CHEST

Lung-Dominant Connective Tissue Disease
Clinical, Radiologic, and Histologic Features

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BACKGROUND: Lung-dominant connective tissue disease (LD-CTD) is a disease concept for interstitial pneumonia; however, it has not been robustly validated. This study was conducted to elucidate the clinical, radiologic, and histologic features of LD-CTD.

METHODS: We retrospectively reviewed 44 consecutive patients with serologically defined LD-CTD who underwent surgical lung biopsy. Patients were identified as having LD-CTD if they had specific autoantibodies but did not meet the criteria for connective tissue disease. We conducted a multidisciplinary diagnosis and evaluated major histologic patterns according to the current idiopathic interstitial pneumonias (IIPs) classification of 2013. Characteristic histologic features for LD-CTD (eg, prominent plasmacytic infiltration, lymphoid aggregates with germinal centers), high-resolution CT (HRCT) scan patterns, and prognosis were also assessed.

RESULTS: The major histologic patterns were usual interstitial pneumonia (UIP) in 25 patients and nonspecific interstitial pneumonia (NSIP) in 13 patients. Two or more characteristic histologic features for LD-CTD were observed in 15 patients with histologic UIP (h-UIP) and 11 patients with histologic NSIP (h-NSIP). Fifteen patients with h-UIP (60%) showed an inconsistent UIP pattern on HRCT scan. After multidisciplinary discussion (MDD), 18 patients with h-UIP were labeled as having unclassifiable IIP. The annual change in percent predicted FVC improved significantly in patients with h-NSIP ($P = .002$), who also had better survival than those with h-UIP ($P = .031$). In contrast, survival was not associated with HRCT scan pattern ($P = .79$).

CONCLUSIONS: The major histologic patterns in LD-CTD were UIP followed by NSIP. Two-thirds of patients had characteristic histologic features for LD-CTD. A majority of patients with h-UIP were considered to have unclassifiable IIP based on MDD. Patients with h-UIP had worse survival than those with h-NSIP. CHEST 2015; 148(6):1438-1446

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ABBREVIATIONS: ANA = antinuclear antibody; anti-Jo1 = anti-tRNA synthetase; CS = corticosteroid; CTD = connective tissue disease; h-NSIP = histologic nonspecific interstitial pneumonia; HRCT = high-resolution CT; h-UIP = histologic usual interstitial pneumonia; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LD-CTD = lung-dominant connective tissue disease; MDD = multidisciplinary discussion; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; %FVC = percent predicted FVC; PFT = pulmonary function test; SLB = surgical lung biopsy; UIP = usual interstitial pneumonia

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Current guidelines for the diagnosis and management of idiopathic interstitial pneumonias (IIPs) recommend an evaluation for underlying connective tissue disease (CTD), including serologic and other markers.[1,2] There are some patients with IIPs who have specific autoantibodies even in the absence of extrathoracic features of a definite CTD, and Fischer et al[1] proposed a new term for those patients: lung-dominant CTD (LD-CTD). It is important to know whether LD-CTD has a similar natural history to classifiable forms of CTD-interstitial lung disease (ILD) and whether the approach to the management of LD-CTD should be similar to that of CTD-ILD or to that of IIPs. However, little is known about its clinical features and high-resolution CT (HRCT) scan and histologic findings.

Among the histologic findings of LD-CTD, the frequency of major histologic patterns, such as usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP), is unknown. Also unknown is how disease behavior and survival are affected by histologic pattern and

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characteristic histologic features known to be associated with CTD, such as lymphoid aggregates with germinal centers and prominent plasmacytic infiltration. The aim of this study was to elucidate the clinical features, HRCT scan patterns, histologic patterns, multidisciplinary diagnosis, and clinical courses of serologically defined LD-CTD in patients who underwent surgical lung biopsy (SLB).

Materials and Methods

Study Subjects

Two hundred six consecutive patients who underwent SLB for diagnosis of ILD between January 2007 and December 2011 in Tosei General Hospital were retrospectively reviewed. Serologically defined LD-CTD was diagnosed when the following criteria were satisfied: (1) presence of any one of the following autoantibodies at initial evaluation: antinuclear antibody (ANA) > 1:320, nucleolar-ANA, rheumatoid factor (> 60 IU/mL), cyclic anticitrullinated peptide, anti-Sclero 70, anti-Ro/SSA, anti-La/SSB, anti-double-stranded DNA, anti-Smith, anti-ribonucleoprotein, anti-tRNA synthetase (anti-Jo1), and anti-centromere antibodies; (2) absence of a definite diagnosis of CTD (CTD was diagnosed when patients fulfilled American College of Rheumatology criteria[3-8]) or other known causes of ILD, including hypersensitivity pneumonitis and sarcoidosis.

Sixty-three patients were excluded from this study. They included patients with CTD-IP (n = 27), hypersensitivity pneumonitis (n = 23), sarcoidosis (n = 1), and others (n = 12). Among the remaining 143 patients, 44 patients were classified as serologically defined LD-CTD and included in this study. This study was approved by Tosei General Hospital institutional review board (IRB No. 263).

Data Collection

Clinical data were obtained retrospectively from patient records. We evaluated patient characteristics, pulmonary function tests (PFTs), Pao_2, BAL, and serologic test results. These tests were conducted in all patients who participated in this study within 1 month before biopsy. Spirometry (CHESTAC-55V; Chest M.I., Inc) and the diffusing capacity of the lung for carbon monoxide (CHESTAC-55V; Chest M.I., Inc) were measured according to the American Thoracic Society/European Respiratory Society recommendation as physiologic assessments and examined within 1 month before biopsy.[9,10] Abnormal cell counts in BAL fluid were defined by neutrophils > 3%, lymphocytes > 15%, and eosinophils > 1%.[11]

Histologic Assessment

The biopsy slides were all reviewed by two experienced pulmonary pathologists (J. F. and K. O.) who were blinded to clinical and radiologic information. Major histologic patterns were classified according to the current IIPs classification 2013.[2] Consensus diagnoses were made by these pathologists in cases of initial disagreement. In addition, characteristic histologic features for LD-CTD, including lymphoid aggregates with germinal centers, extensive pleuritis, prominent plasmacytic infiltration, and dense perivascular collagen, were evaluated in all biopsy specimens[1] (Figs 1A-C).

Radiologic Assessment

HRCT scans within 1 month before SLB were randomized and reviewed by two expert thoracic radiologists (K. F. and T. J.) who were blinded to clinical information and histologic diagnosis. The probability of UIP was evaluated and categorized by the criteria of the American Thoracic Society/European Respiratory Society/Japanese Thoracic Society/Latin American Thoracic Association guideline for idiopathic pulmonary fibrosis (IPF) (eg, UIP pattern, possible UIP pattern, and inconsistent UIP pattern).[12] Disagreements on the diagnosis were resolved by consensus. HRCT scan was performed with 1.0-mm-thick sections.

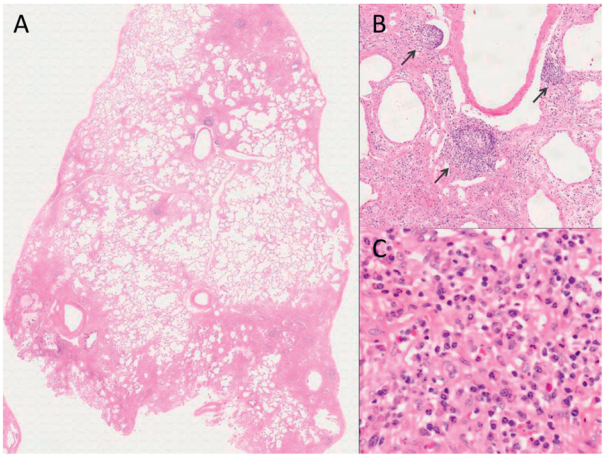

Figure 1 – *A-C, Characteristic histologic features for lung-dominant connective tissue disease (hematoxylin-eosin, original magnifications: A, ×1; B, ×40; C, ×200). Representative patient photomicrographs of histologic usual interstitial pneumonia pattern (A) with lymphoid aggregates with germinal centers (arrows) (B) and prominent plasmacytic infiltration (C).*

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