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Broader criteria of undifferentiated connective tissue disease in idiopathic interstitial pneumonias

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KEYWORDS
IIPs — idiopathic interstitial pneumonias;
IPF — idiopathic pulmonary fibrosis;
NSIP — nonspecific interstitial pneumonia;
SLB — surgical lung biopsy;
UCTD — undifferentiated connective tissue disease

Summary
Background: Kinder et al. proposed a broader definition of undifferentiated connective tissue disease (UCTD) and reported that the entity of nonspecific interstitial pneumonia (NSIP) is a lung manifestation of this more broadly defined UCTD. However, a retrospective study did not support their findings and its clinical significance remains unclear.
Methods: We prospectively evaluated the significance of this broadly defined UCTD in idiopathic interstitial pneumonias (IIPs) in consecutive patients with surgical lung biopsy. Patients were evaluated with a symptoms check list and underwent comprehensive serologic testing as screening for UCTD. Clinical characteristics, high-resolution CT images, lung biopsy specimens, serial FVC change, and survival were analyzed.
Results: Among 76 patients with IIPs, 24 patients (32%) fulfilled the UCTD criteria. Diagnosis of 24 patients with UCTD was usual interstitial pneumonia in 12 (50%), NSIP in 7 (29%), and unclassifiable interstitial lung disease (ILD) in 5 (21%). The diagnosis of 52 patients who did not have UCTD was idiopathic pulmonary fibrosis in 27 (52%), NSIP in 11 (21%), unclassifiable ILD in 13 (25%) and cryptogenic organizing pneumonia in 1 (2%). One-year and two-year FVC changes showed no significant difference between UCTD and non-UCTD, however, significant differences in FVC change were observed among histopathological diagnoses both in UCTD and in

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non-UCTD. In multivariate survival analysis, %FVC and histopathological UIP pattern were independent predictors for survival but UCTD diagnosis was not.
Conclusions: A diagnosis of UCTD was not useful in discriminating NSIP or in predicting disease progression and prognosis in our cohort of IIPs. Histopathological UIP pattern was an independent predictor for mortality irrespective of a diagnosis of UCTD.

Summary at a glance

In our cohort of idiopathic interstitial pneumonias with surgical lung biopsy, a diagnosis of broader criteria of undifferentiated connective tissue disease was not useful in discriminating NSIP and in predicting disease progression and prognosis.

Introduction

Some patients with interstitial pneumonia have features of a systemic autoimmune disease, but do not fulfill the criteria for a defined connective tissue disease (CTD). Such conditions have been defined as undifferentiated CTD (UCTD). Kinder et al. proposed a broader definition of undifferentiated CTD (UCTD) for such patients, and reported that most interstitial lung disease (ILD) patients with this broadly defined UCTD had nonspecific interstitial pneumonia (NSIP) pattern on biopsy and that most patients diagnosed with idiopathic NSIP met their definition of UCTD [1]. They also demonstrated that patients with UCTD-related ILD had a better clinical course in serial pulmonary function testing than those with idiopathic pulmonary fibrosis (IPF) [2]. They concluded that the clinical entity idiopathic NSIP appears to be an autoimmune disease and furthermore, is the lung manifestation of UCTD.

Although NSIP is reported to be a major histopathological pattern in ILD associated with CTD, a significant minority were reported to show patterns other than NSIP, such as usual interstitial pneumonia (UIP) [3—5]. In addition, Corte et al. reported from a recent retrospective study that the UCTD criteria adopted by Kinder et al. are not helpful because such a broad and nonspecific classification is far too prevalent in both NSIP and IPF [6]. Their results conflict with Kinder's reports.

Multidisciplinary evaluation system has recently progressed in IIPs, especially in IPF [7,8]. In addition, patients with findings suggesting, but not meeting, criteria for a defined CTD, are still accepted as IIPs by the recently revised IIPs criteria [8]. Therefore, evaluation of the significance of UCTD in the category of IIPs by current diagnostic definitions is crucial.

We aimed to study the significance of the more broadly defined UCTD by analyzing the prevalence, multidisciplinary evaluation results, changes in lung function and prognosis of UCTD-related IIPs compared to those of non-UCTD-related IIPs in consecutive patients with surgical lung biopsy (SLB). Some of the results of this study have been previously reported in the form of an abstract [9].

Methods

Study subjects

This is a prospective clinical descriptive study of consecutive patients diagnosed with interstitial pneumonia based on clinical, radiological, and histopathological evaluation by SLB just at one hospital. The study was approved by the institutional ethics committee there (IRB No. 165), and all enrolled patients provided informed consent. Data from patients enrolled from April 2009 to March 2011 were available for analysis.

As part of their initial assessment, patients were evaluated with a symptoms check list and underwent comprehensive serologic testing as screening for UCTD [1]. Rheumatologists were consulted if a patient had any features for UCTD. ILD patients who met American College of Rheumatology criteria for a CTD were excluded. Subjects with environmental exposures and other known causes of ILD were excluded. In this study, we included UCTD-related ILD under the category of IIPs.

Measurement

Baseline data included age, gender, smoking history, need for long-term oxygen therapy, pulmonary function testing, laboratory testing, high-resolution computed tomography (HRCT), and histopathology.

All patients underwent spirometry (CHESTAC-55V; Chest, Tokyo, Japan), according to the method described in the American Thoracic Society 1995 update [10]. Single-breath diffusing capacity of the lung for carbon monoxide (DLco) was also measured with the same equipment. The values for FVC, forced expiratory volume in 1 s and DLco were related to % predicted values [11]. Bronchoalveolar lavage was performed within the 3 months preceding SLB.

Histopathology evaluation

All lung biopsy specimens were evaluated by two lung pathologists with experience and advanced training in the evaluation of diffuse lung disease, and were classified using the histopathologic patterns described in the ATS/ERS International Consensus Classification of the IIPs [8,12] and in the current IPF guideline [7]. If there was disagreement in the assessment of the findings, consensus was reached with discussion between the assessors.

HRCT evaluation

HRCT scans were reviewed by two thoracic radiologists with 25 and 21 years of experience blinded to patient data for all