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Clinical Characteristics of Connective Tissue Disease-Associated Interstitial Lung Disease in 1,044 Chinese Patients

Yang Hu, PhD; Liu-Sheng Wang, MD; Ya-Ru Wei, MD; Shan-Shan Du, MS; Yu-Kui Du, MS; Xian He, MS; Nan Li, PhD; Ying Zhou, PhD; Qiu-Hong Li, MS; Yi-Liang Su, MS; Fen Zhang, MS; Li Shen, MS; Dong Weng, PhD; Kevin K. Brown, MD, PhD; and Hui-Ping Li, MD, PhD

BACKGROUND: Because the prevalence of connective tissue disease (CTD)-associated interstitial lung disease (ILD; CTD-ILD) in China is unknown, we wanted to analyze the clinical characteristics of this disease in Chinese patients.

METHODS: The medical records of patients who received a diagnosis of ILD and treated in Shanghai Pulmonary Hospital from January 1999 to January 2013 were reviewed. Based on the records, patients who also received a diagnosis of CTD were identified, and their records of follow-up examinations for a minimum of 12 months until the end of December 2013 were reviewed.

RESULTS: Of the 2,678 patients who received a diagnosis of ILD, 1,798 (67%) were identified as having CTD-ILD; 299 (11.2%) had idiopathic pulmonary fibrosis (IPF). Complete clinical data were available for 1,044 patients with CTD-ILD and 178 with IPF. We found that 332 of the 1,044 patients with CTD-ILD (32%) did not receive an accurate diagnosis at the initial hospital admission, 195 (18.7%) of the 1,044 patients showed persistent negative test results for autoantibodies, and 262 (25.1%) of the 1,044 patients had negative autoantibodies at the initial hospital admission and then became positive at follow-up examinations. Of the 288 patients who had confirmed CTD-ILD, 41 (14%) showed pulmonary symptoms as the initial clinical manifestation (PSIM) and 247 (86%) showed extrapulmonary symptoms as the initial clinical manifestation (EPSIM). For the 756 patients who had undifferentiated CTD-ILD, the proportion of PSIM and EPSIM was 44% and 56%, respectively. For patients who presented with PSIM, 23 who had confirmed CTD-ILD (56%) and 216 who had unconfirmed CTD-ILD (65%) did not receive an accurate diagnosis at the initial visit but were ultimately diagnosed at subsequent follow-up examinations.

CONCLUSIONS: Patients with CTD-ILD do not receive an accurate diagnosis at the initial hospital admission possibly because of negative serologic test results for autoantibodies and the absence of obvious extrapulmonary symptoms. Thus, patients with ILD should be examined for extrapulmonary symptoms and tested for autoantibodies at follow-up examinations.

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KEY WORDS: interstitial lung disease; pulmonary epidemiology; pulmonary fibrosis

ABBREVIATIONS: CCTD = confirmed CTD-ILD; CTD = connective tissue disease; DLCO = diffusing capacity; EPSIM = extrapulmonary signs and symptoms as initial manifestation; HR = high-resolution; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; PSIM = pulmonary signs or symptoms as initial manifestation; UCTD = undifferentiated CTD-ILD; UIP = usual interstitial pneumonia

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Hu, N. Li, Zhou, Weng, H.-P. Li, Wang, and Wei; Mss S.-S. Du, He, Q.-H. Li, Zhang, and Shen; and Mssrs Y.-K. Du and Su), Shanghai Pulmonary Hospital, Tongji University, School of Medicine, Shanghai, China; and the Department of Medicine (Dr Brown), National Jewish Health, Denver, CO.

Drs Hu, Wang, and Wei contributed equally to this manuscript.

Connective tissue disease (CTD)-associated interstitial lung disease (ILD) is also called autoimmune-featured ILD or the newly proposed term "interstitial pneumonia with autoimmune features" (IPAF).[1] Although the controversy surrounding these names has not been resolved, they all consistently refer to ILD with some features of CTD. CTD-ILD is a common pulmonary complication of CTD and a predominant type of ILD. The reported prevalence of CTD-ILD varies greatly in different studies. Karakatsani et al[2] found that 12.4% of 967 Greek patients with ILD had CTD-ILD. Alhamad[3] examined patient records in a single center in Saudi Arabia and found that 34.8% of 330 patients with ILD had CTD-ILD.

Patients with CTD-ILD are often receive a diagnosis of other types of ILD because of the similar clinical presentation and imaging characteristics of CTD-ILD compared with those of other ILDs. Castelino and Varga[4] reviewed the records of 50 patients with ILD who were followed up by both a pulmonologist and rheumatologist for 12 months and found that 28% of them initially received a diagnosis of idiopathic pulmonary fibrosis (IPF), but they ultimately received a diagnosis of CTD-ILD on follow-up examination. Some patients with CTD-ILD have pulmonary symptoms as the initial manifestation of the disease, so-called lung-dominant CTD; these patients are more likely to receive a diagnosis of other diseases such as IPF, but not CTD-ILD, which may lead to an underestimation of the prevalence of CTD-ILD. Because the treatment plans for CTD-ILD and IPF are different, the accurate diagnosis of CTD-ILD is crucial for satisfactory patient outcomes.

To the best of our knowledge, the prevalence of CTD-ILD in China remains unknown. The purposes of this study were to analyze retrospectively the clinical, imaging, treatment, and outcome data of patients who received a diagnosis of CTD-ILD and treated in Shanghai Pulmonary Hospital over the past 13 years and to summarize the clinical characteristics of CTD-ILD.

Materials and Methods

Patients

A total of 2,678 patients were identified who received a diagnosis of ILD at Shanghai Pulmonary Hospital between January 1999 and January 2013; among them, 1,798 patients received a diagnosis of CTD-ILD. In total, 1,044 patients who received a diagnosis of CTD-ILD were followed up until December 31, 2013, and had complete clinical data including medical history, test results for pulmonary function and serum autoantibodies, and records of treatment and prognosis. Of the 2,678 patients, 299 (11.2%) received a diagnosis of IPF based on the latest international guidelines[5]; among them, 178 patients with available complete clinical data were used as the control group and were evaluated simultaneously. Figure 1 illustrates the process of patient screening. All patients were hospitalized for some period. After being discharged, they were treated continuously in the hospital as outpatients. The patients were followed up every 3 to 6 months. If their condition deteriorated, the patients were hospitalized again. Thus, the patients in this study were inpatients at some point and outpatients at other times.

Diagnostic Criteria

Patients received a diagnosis of ILD according to the guidelines described in *Goldman's Cecil Medicine*, 24th edition, chapter 92.[6] Briefly, the diagnosis of ILD should meet the following criteria: (1) clinical symptoms are dry cough, wheezing, and chest tightness; (2) signs are velcro-like rales that can be heard at the bottom of the lung bilaterally, and clubbing; (3) lung function examinations show restrictive ventilatory dysfunction and reduced diffusion capacity; and (4) high-resolution (HR) CT scans show diffuse bilateral ground-glass opacities, fine reticular opacities, and honeycomb appearance. All of the patients in this study were examined by rheumatologists. The diagnostic criteria for CTD in this study followed the recommendations by the American Rheumatism Association and the American College of Rheumatology.[7-12] Patients with ILD for whom rheumatologists also confirmed the diagnosis of one type of CTD were considered to have the diagnosis of confirmed CTD-ILD (CCTD-ILD) in this study. Patients with ILD for whom rheumatologists did not confirm a diagnosis of CTD were considered to have a diagnosis of undifferentiated CTD-ILD (UCTD-ILD). Diagnostic criteria for UCTD-ILD were established based on previous reports[13,14] and are listed in Table 1. The UCTD-ILD diagnostic criteria in this study are similar to the diagnostic guidelines for IPAF, which were described in the most updated statement for IPAF.[1] Some patients with UCTD-ILD had one or more positive serologic test results but failed to meet diagnostic criteria for CTD. Some patients with UCTD-ILD who had persistent negative serum autoantibodies were diagnosed based on systemic symptoms or a biopsy of the lip or muscle. Based on the clinical presentation of acute exacerbation of IPF,[5] we established the following definition for acute exacerbation of CTD-ILD: (1) an established diagnosis of CTD-ILD; (2) progressive dyspnea within 1 month and hypoxemia in room air; (3) new bilateral radiographic opacities on CT scan; and (4) absence of an identifiable cause including pulmonary embolism, pneumothorax, congestive heart failure, and obvious pneumonia. The diagnostic criteria for IPF follow the latest international guidelines.[5] Briefly, other causes of ILD should be excluded first. Chest images on HR CT scans show a confident usual interstitial pneumonia (UIP) pattern. For patients without a confident UIP pattern on HR CT scan, the diagnostic results of lung biopsy should be UIP. Serologic tests were performed on all patients with IPF.

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CORRESPONDENCE TO: Hui-Ping Li, MD, PhD, Department of Respiratory Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, 507 Zheng Min Road, Shanghai 200433, China; e-mail: liw2013@126.com

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