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A Retrospective Study on Clinical Characteristics of Patients with Rheumatoid Arthritis-Interstitial Lung Disease Based on Chest CT Scan

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ABSTRACT

Objective: To study the clinical characteristics of patients with rheumatoid arthritis-interstitial lung disease (RA-ILD).

Methods: A total of 120 RA patients undergoing chest CT scan were selected, and their clinical and auxiliary examination data were retrospectively analyzed.

Results: There were 53 RA-ILD patients (44.16%) (RA-ILD group), with an average age of (54.39 ± 11.24) years old, and 67 patients with RA alone (55.83%) (simple RA group) aged (53.21 ± 11.69) on average. The patients were older, the proportions of patients with a course of RA >10 years, and a history of smoking and a history of drug allergy were higher ($P<0.05$), the joint lesions were severer ($P<0.05$), the content of serum anti-cyclic citrullinated peptide (CCP) antibody, immunoglobulin G (IgG), IgA and globulin was higher, and the content of complement C4 was lower in RA-ILD group than those in simple RA group ($P<0.05$). RA-ILD was mainly manifested as cough (35/66.04%), progressive chest tightness (19/35.85%), expectoration (7/13.21%), exertional shortness of breath (11/20.75%), lung wet rales (6/11.32%), lip cyanosis (3/5.66%) and $P_2>A_2$ (1/1.89%). Mesh-like shadow (26/55.32%) and ground-glass opacity (8/17.02%) were the main manifestations of RA-ILD in chest X-ray plain films, and the lesions were mostly distributed in the peripheral zone of the two lower lung fields. Mesh-like shadow (31/58.49%), ground-glass opacity (22/41.51%) and fibrous cord-like shadow (17/32.08%) were common chest CT findings, and the lesions were mostly distributed near the pleura in the two mid-lower lung lobes.

Conclusion: RA often involves the lungs, causing ILD. The occurrence of RA-ILD is related to age, course of RA >10 years, histories of smoking and drug allergy, severity of RA and anti-CCP antibody. The proportion of RA-ILD patients without respiratory manifestations is relatively high, and mesh-like shadow, ground-glass opacity and fibrous cord-like shadow are common chest CT findings.

KEYWORDS: rheumatoid arthritis; interstitial lung disease; chest; CT scan; pulmonary function

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic erosive arthritis, and also the most common connective tissue disease. RA is pathologically featured by synovitis and the resulting destruction of articular cartilage and bone, ultimately leading to joint deformity [1]. About 75% of patients will become disabled within 3 years if there is no regular treatment [2]. RA is distributed around the world, and its prevalence rate is 0.18-1.07% in different populations, with a certain racial difference, which is higher in Indians than that in the white people, and also higher in the white people than that in the Asian yellow people [3]. RA can occur in all age groups, mostly 30-50 years old, and it is generally more common in women than men. More than half of RA patients will have lung-pleural disease, dominated by interstitial lung disease (ILD) [4]. RA-ILD often has an insidious onset, and a poor prognosis when progressing to late stage. According to statistics, the mortality rate of RA-ILD is 3 times higher than that of RA alone. RA-ILD

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complicated with lung infection is the second major cause of death in RA patients [5]. Non-specific interstitial pneumonia (NSIP) is the main pathological type of RA-ILD, which, confirmed by lung biopsy, accounts for 60-70% of systemic sclerosis and Sjogren's syndrome-ILD [6]. In addition, another characteristic of RA-ILD is that multiple pathological types can coexist [7]. A variety of pathological types of ILD have been observed in patients with RA, dominated by NSIP, and usual interstitial pneumonia (UIP) is also a common one [8].

In this study, the clinical data and auxiliary examination results of 120 RA patients (including 53 RA-ILD patients) were retrospectively analyzed, aiming to deepen the understanding of RA-ILD.

MATERIALS AND METHODS

Subjects

A total of 120 RA patients admitted to the Department of Rheumatology and Immunology of our hospital from January 2014 to March 2019 were selected, including 64 males and 56 females with an average age of (53.37±12.65) years old and an average course of RA of (12.16±7.69) years. 30 cases underwent chest CT scan, while the remaining 90 cases underwent chest HRCT scan.

Inclusion criteria: 1) Patients meeting the diagnostic criteria for RA of the American College of Rheumatology (ACR) in 1987, or the RA classification criteria and scoring system newly proposed by the ACR and the European League Against Rheumatism in 2009, and 2) those who underwent general chest CT or HRCT scan during hospitalization [9].

Exclusion criteria: 1) Patients with respiratory diseases, such as tuberculosis, chronic bronchitis and bronchiectasis, 2) those with other connective tissue diseases, 3) those with occupational diseases such as pneumoconiosis, a history of exposure to beryllium or asbestos, or a history of using bleomycin or amiodarone, or 4) those with severe dysfunction in the heart, liver or kidney.

Collection of case data

(1) Clinical data: Gender, age, course of RA, histories of smoking and drug allergy, and respiratory and articular manifestations.

(2) Laboratory examinations: Rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin G (IgG), IgA and IgM, complement C3 and C4, serum total protein, albumin, and globulin.

(3) Radiological examination: X-ray plain films of both hands and wrist joints were taken. According to the severity of joint lesions, the X-ray changes were classified into stage Ⅰ-Ⅳ. Anteroposterior chest X-ray plain films were taken, and general chest CT or HRCT scan was performed.

(4) Pulmonary function: The pulmonary function index was expressed as the percentage of the measured value calculated by the normal value formula in the predicted value.

Grouping criteria

Whether ILD occurs was determined according to the chest CT findings, and the 120 RA patients were divided into RA-ILD group (n=53) and simple RA group (n=67). The chest CT findings for the diagnosis of ILD included interlobular septal thickening, mesh-like shadow, ground-glass opacity, honeycomb-like cyst, nodular shadow, tractive bronchiectasis, bronchial vascular bundle thickening, fibrous cord-like shadow and subpleural curvilinear shadow.

Statistical analysis

SPSS 15.0 software was used for data analysis. Numerical data were expressed as constituent ratio and rate, and quantitative data were represented as mean ± standard deviation ($\bar{\chi} \pm s$). Independent-samples *t* test and Pearson χ^2 test were performed for statistical inference.

RESULTS

Clinical data

There were 53 RA-ILD patients (44.16%) with an average age of (54.39 ± 11.24) years old, and 67 patients with RA alone (55.83%) aged (53.21 ± 11.69) on average. The patients were older, the proportions of patients with a course of RA >10 years, a history of smoking and a history of drug allergy were higher ($P<0.05$), the joint lesions were severer ($P<0.05$), the content of serum anti-CCP antibody, IgG, IgA and globulin was higher, and the content of complement C4 was lower in RA-ILD group than those in simple RA group ($P<0.05$). There were no significant differences in gender constituent ratio, joint lesion mobility and RF between the two groups (Table 1-3).

Respiratory system manifestations

RA-ILD was mainly manifested as cough (35/66.04%), progressive chest tightness (19/35.85%), expectoration (7/13.21%), exertional shortness of breath (11/20.75%), lung wet rales (6/11.32%), lip cyanosis (3/5.66%) and $P_2>A_2$

(1/1.89%). It occurred before the onset of articular symptoms in 3 cases (5.67%), and 5 years after the occurrence of RA in 41 cases (77.36%). The remaining 10 (18.87%) RA-ILD patients had no respiratory symptoms.

Table 1. **Clinical data of RA-ILD and simple RA groups**

Item	RA-ILD group		Simple RA group		P
	n	Constituent ratio (%)	n	Constituent ratio (%)	
Male/female	28/25	52.83/47.17	36/31	53.73/46.27	0.262
Course of RA ≤10 years	16	30.19	39	58.21	0.026
Course of RA >10 years	37	69.81	28	41.79	
Smoking history	22	41.51	11	16.42	0.017
Drug allergy history	8	15.09	3	4.76	0.009

Table 2. **Severity and mobility of joint lesions of RA-ILD and simple RA groups**

Item	RA-ILD group (n=53)	Simple RA group (n=67)	P
Severity of joint lesions			
Number of joints involved (n)	11.58±2.96	7.14±2.83	0.006
Number of deformed joints (n)	3.16±2.82	1.84±1.15	0.012
X-ray stage of wrist joints of both hands (n)	3.57±1.36	2.06±0.86	0.019
Mobility of joint lesions			
Number of swollen joints at admission (n)	7.45±2.16	7.89±2.24	0.481
Number of tender joints at admission (n)	8.16±3.08	6.02±2.78	0.327
CRP (mg/L)	38.56±12.52	35.48±11.89	0.294
ESR (mm/h)	46.22±15.74	42.61±14.65	0.237

Table 3. **Laboratory indices of RA-ILD and simple RA groups**

Item	RA-ILD group (n=53)	Simple RA group (n=67)	P
RF (IU/mL)	98.15±26.58	92.47±25.11	0.267
Anti-CCP antibody (RU/mL)	416.18±92.24	307.17±84.16	0.031
Complement C3 (mg/mL)	2.18±0.31	2.33±0.34	0.154
Complement C4 (mg/mL)	0.32±0.08	0.61±0.11	0.042
IgM (mg/mL)	2.11±0.82	2.01±0.76	0.811
IgG (mg/mL)	13.25±2.41	10.36±2.06	0.024
IgA (mg/mL)	4.51±1.16	2.73±1.08	0.019
Total protein (g/L)	66.15±8.27	64.18±8.34	0.394
Albumin (g/L)	38.61±7.34	40.74±7.61	0.218
Globulin (g/L)	32.71±5.62	26.81±5.27	0.016

Table 4. **Chest CT and X-ray manifestations of RA-ILD patients [n (%)]**

Manifestation	X-ray plain film (n=47)	Ordinary CT (n=18)	HRCT (n=35)	Total CT (n=53)
Mesh-like shadow	26(55.32)	8	23	31(58.49)
Ground-glass opacity	8(17.02)	7	15	22(41.51)
Fibrous cord-like shadow	0(0)	3	14	17(32.08)
Increase and thickening of lung markings	11(23.40)	5	12	17(32.08)
Nodular shadow	2(4.26)	1	4	5(9.43)
Honeycomb-like cyst	3(6.38)	2	3	5(9.43)
Tractive bronchiectasis	0(0)	0	6	6(11.32)
Emphysema	0(0)	2	2	4(7.55)
Consolidation shadow	0(0)	1	1	2(3.77)
Subpleural curvilinear shadow	0(0)	0	2	2(3.77)
Bronchial vascular bundle thickening	0(0)	0	3	3(5.67)
Pleural effusion or pleural thickening	0(0)	7	11	18(33.96)
Enlargement of mediastinal lymph nodes	0(0)	5	12	17(32.08)

Chest CT and X-ray manifestations

Mesh-like shadow (26/55.32%) and ground-glass opacity (8/17.02%) were the main manifestations of RA-ILD in chest X-ray plain films, and the lesions were mostly distributed in the peripheral zone of the two lower lung fields. Mesh-like shadow (31/58.49%), ground-glass opacity (22/41.51%) and fibrous cord-like shadow (17/32.08%) were common chest CT findings, and the lesions were mostly distributed near the pleura in the two mid-lower lung lobes (Table 4, Figure 1-4).

In simple RA group, 20 cases were diagnosed with ILD using chest X-ray plain films. In RA-ILD group, 14 cases had no abnormalities on chest X-ray plain films. The misdiagnosis rate and the missed diagnosis rate of chest X-ray plain films for RA-ILD was 29.85% and 26.42%, respectively

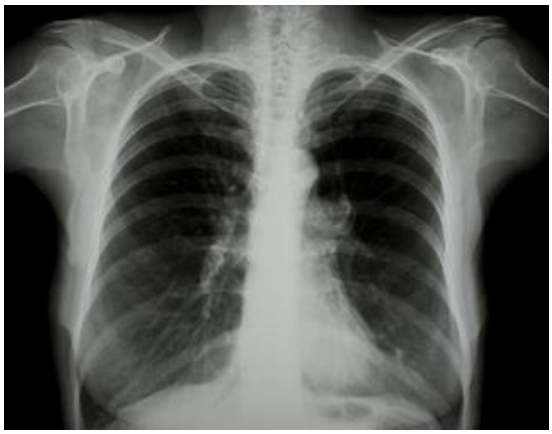

Figure 1. **Increase and disorder of lung markings of the two lower lung fields, with mesh-like shadow.**

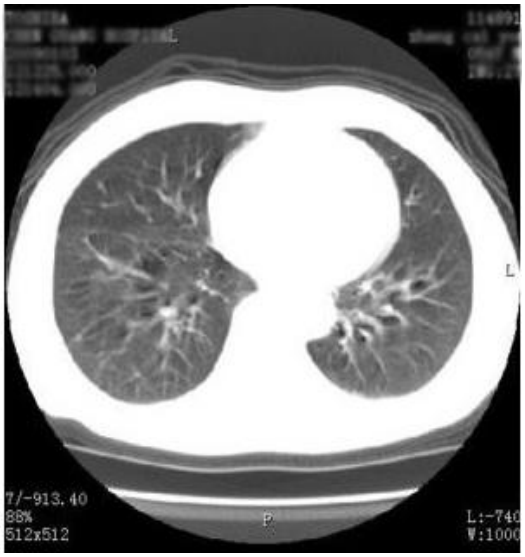

Figure 2. **Increase and disorder of right lung markings, with mesh-like shadow.**

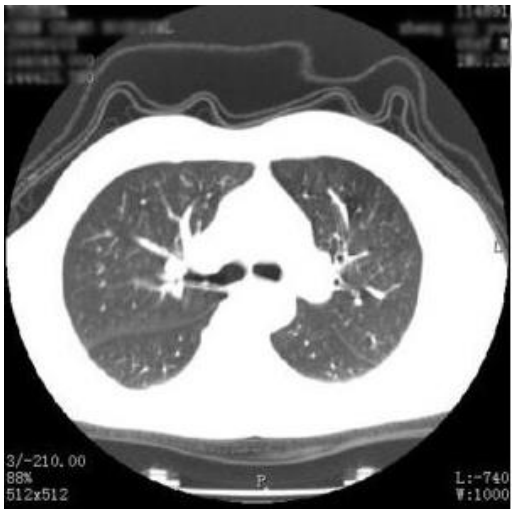

Figure 3. **Honeycomb-like cysts of different sizes near the pleura in the two lower lung lobes.**

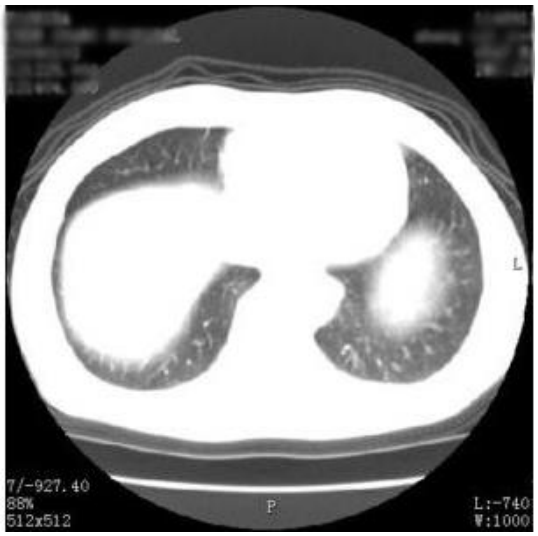

Figure 4. **Fibrous cord-like shadow, ground-glass opacity and mesh-like shadow in the right lung.**

Pulmonary function manifestations

According to the measurement results of pulmonary function, there were 14 (26.42%) and 8 (11.94%) abnormal cases, respectively, in RA-ILD group and simple RA group. RA-ILD was manifested as decline in diffusion function (10/18.87%), small airway dysfunction (7/13.21%), and restrictive (5/9.43%) and mixed (1/1.89%) ventilatory dysfunction. Simple RA was manifested as decline in diffusion function (11/16.42%), small airway dysfunction (6/8.96%) and mixed ventilatory dysfunction (2/2.99%).

DISCUSSION

At present, it is mostly believed that smoking, male, high age, a long course of RA, repeated and severe disease, positive human leukocyte antigen DR4 and α1-antitrypsin gene mutation are risk

factors for RA-ILD [10]. However, there are also different views. Whether the high level of RF or anti-CCP antibody in serum is related to the occurrence of RA-ILD also remains controversial. In another study, it was pointed out that ILD can also be caused by drugs, such as methotrexate, leflunomide and tumor necrosis factor-α antagonists [11]. Due to differences in the course and condition of RA in patients studied, and the examination methods used by clinicians, the incidence rate of ILD in RA is 4-80% according to reports in domestic and foreign countries [12]. Wang *et al.* pointed out that the prevalence rate of ILD and RA was 44% (28/63) and 42.7% (47/110), respectively. In this study, 53 out of 120 RA patients had RA-ILD, accounting for 44.17%, consistent with the above results [13]. It was confirmed that age, course of RA >10 years, histories of smoking and drug allergy, severity of RA and anti-CCP antibody were related to the occurrence of RA-ILD, while gender and RF had no correlation with the disease. Moreover, the indices for RA activity such as ESR and CRP displayed no significant differences between the two groups. The possible reason is that the data collected in this study fail to reflect the entire course of disease, and the acute-phase reactants are interfered by many factors *in vivo* and *in vitro*.

Whether the relapse of RA is related to the occurrence of ILD needs to be studied. Chest X-ray plain film is an important method for diagnosing RA-ILD, but it has high misdiagnosis and missed diagnosis rates [14]. The misdiagnosis rate and missed diagnosis rate was 29.85% and 26.42%, respectively, in this study. Chest HRCT is the most commonly used method for diagnosing and evaluating the condition of disease currently, and its specificity in diagnosing ILD can reach 90%, which can be used to fully, accurately and safely understand the lesion involvement scope. In this study, it was observed that mesh-like shadow was the most common manifestation of RA-ILD, and other main manifestations included ground-glass opacity, fibrous cord-like shadow and increase and thickening of lung markings, followed by nodular shadow, honeycomb-like cyst and tractive bronchiectasis, but emphysema, consolidation shadow, subpleural curvilinear shadow and bronchial vascular bundle thickening were rarely seen. The above multiple and diverse changes were mainly distributed in the peripheral zone of the two mid-lower lung lobes. Sathi *et al.* pointed out that ground-glass opacity was the most common manifestation of RA-ILD in chest CT [15]. In the study on RA patients, Horai *et al.* found that bronchiectasis was the most common chest manifestation, followed by ground-glass opacity, and ground-glass opacity, mesh-like shadow, honeycomb-like cyst and consolidation shadow were not associated with the course of RA, while patients with a long course of RA are more prone to bronchiole abnormality [16]. In addition, it is reported that RA-ILD is often complicated with pleural thickening, pleural effusion, and enlargement of mediastinal lymph nodes. Some cases of RA-ILD have an insidious onset and unobvious early respiratory manifestation, so it is easily neglected [17]. A study has shown that up to 67.7% and 67% of patients diagnosed with RA-ILD by chest HRCT have no respiratory manifestations [18]. In this study, the results manifested that the proportion of RA-ILD patients without respiratory manifestations was significantly lower than that in foreign reports. The possible reason is that the study population and sample size were different, and some potential RA-ILD patients did not undergo chest CT scan due to no respiratory manifestations, leading to missed diagnosis.

Some patients with simple RA suffer from lung dysfunction such as decline in diffusion capacity for carbon monoxide of lung (DLCO), indicating that lung function impairment in RA-ILD patients may precede chest CT findings [19]. Decline in DLCO is a sensitive index for ILD, which can be up to more than 80% in RA-ILD patients [20]. In this study, it was proved that RA-ILD was mainly manifested as decline in DLCO, which may be related to the different study population and few complete cases. Recently, it has been found that the chest HRCT findings of RA-ILD are significantly related to the pathological type. The mesh-like shadow with or without honeycomb-like cyst highly suggests that the pathological type is UIP, while ground-glass opacity often suggests that the pathological type is NSIP [21]. In this study, mesh-like shadow was the most common chest CT manifestation of RA-ILD patients. It is speculated that UIP may be the major pathological type of RA-ILD, consistent with most viewpoints, but the results remain to be confirmed by pathological biopsy.

In conclusion, RA often involves the lungs, causing ILD. Chest CT scan and pulmonary function measurement are the basic examination means. RA-ILD is often characterized by insidious onset, and whether ILD occurs cannot be determined through the presence or absence of respiratory manifestations in clinic. Older patients with a course of RA >10 years, histories of smoking and drug allergy, severe condition of RA, and a high level of anti-CCP antibody should undergo chest CT

scans, the pulmonary function should be measured and dynamically observed, and RA-ILD should be treated as early as possible, so as to prevent missed diagnosis and misdiagnosis. For ILD patients without obvious symptoms of RA, RA-ILD should be differentially diagnosed combined with autoantibody detection and chest CT findings.

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