Table 3
Demographic, clinical and laboratory data of systemic lupus erythematosus (SLE) patients with and without pulmonary involvement (n = 111)

	Pulmonary involvement (n = 18)	No pulmonary involvement (n = 93)	P value
Demographic characteristics			
Female/male	1:0.29	1:0.39	0.77
Age at SLE diagnosis, median (quartile), m	136.50 (121–147)	136 (92–156)	0.75
Clinical characteristics, n (%)			
Fever	11 (61.1)	52 (55.9)	0.80
Cutaneous	13 (72.2)	66 (71.0)	0.98
Arthritis	6 (33.3)	16 (17.2)	0.19
Mucosal lesion	5 (27.8)	15 (16.1)	0.31
Nephritis	14 (77.8)	49 (52.7)	0.07
Pericarditis	10 (55.6)	8 (8.6)	< 0.001
Gastrointestinal involvement, except hepatitis	3 (16.7)	11 (11.8)	0.70
Hepatitis	4 (22.2)	10 (10.8)	0.24
Hematologic abnormalities	12 (66.7)	45 (48.4)	0.20
Neuropsychiatric manifestations	5 (27.8)	6 (6.5)	0.02
Laboratory findings			
Low complement 3 level	16 (88.9)	58 (62.4)	0.03
Low complement 4 level	16 (88.9)	66 (71.0)	0.15
Anti-dsDNA antibody positivity	16(88.9)	82 (88.2)	1.00
Anti-Sm antibody positivity	11 (61.1)	14 (15.1)	< 0.001
Anti-Ro antibody positivity	7 (38.9)	41 (44.1)	0.80
ANCA positivity	16 (88.9)	17 (18.3)	< 0.001

	Pulmonary involvement (n = 18)	No pulmonary involvement (n = 93)	P value
Anti-RNP antibody positivity	12 (66.7)	15 (16.1)	< 0.001
Anti-SSB antibody positivity	5 (27.8)	18 (19.4)	0.53

Discussion

In the present study, we have determined the prevalence of pulmonary involvement in SLE to be 16.2% in the Southeast region of China. The frequency of symptomatic pulmonary involvement at diagnosis in children with SLE ranges from 7.6% -75%[1, 9, 10]. The wide range of prevalence found in the previous studies may be due to known racial and ethnic phenotypic variability, as well as different approaches taken to determine the presence of pulmonary involvement with SLE.

The types of pulmonary manifestations reported are diverse, and may involve any portion of the pulmonary organ system including the pleura, diaphragm, parenchyma, and vasculature[3]. However, the most common pulmonary involvement appears to be pleuritis, which affects 12.5–32% of children with SLE during the course of their disease[2, 11]. In our study, pleuritis affects 7.2% (8/111) of children with SLE. Moreover, 94.4% of the children with pulmonary involvement display bilateral presentation. The high prevalence of bilateral involvement in our study is in line with the previous studies[1, 9, 12].

The presence of anti-RNP antibody was described to be specific (specificity ranging from 84–100%) of mixed connective tissue disease[13]. Previous reports found that positive anti-RNP antibody are risk factors for pulmonary arterial hypertension in patients with SLE[14 – 16]. Anti-RNP positivity is also reported to be associated with a more frequent pulmonary involvement in other connective tissue disease[17]. Our results are the first study that emphasize the role of anti-RNP positivity in predicting occurrence of pulmonary involvement in childhood SLE.

In our study, ANCA positivity was also independently associated with pulmonary involvement in children with SLE. ANCA is a group of autoantibodies against specific antigens such as neutrophil cytoplasmic granules and monocyte lysosomes. The discovery of ANCA helped establish ANCA-associated vasculitis as a separate and well-defined clinical entity[18, 19]. Previous studies reported that the positive rate of ANCA in patients with SLE ranges from 25–69%[20–22]. In our study, 33 of the 111 SLE children were positive for ANCA, with a positive rate of 29.7%, which was consistent with the previous reports. The relationship between positive ANCA and pulmonary involvement has also reported in previous studies, especially in adult patients[20, 22]. Therefore, when the children with SLE is found to have positive ANCA, it should be alert to the occurrence of pulmonary involvement.

Our study has some limitations. First, it is a retrospective study. it is possible that some patient information could have been missed despite efforts by the authors to record all pertinent details. Second, the data which were collected from a single center may have introduced bias. Third, the total number excluded in our study is relatively small. Thus, a multicenter, prospective study is warranted to evaluate pulmonary manifestations in children with SLE.

Conclusions

In conclusion, lung involvement was frequent in SLE patients from Southeast China. Anti-RNP antibody and ANCA were significantly associated with abnormal HRCT findings.

List Of Abbreviations

SLE systemic lupus erythematosus

HRCT high resolution computerized tomography

RNP ribonucleoprotein

ANCA anti-neutrophil cytoplasmic antibodies

SD standard deviation

Declarations

Ethics approval and consent to participate

This investigation was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Research Committee of Children's Hospital of Soochow University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YDY and ZRC conceived the idea and supervise the project, JM collected patient samples and data.CHZ contributed to the design of the study and analysis of the literature.WJJ, GD and TW wrote the manuscript.All authors read and approved the final manuscript.

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Figures

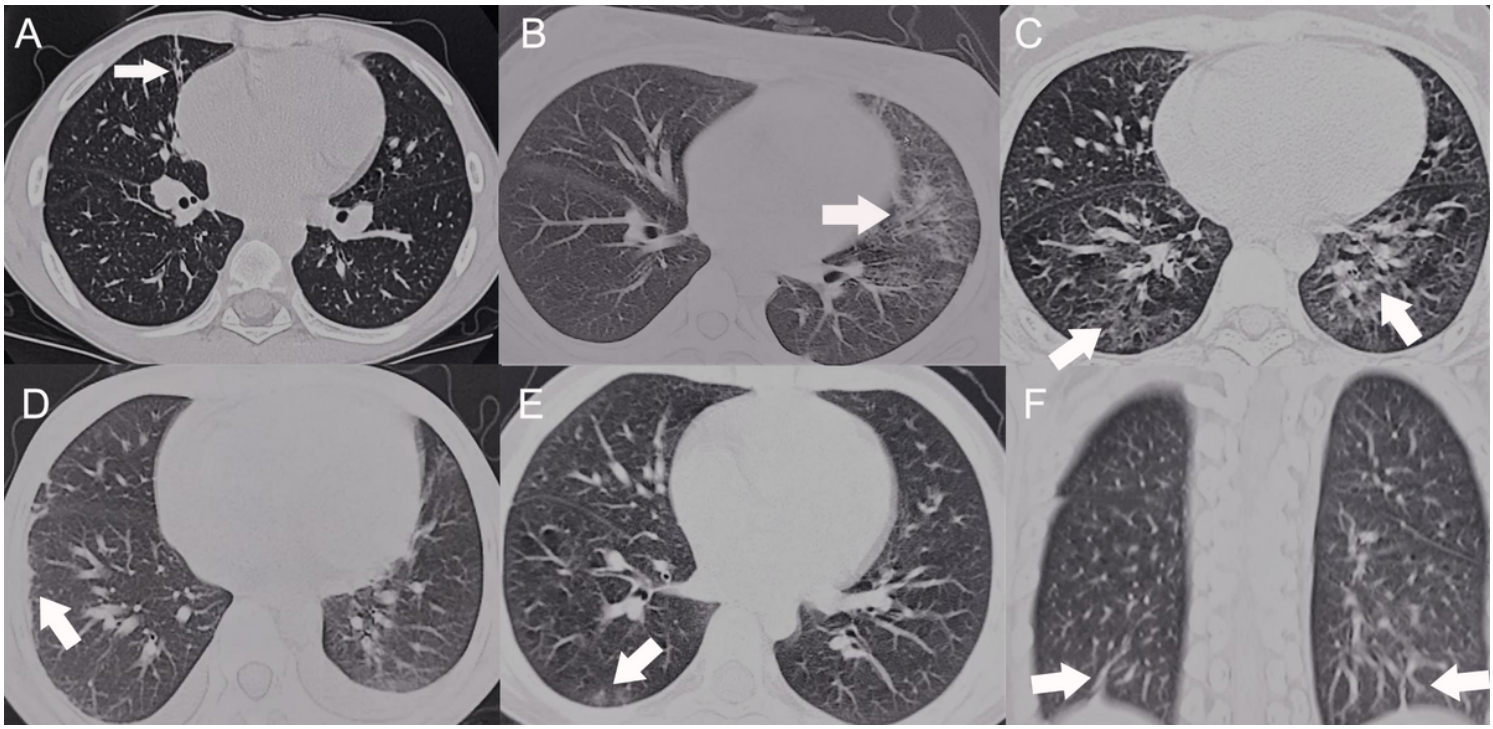

Figure 1

HRCT scans of the SLE patients with pulmonary involvement. (A) Fibrotic streak; (B) Reticular pattern; (C)Mosaic perfusion; (D) Pleural thickening (E) Ground glass opacity; (F) Subpleural interlobular septal thickening.