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ORIGINAL ARTICLE

Association of Interstitial Lung Disease With Clinical Characteristics of Chinese Patients With Systemic Lupus Erythematosus

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ABSTRACT

Objectives: This study aims to evaluate the frequency and clinical and laboratory features of interstitial lung disease (ILD) in Chinese patients with systemic lupus erythematosus (SLE) and to evaluate the association of ILD with the clinical features.

Patients and methods: The study included 505 SLE patients (64 males, 441 females; mean age 35.3±15.3 years; range, 14 to 87 years) who were categorized into two groups as 449 patients without ILD and 56 patients with ILD based on evidence obtained from high-resolution computed tomography images. The demographic data, clinical and laboratory findings, SLE disease activity index score, and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index of all patients were also recorded and statistically analyzed.

Results: The ILD frequency in patients with SLE was 11.1%. Compared to the group of SLE patients without ILD, the group of SLE patients with ILD possessed the following statistical differences: elderly age, longer illness duration, lower level of anti-double-stranded deoxyribonucleic acid, and higher level of serum complement 3, increased ratios of Raynaud's phenomenon, moist rales and tachypnea. Multivariate logistic regression results suggested that elderly age (≥60 years), long illness duration (1-10 years, ≥10 years), Raynaud's phenomenon, and tachypnea were statistically associated with the occurrence of ILD in SLE patients.

Conclusion: Chinese SLE patients who possessed the factors that were statistically associated with ILD, namely, elderly age (≥60 years old), long illness duration (≥1 years), Raynaud's phenomenon, and tachypnea, were recommended to be monitored for the possibility of ILD.

Keywords: Interstitial lung disease, systemic lupus erythematosus.

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse pulmonary parenchymal disorders characterized by pulmonary interstitial fibrosis, alveolitis, impaired lung diffusion capacity, and abnormal restricted ventilation function. ILD may be broadly categorized into groups of known or unknown causes. Common known causes include connective tissue diseases (CTDs). As reported in 2004, 15% of patients with ILD had underlying CTD,[1] or one-third of patients with ILD were connected with CTD in 2018.[2] The percentage may vary due to inadequate classification and diagnostic criteria.[3] Immune reaction, excessive collagen deposition, fibroblast proliferation, alveolar fibrillation, pulmonary interstitial substance, and tissues around the trachea are also involved, but their mechanism is still poorly understood.[4] The diagnosis of idiopathic interstitial pneumonia (IIP) depends on multidisciplinary discussion (MDD) and close communication among clinicians, radiologists, and pathologists (CRPs) with appropriate MDD/CRP instead of the previous gold standard of histologic diagnosis.[5] Similar to the diagnosis of idiopathic pulmonary fibrosis, the pulmonary high-resolution computed tomography

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(HRCT) patterns of systemic lupus erythematosus (SLE)-associated ILD (SLE-ILD) can be classified into usual interstitial pneumonia (UIP) and possible UIP, inconsistent with UIP.[6]

Several studies on connective tissue disease-associated interstitial lung disease (CTD-ILD) focused on scleroderma-associated interstitial lung disease (SSc-ILD) and rarely on SLE-ILD. SSc-ILD and SLE-ILD are quite different in clinical manifestation, treatment, and prognosis. SLE is the most common CTD with many organs injured, and lungs are often involved.[7] ILD is not only a complication of SLE but also a predictor of poor prognosis.[8] Occasionally, ILD is the primary manifestation of SLE.[9,10] In the past, diagnosing ILD in patients with SLE was often omitted or delayed due to many reasons, such as subtle course of ILD, lack of lung biopsy, bronchoscopy, or HRCT. Many Chinese patients with SLE may benefit from timely diagnosis and proper treatment of ILD given that China has a high incidence rate of SLE.[11] In this study, we aimed to evaluate the frequency and clinical and laboratory features of ILD in Chinese patients with SLE and to evaluate the association of ILD with the clinical features.

PATIENTS AND METHODS

The medical records of 505 patients with SLE (64 males, 441 females; mean age 35.3±15.3 years; range, 14 to 87 years) in the Department of Rheumatology, Fujian Medical University Union Hospital between January 2013 and December 2017 were collected following the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria.[12] Patients with SLE were excluded if they were complicated with the following conditions: pulmonary alveolar hemorrhage, overlapping syndrome, cardiovascular disease (such as pulmonary hypertension, congenital heart disease, and left heart failure), other lung diseases (such as pulmonary tuberculosis, chronic obstructive pulmonary emphysema, and lung neoplasm), pregnancy, history of smoking, or environmental dust exposure. The study protocol was approved by the Fujian Medical University Union Hospital Ethics Committee (2018ky038). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 56 patients with SLE were distributed into the ILD group based on HRCT image evidence of ILD, such as ground-glass reticular opacities, honeycomb change, and thick-walled interlobular septum (one patient was diagnosed as UIP, three patients were diagnosed as possible UIP, and 52 patients were diagnosed as inconsistent with UIP). The other 449 patients with SLE were classified as the non-ILD group.

All patients' clinical manifestations were examined and the demographic and clinical characteristics, including disease duration, malar rash, epilepsy, arthritis, oral ulcer, photosensitivity, Raynaud's phenomenon, serositis, dyspnea, moist rales, and visceral damage were recorded.

We also gathered laboratory parameters, such as blood and urine routine, biochemical markers, 24-hour urine protein, immunoglobulin, complements (Cs) 3 and 4, and auto-antibodies (such as anti-double-stranded deoxyribonucleic acid [anti-dsDNA], anti-Sjögren's syndrome type A, anti-Sjögren's syndrome type B, anti-Sm, anti-U1 ribonucleoprotein (anti-U1 RNP), anti-cardiolipin antibodies, and beta-2 glycoprotein 1). Inflammatory indices, including erythrocyte sedimentation rate and C-reactive protein level, were also obtained. Disease activity was assessed using the SLE Disease Activity Index score,[13] and organ damage was evaluated with the SLICC/American College of Rheumatology (SLICC/ACR) Damage Index (DI).[14] All laboratory data were measured in the Department of Laboratory Medicine, Fujian Medical University Union Hospital.

Suspected patients with ILD by way of regular computed tomography (CT) received further HRCT scan. The three CT instruments were GE Discovery CT 750HD (General Electric Company, Waukesha, USA), GE Revolution CT (General Electric Company, Waukesha, USA), and SOMATOM Definition (Siemens Company, Berlin, Germany). Confirmation of suspected ILD on HRCT scan by a designated radiologist was required.

Statistical analysis

Data distribution was tested by the Shapiro-Wilk test. The results were reported as the mean ± standard deviation, quartile or number (percentage). Non-normally distributed data or ranked data were compared between the

Table 1. Demographic and clinical features of patients with systemic lupus erythematosus

Characteristics	Non-ILD group (n=449)		ILD group (n=56)			
	n	%	n	%	χ^2	*p*
Age (year)					13.553	0.001
≤44	319	71.0	28	50		
45-59	101	22.5	18	32.1		
≥60	29	6.5	10	17.9		
Sex						
Female	392	87.3	49	87.5	0.002	0.967
Body mass index (kg/m^2)					5.348	0.069
<18.5	77	17.1	6	10.7		
18.5-23.9	315	70.2	37	66.1		
≥24	57	12.7	13	23.2		
SLE duration (year)					14.746	0.001
<1	250	55.7	16	28.6		
1-10	167	37.2	33	58.9		
≥10	32	7.1	7	12.5		
Dry cough	100	22.3	18	32.1	2.709	0.1
Moist rales	40	8.9	11	19.6	6.319	0.012
Malar rash	164	36.5	20	35.7	0.014	0.905
Epilepsy	8	1.8	0	0.0	1.014	0.314
Fever	160	35.6	20	35.7	0	0.991
Arthritis	221	49.2	33	58.9	1.877	0.171
Photosensitivity	58	12.9	6	10.7	0.218	0.64
Serositis	112	24.9	10	17.9	1.365	0.243
Neuropsychological involvement	40	8.9	1	1.8	3.386	0.066
Myalgia/myasthenia	11	2.4	2	3.6	0.25	0.617
Xerostomia/xeroma	37	8.2	4	7.1	0.08	0.777
Oral ulcer	41	9.1	6	10.7	0.148	0.701
Raynaud's phenomenon	49	10.9	19	33.9	22.635	<0.001
Alopecia	60	13.4	9	16.1	0.31	0.578
Livedo reticularis	4	0.9	0	0.0	0.503	0.478
Finger tip vasculitis	17	3.8	3	5.4	0.323	0.57
Peripheral neuritis	7	1.6	0	0.0	0.885	0.347
Malar rash	120	26.7	11	19.6	1.3	0.254
Tachypnea	50	11.1	17	30.4	15.986	<0.001
SLEDAI					5.579	0.134
0-4	140	90.3	15	9.7		
5-9	156	85.2	27	14.8		
10-14	91	89.2	11	10.8		
≥15	62	95.4	3	4.6		
SDI					4.845	0.183
0	267	90.8	27	9.2		
1	118	86.8	18	3.2		
2	31	91.2	3	8.8		
≥3	33	80.5	8	19.5		
Abnormal electrocardiogram	244	54.3	34	60.7	0.817	0.366

ILD: Interstitial lung disease; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

two groups with the Mann-Whitney U test. Categorical data were compared with the Chi-square test. After collinearity diagnosis, multivariate logistic regression was adopted to report the correlation between the selected variables and ILD in all patients with SLE. Data analysis was performed using the PASW version 17.0 software for Windows (SPSS Inc., Chicago, IL, USA). A difference was considered significant if the two-sided p value was less than 0.05.

Table 2. Laboratory findings of patients with systemic lupus erythematosus

Characteristics	Non-ILD group (n=449)				ILD group (n=56)					
	n	%	Mean±SD	Quartile	n	%	Mean±SD	Quartile	χ^2	*p*
Leukopenia	171	38.1			22	39.3			0.03	0.86
Anemia	275	61.2			32	57.1			0.352	0.55
Thrombocytopenia	117	26.1			9	16.1			2.652	0.1
Urine protein	282	62.8			30	53.6			1.798	0.18
Urine RBC	172	38.3			18	32.1			0.806	0.37
Albumin (g/L)			25.5±36.1	30.97			28.5±36.8	32.35		0.26
Globulin (g/L)			29.4±38.8	34.64			31.1±39.2	35.93		0.24
Creatinine (μmol/L)			45.0±71.0	72.72			49.0±71.0	60.85		0.97
LDH (IU/L)			164.0±273.0	265.37			175.8±272.0	265.21		0.61
ESR (mm/h)			26.0±61.5	50.90			31.0±70.3	52.48		0.61
Abnormal CRP	210	46.8			28	50.0			0.208	0.65
IgG (g/L)			12.7±20.5	17.50			14.1±20.3	18.38		0.82
IgM (g/L)			1.2±1.4	1.21			0.8±1.3	1.15		0.62
IgA (g/L)			1.8±3.2	2.59			1.9±3.4	2.88		0.23
C3 (g/L)			0.3±0.7	0.53			0.4±0.9	0.64		0.03
C4 (g/L)			0.1±0.2	0.11			0.1±0.2	0.13		0.2
Rheumatoid factor	172	38.3			25	44.6			0.84	0.36
Anti-dsDNA (IU/mL)			4.4±32.0	22.10			2.0±24.0	16.79		0.02
Anti-cardiolipin IgM	37	8.2			2	3.6			1.523	0.22
Anti-cardiolipin IgG	90	20.0			15	26.8			1.374	0.24
Anti-β2GP1	86	19.2			6	10.7			2.38	0.12
Anti-ANCA	21	4.7			5	8.9			1.843	0.18
Anti-U1RNP	222	49.4			35	62.5			3.396	0.07
Anti-SM	150	33.4			23	41.1			1.298	0.25
Anti-SSA	294	65.5			32	57.1			1.512	0.22
Anti-SSB	114	25.4			12	21.4			0.417	0.52
Anti-SCL-70	6	1.3			0	0.0			0.757	0.38
Anti-PM-SCL	17	3.8			1	1.8			0.58	0.45
Anti-JO-1	3	0.7			0	0.0			0.376	0.54
Anti-centromere	11	2.4			3	5.4			1.561	0.21
Anti-PCNA	6	1.3			0	0.0			0.757	0.38
Anti-nucleosome	228	50.8			22	39.3			2.631	0.11
Anti-histone	164	6.5			17	30.4			0.824	0.36
Anti-rRNP	189	42.1			21	37.5			0.432	0.51
Anti-mitochondrial	65	14.5			7	12.5			0.159	0.69

ILD: Interstitial lung disease; SD: Standard deviation; RBC: Red blood cell; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; Ig: Immunoglobulin; C: Complement; dsDNA: Double-stranded deoxyribonucleic acid; β2GP1: beta-2 glycoprotein 1; ANCA: Antineutrophil cytoplasmic antibodies; U1RNP: U1 ribonucleoprotein; SM: Smith; SSA/SSB: Anti-Ro/anti-La; Anti-SCL-70: Anti-topoisomerase I; PM/SCL: Polymyositis-scleroderma; JO-1: Histidyl-tRNA synthetase; PCNA: Proliferating cell nuclear antigen; RNP: Ribonucleoprotein.

Table 3. Significant variables observed on single factor unconditional logistic regression and variance inflation factor diagnosis

Variables	VIF
Age (year)	1.082
Systemic lupus erythematosus duration (year)	1.073
SDI	1.102
Raynaud's phenomenon	1.102
Tachypnea	1.177
Moist rales	1.155
Complement 3	1.191
Anti-double-stranded deoxyribonucleic acid	1.245
Anti-U1 ribonucleoprotein	1.051

VIF: Variance inflation factor; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

RESULTS

Among the 505 enrolled patients with SLE, 56 patients who fulfilled both the SLICC criteria of SLE and the ILD criteria previously described were recruited as test subjects (the ILD group). The other 449 patients with SLE were considered controls (the non-ILD group). No significant differences were found between the two groups in terms of sex and body mass index. However, differences existed in age and illness duration (Table 1). SLE patients with ILD possessed such features as elderly age and longer illness duration.

The ILD group showed increased ratios of Raynaud's phenomenon, moist rales, and tachypnea (Table 1). In laboratory tests, remarkable differences were found in the items of anti-dsDNA and C3 between the two groups (Table 2). The ILD group presented lower level of anti-dsDNA and higher level of serum C3. The other items did not exhibit any difference.

Single-factor unconditional logistic regression was used to report the correlation between ILD and all the factors involved (Table 3). Among the items, age, illness duration, Raynaud's phenomenon, tachypnea, moist rales, C3, and anti-dsDNA were selected. In addition, no collinearity existed among them (variance inflation factor <3). After multivariate unconditional logistic regression, age (≥60 years), illness duration (1-10 years, ≥10 years), Raynaud's phenomenon, and tachypnea were considered statistically associated with ILD in SLE (Table 4).

DISCUSSION

Interstitial lung disease is a complication of SLE and has a substantial adverse effect on the quality of life, even leading to morbidity and mortality.[15] The ILD frequency in patients with SLE varies from 1 to 15%, depending on the population and criteria used for diagnosis.[16-18] In our study, the frequency was 11.1%. Timely recognition of pulmonary involvement in

Table 4. Significant variables for interstitial lung disease in patients with systemic lupus erythematosus observed in multivariate unconditional logistic regression

Variables	Odds ratio	95% CI	*p*
Age (year)		1,648-11,509	0.003
≤44	1		
≥60	4,355		
SLE duration (year)			
≤1	1		
2-10	2,446	1,241-4,822	0.01
≥10	3,586	1,217-10,568	0.02
Raynaud's phenomenon			
Absence	1		
Presence	3,049	1,449-6,415	0.003
Tachypnea			
Absence	1		
Presence	2,561	1,163-5,639	0.02

CI: Confidence interval; SLE: Systemic lupus erythematosus.

patients with SLE is important to initiate appropriate therapy; however, large-scale research on SLE-ILD is currently limited. In this study, many items were tested in 505 patients to determine the possible association with ILD.

In our data, age and illness duration were statistically different between the non-ILD group and the ILD group. As a kind of chronic progressive disease, organs were injured gradually with SLE progression. Lung involvement was identified in 3% at the onset of SLE and developed in an additional 7% over the period of observation.[18] Moreover, some chronic ILD cases recurred after recovery or developed insidiously, and such an incidence increased with age and disease duration in patients with SLE.[19,20] Medlin et al.[21] found that pulmonary manifestations of SLE are more common in late-onset patients with SLE compared with their young peers, particularly on ILD and serositis. Consistent with the report of Mittoo and Fell,[17] our study also indicated that age (≥60 years) and SLE duration (1-10 years, ≥10 years) were not only the prominent clinical features but also the fundamentally associated factors for ILD in SLE.

In this study, tachypnea was believed to be an important characteristic that can be easily determined clinically. Karim et al.[22] reported that less than 1% of patients developed progressive loss of lung volume with associated dyspnea. However, we hypothesized that reduced lung volume caused by diaphragmatic dysfunction, pleural adhesions, or destruction of lung parenchyma due to immune complex in patients with SLE may result in tachypnea. When the lung disease progresses, patients can develop pulmonary hypertension, hypoxemia, and pleuritic chest pain, thereby aggravating the symptoms of tachypnea.[23]

With the development of the disease, the kidneys are also often damaged, particularly in late-onset SLE, and pulmonary involvement is sometimes detected in elderly patients with SLE.[24] However, the results of this study did not show a significant difference between the two groups with regard to serum creatinine, urine red blood cell, and urine protein.

Systemic Lupus International Collaborating Clinics/ACR DI is often used to quantify the presence of irreversible organ damage.[25] However, SLICC/ACR DI was not a precise marker for ILD in SLE in our study, possibly because it was easily affected by many factors.

Serologic testing is often performed in patients, but it does not always indicate the association between ILD and non-ILD.[6] The frequency of detectable items in patients with ILD is not always different from that in healthy controls.[26] The levels of anti-dsDNA and C3 usually indicate the disease activity of SLE or the clinical features of SLE-ILD.[27-29] In addition, statistically low level of anti-dsDNA and statistically high level of C3 were found in the SLE-ILD groups in our study. We presumed that many of those patients with lupus gradually formed chronic progressive pulmonary interstitial fibrosis after the onset of SLE. Subsequently, lupus disease activity declined due to the management of glucocorticosteroids when SLE-ILD could be diagnosed with HRCT. Anti-U1RNP is a risk factor of ILD in patients with SLE,[17] but it was not manifested in this study possibly because of sampling error and small sample size. Raynaud's phenomenon is a kind of medical condition in which blood flow is reduced due to spasm of arteries, and it can occur in various parts, such as in the fingers, heart, and lung.[30] Repeated spasm of pulmonary small vessels is one of the causes of pulmonary ischemia and fibrosis. In this study, Raynaud's phenomenon was also an apparent characteristic and statistically associated factor with ILD in patients with SLE.

High-resolution computed tomography scan is an important examination in SLE with pulmonary symptoms. It can identify the signs of ILD with high sensitivity,[31] and HRCT findings are most closely associated with a pathologic diagnosis of interstitial pneumonia.[32] This tool is extremely helpful for screening, diagnosis, follow-up, and efficacy assessment, along with reducing the risk and suffering of invasive examination.

Although in-depth understanding of CTD-ILD has been achieved, many questions still require further investigation. Several possible biomarkers and pharmacologic treatment of ILD are expected to be found. For instance, Krebs von den Lungen-6, which has been used as a marker of lung cancer, contributes to the progression and prognosis of IIP.[33-35] Surfactant protein A is also an important serum marker for ILD.[36,37] In patients with CTD-ILD, serum carcinoembryonic antigen and carbohydrate

antigen 19-9 are elevated and can be indicators of disease severity.[38] Aside from immunosuppressive therapy, such as cyclophosphamide[2] and corticosteroids,[39] anti-fibrosis medicine, including pirfenidone and nintedanib,[40] is now applied to treat ILD. Prompt treatment of ILD with new anti-fibrosis therapy and immunosuppression can improve the outcome of patients with SLE-ILD.

The limitations of this retrospective study were the small sample and not gathering pulmonary pathological data. Thus, patients with SLE along with possible UIP or inconsistent with UIP should undergo lung biopsy.

In conclusion, in this study, the ILD frequency in Chinese patients with SLE was 11.1%. The major clinical characteristics of SLE patients with ILD included elderly age, longer illness duration, lower level of anti-dsDNA, higher level of serum C3, increased ratios of Raynaud's phenomenon, moist rales and tachypnea. Long illness duration (≥1 year), age (≥60 years old), Raynaud's phenomenon, or tachypnea were statistically associated with ILD in Chinese patients with SLE. Thus, patients with SLE with the above clinical characteristics are recommended to receive regular examination of lung HRCT scan to investigate possible ILD to reduce the influence of ILD on survival and quality of life.

Declaration of conflicting interests

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