Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Clinico-radio-pathological characteristics of unclassifiable idiopathic interstitial pneumonias

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ARTICLE INFO

Article history:
Received 9 March 2017
Received in revised form
26 August 2017
Accepted 1 September 2017

Keywords:
Fibroblastic foci
Interstitial pneumonia with autoimmune features
Multidisciplinary discussion
Unclassifiable idiopathic interstitial pneumonia

ABSTRACT

Background: The purpose of this study was to clarify the clinico-radio-pathological characteristics and prognostic factors of unclassifiable-idiopathic interstitial pneumonias (U-IIPs) diagnosed by surgical lung biopsy.

Methods: Among 86 patients with interstitial pneumonia who underwent surgical lung biopsy from January 2005 to September 2013, 33 (38.4%; 16 male patients; mean age, 64.4 ± 8.8 years) were diagnosed with U-IIPs. They were subsequently categorized into rapidly progressive ($n = 7$), slowly progressive ($n = 7$), and stable ($n = 19$) groups based on the decrease of the percent predicted forced vital capacity or percent predicted diffusing capacity of the lung carbon monoxide and the occurrence of acute exacerbation. The clinico-radio-pathological features and survival rates of the patients who were followed up for at least 3 years were examined. These cases were reevaluated retrospectively by multidisciplinary discussion.

Results: The rapidly progressive group had a significantly poorer prognosis than that of the other groups ($p < 0.0001$). Although there were no significant pattern differences on the chest high-resolution computed tomography, the fibrosis scores were significantly higher in the rapidly progressive group ($p = 0.002$). Furthermore, the percentage of fibroblastic foci assessed by the pathological analysis was also significantly higher in the rapidly progressive group ($p = 0.006$). Nine (27.3%) patients developed connective tissue diseases during follow-up.

Abbreviations: CF, centrilobular fibrosis; CHP, chronic hypersensitivity pneumonitis; CVD-IP, collagen vascular disease-related interstitial pneumonia; DLco, diffusing capacity of the lung carbon monoxide; FF, fibroblastic foci; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonias; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; MPA, microscopic polyangiitis; NSIP, idiopathic nonspecific interstitial pneumonia; PPFE, idiopathic pleuroparenchymal fibroelastosis; SLB, surgical lung biopsy; U-IIP, unclassifiable-idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia

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http://dx.doi.org/10.1016/j.resinv.2017.09.001

Please cite this article as: Nakamura Y, et al. Clinico-radio-pathological characteristics of unclassifiable idiopathic interstitial pneumonias. Respiratory Investigation (2017), http://dx.doi.org/10.1016/j.resinv.2017.09.001

Conclusions: The radiologic patterns were not significantly different among the three clinical U-IIPs subgroups. Nevertheless, our findings suggested that the fibrosis scores and the percentage of fibroblastic foci could provide a prognostic assessment in U-IIPs.

1. Introduction

According to the 2013 American Thoracic Society/European Respiratory Society classification system, idiopathic interstitial pneumonias (IIPs) are now divided into three categories: (1) major IIPs, including idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia; (2) rare IIPs, including idiopathic lymphoid interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis (PPFE); and (3) unclassifiable IIPs (U-IIPs) [1].

The appropriate classification of IIPs requires a multidisciplinary approach with inputs from experienced pulmonologists, chest radiologists, and lung pathologists. As a result, some patients cannot be classified into a specific diagnostic category owing to overlapping histopathological features and major discrepancies among the clinical, radiological, and histologic features.

Ryerson et al. [2] reported that the incidence of the unclassifiable interstitial lung disease (ILD) was almost 10% ($n = 132$) in a cohort of 1370 patients with ILD. The most common reason for the diagnosis of unclassifiable ILD was the missing histopathological assessment owing to the high risk of surgical lung biopsy (SLB) or patient unwillingness. Therefore, to date, the clinico-radio-pathological characteristics of U-IIPs diagnosed by SLB have not been characterized clearly. The purpose of this study was to clarify the clinico-radio-pathological features and prognostic factors of U-IIPs diagnosed by a multidisciplinary approach.

2. Materials and methods

This study was approved by our institutional review board on July 28, 2016 (Toho University Omori Medical Center ethical committee; approval number M16074). Written informed consent for the study protocols was obtained from all patients (including a general informed consent).

We had a multidisciplinary discussion (MDD) conference with experienced radiologists and lung pathologists in Toho University Omori Medical Center and sequentially discussed and reevaluated approximately two U-IIPs cases, which had been diagnosed as U-IIPs at the previous MDD conference, once every two months since September 2013 according to the 2013 American Thoracic Society/European Respiratory Society classification system [1]. The reason for the diagnosis of U-IIPs is the major discrepancy among the clinical, radiological, histological features in all cases due to the presence of overlapping or concurrent histological features.

2.1. Patients

The medical records of 86 patients with interstitial pneumonia who underwent SLB at our hospital between January 2005 and September 2013 were retrospectively examined, and a total of 33 patients (38.4%; 16 males, 17 females; mean age, 64.4 ± 8.8 years) diagnosed with U-IIPs were identified. Other diagnoses included IPF ($n = 23$, 26.7%), NSIP ($n = 21$, 24.1%), chronic hypersensitivity pneumonitis (CHP) ($n = 5$, 5.8%), cryptogenic organizing pneumonia ($n = 2$, 2.3%), and PPFE ($n = 2$, 2.3%).

Patients with U-IIPs in this cohort were retrospectively categorized into three groups. The rapidly progressive group included patients with more than 10% decrease in the percent predicted forced vital capacity (%FVC), more than 15% decrease in the percent predicted diffusing capacity of the lung carbon monoxide (%DLco), or acute exacerbation within 12 months after diagnosis ($n = 7$). The slowly progressive group included patients with 5–10% decrease in %FVC, 10–15% decrease in %DLco, or acute exacerbation within 24 months compared with evaluations from 6 months earlier ($n = 7$). The stable group included patients who did not meet any of the criteria based on %FVC and %DLco within 24 months ($n = 19$). The clinico-radio-pathological features and survival rates of the patients who were followed up for at least 3 years (median, 60.5 ± 56.6 months) were examined.

Acute exacerbation of IIPs was defined according to the Japanese criteria [3] during chronic clinical course of IIPs as follows: (1) exacerbation of dyspnea within a month, (2) newly developing bilateral density elevation on high-resolution computed tomography (HRCT) scans, and (3) deterioration of hypoxemia (decrease of PaO_2 more than 10 mmHg under similar conditions). The gender (sex), age, and physiology (GAP) index was evaluated [4]. The cumulative amount of tobacco consumption expressed as the smoking index was defined as the number of cigarettes consumed per day multiplied by the years of smoking [5].

2.2. Clinical approach

We evaluated the results of the (1) serum marker tests including the Krebs von den Lungen-6, surfactant protein D, antinuclear antibody, and auto-antibodies related to connective tissue diseases, (2) pulmonary function tests (Chestac-33, CHEST Co. Ltd, Tokyo, Japan), (3) chest helical CT scans (Aquilion 16, Toshiba, Tokyo, Japan), and (4) Doppler echocardiography at initial admission for preoperative inspection. We also surveyed the classification criteria for interstitial pneumonia with autoimmune features (IPAF) prior to surgery [6]. We reviewed the records to ensure that the follow-up evaluations with the pulmonary function tests were performed every 3–6 months, similar to those done for IPF.

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