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Interstitial Pneumonia Related to Undifferentiated Connective Tissue Disease

Pathologic Pattern and Prognosis

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BACKGROUND: Undifferentiated connective tissue disease (UCTD) involves conditions characterized by both having symptoms of connective tissue disease (CTD) and autoantibodies but not fulfilling the criteria of a specific CTD. The frequency or prognosis of the usual interstitial pneumonia (UIP) pattern in UCTD is unknown, which may be confused with idiopathic pulmonary fibrosis (IPF). This study aimed to investigate the frequency of the UIP pattern in interstitial pneumonia related to UCTD and compare its prognosis with that of IPF and UCTD-nonspecific interstitial pneumonia (UCTD-NSIP).

METHODS: The medical records of 788 patients presumptively diagnosed with idiopathic interstitial pneumonia at Asan Medical Center from January 2005 to December 2012 were retrospectively reviewed. UCTD was diagnosed according to the criteria by Corte and colleagues, and the prognoses were compared between UCTD-UIP and UCTD-NSIP and between UCTD-UIP and IPF.

RESULTS: Among 105 patients with UCTD (13.3% of total subjects), 44 had a UIP pattern (by surgical lung biopsy: 24; by high-resolution CT scan: 20), 29 had a nonspecific interstitial pneumonia pattern (by surgical lung biopsy), and nine had an organizing pneumonia pattern (by biopsy). The overall survival of the UCTD-UIP group was shorter than that of the UCTD-NSIP group ($P = .021$) but significantly better than that of the IPF group ($P = .042$).

CONCLUSIONS: A UIP pattern, which seems to be frequent in UCTD, showed a poorer prognosis than that of UCTD-NSIP. However, the prognosis of UCTD-UIP was significantly better than that of IPF, highlighting the importance of searching for underlying UCTD in suspected IPF cases.

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ABBREVIATIONS: ANA = antinuclear antibody; CTD = connective tissue disease; DLCO = diffusing capacity of the lung for carbon monoxide; ENA = extractable nuclear antigen; HRCT = high-resolution CT; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RF = rheumatoid factor; UCTD = undifferentiated connective tissue disease; UCTD-IP = interstitial pneumonia related to undifferentiated connective tissue disease; UIP = usual interstitial pneumonia

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Undifferentiated connective tissue disease (UCTD) is a clinical entity as described in the rheumatology community characterized by features that are suggestive of connective tissue disease (CTD) but not fulfilling the classification criteria for a specific CTD.[1,2] Kinder et al[3] reported that most patients with a nonspecific interstitial pneumonia (NSIP) pattern on surgical lung biopsy met their case definition of UCTD. Later, several authors also reported the common occurrence of UCTD in surgical lung biopsy-proven NSIP,[4-6] suggesting that most idiopathic NSIP may actually be the lung manifestation of UCTD.[3] However, the diagnostic criteria for UCTD differ, and Kinder et al[3] used broad criteria, including nonspecific features like elevated erythrocyte sedimentation rate or gastroesophageal reflux, that might result in an overestimation of UCTD. Furthermore, although the NSIP pattern was first described and seems to be the predominant pattern in UCTD, no study, to our knowledge, has investigated the relative frequency of NSIP or usual interstitial pneumonia (UIP) patterns in UCTD. Vij et al[7] reported that the UIP pattern was the most common pattern in autoimmune-featured interstitial pneumonia, suggesting that the UIP pattern may be more frequent than previously thought.

In other aspects, the prognosis of idiopathic pulmonary fibrosis (IPF) is much poorer than that of a UIP pattern related to classic CTD, with the possible exception of rheumatoid arthritis.[8-10] Moreover, autoantibodies like antinuclear antibody (ANA) and rheumatoid factor (RF) are frequently found in patients with IPF,[11] suggesting that UCTD may also be present but undiagnosed in these patients. Consequently, it is clinically important to know the frequency of UCTD in patients with presumptive diagnosis of IPF and the difference in prognosis between UCTD-UIP and IPF. This study aimed to investigate the relative frequency of UIP and NSIP patterns in patients with UCTD-related interstitial pneumonia (UCTD-IP) and their prognostic differences, and to compare the prognoses for UCTD-UIP and IPF.

Materials and Methods

Study Population

A total of 788 patients seen at Asan Medical Center due to presumptive idiopathic interstitial pneumonia (IIP) from January 2005 to December 2012 were included in this study. Patients with classic CTDs or an exposure history in relation to the possible causes of interstitial lung disease (ILD), such as drugs or environmental agents, were excluded. Data were retrospectively collected from medical records. A thorough systematic history, including any rheumatologic symptoms and signs, with serologic testing for CTD was obtained from all subjects at the time of initial diagnosis and intermittently during follow-up. Many of the patients analyzed here had been included in our previous studies.[12,13] Because this study was a retrospective review of medical records, written informed consent was waived. The study protocol was approved by the institutional review board of Asan Medical Center (approval number 2013-0916).

Autoantibody Test

All patients underwent serologic tests for autoantibodies at the time of diagnosis. ANA was tested in the serum with a commercially available prestandardized kit (ANA/HEp-2 Test System; ZEUS Scientific, Inc). Any sample that had a positive result above 1:160 titer was considered positive. Extractable nuclear antigens (ENAs) were tested with an ENA Combi ELISA kit (BL Diagnostika). A signal-to-cut-off ratio >1.0 was considered positive. ENAs testing included anti-Ro (SS-A), anti-La (SS-B), anti-Scl-70, anti-ribonucleoprotein, and Jo-1 antibodies. RF was measured with a commercially available kit (RapiTexRF; Dade Behring Inc/Siemens Medical Solutions) that uses slide latex agglutination for qualitative measurements. Any sample that had a positive result at above a 1:160 International Unit was considered positive.

Histopathology

Surgical lung biopsy was performed in 363 patients and transbronchial lung biopsy in 11 patients. The biopsy specimen slides of patients with UCTD were rereviewed independently by two pathologists (T. V. C., S. J. J.) who were blind to the clinical findings. Final consensus histopathologic diagnosis was made according to the American Thoracic Society/European Respiratory Society international consensus classification of IIPs.[14]

High-Resolution CT Scan

High-resolution CT (HRCT) scan was performed at baseline in all patients and followed up annually or at a time of acute change in the patient's condition. The HRCT scan images were reviewed in a blind manner by the radiologist (M. Y. K.) with >10 years' experience in ILD. The HRCT scan pattern was categorized as the typical UIP pattern or as a non-UIP pattern.[14] Because the typical UIP pattern in HRCT scans was recently shown to be highly specific for the pathologic UIP pattern in patients with rheumatoid arthritis similar to IPF, we used this HRCT scan pattern for the diagnosis of UCTD-UIP.[15]

Diagnostic Criteria for UCTD and Follow-up Course

The narrower diagnostic criteria for UCTD recommended by Corte et al[4] were used, that is, the presence of one or more of the specific autoantibodies combined with more than one symptom or sign of CTD (including Raynaud's phenomenon, sicca symptoms, arthralgia, morning stiffness, or proximal muscle weakness).[4,16] All final diagnoses were made via the multidisciplinary approach that included experienced pathologists, clinicians, and radiologists. The diagnosis of IPF was reconfirmed according to the new American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society guidelines.[17]

The clinical follow-up courses and survival statuses of the patients until July 2013 were obtained from medical records, National Health Insurance of Korea records, and/or telephone interviews. Treatment responses were categorized as improvement, stable, or deterioration according to the change in the pulmonary function test.[17,18] Improvement/deterioration was defined as a change of $\geq 10\%$ in the FVC and/or $\geq 15\%$ in the diffusing capacity of the lung for carbon monoxide (D_{LCO}).[18]

Statistical Analysis

The comparisons of baseline characteristics and treatments were made using a Student t test for continuous variables and a χ^2 or Fisher exact test for categorical data. All P values were two-tailed, with statistical significance set at $P<.05$. Kaplan-Meier survival analysis was used to evaluate the differences in survival rates and risk factors for mortality were analyzed with Cox proportional hazards models. Statistical analyses were performed with SPSS, version 18.0 for Windows (IBM).