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The usefulness of KL-6 and SP-D for the diagnosis and management of chronic hypersensitivity pneumonitis

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ABSTRACT

Background: It is believed that Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) are useful biomarkers for the diagnosis of various types of interstitial lung diseases, including hypersensitivity pneumonitis (HP). The clinical features of chronic HP are similar to those of idiopathic interstitial pneumonias, especially idiopathic pulmonary fibrosis (IPF).
Objective: We sought to clarify the usefulness of serum KL-6 and SP-D for the diagnosis and management of chronic HP.
Methods: We examined serum KL-6 and SP-D levels and retrospectively evaluated the clinical parameters of acute HP (n = 35), chronic HP (n = 57), IPF (n = 54), collagen vascular disease-associated interstitial pneumonia (CVD-IP) (n = 67), and sarcoidosis (n = 47). We analyzed the relations between the two biomarkers and clinical data in chronic HP.
Results: Serum KL-6 and SP-D levels in acute HP (2710 U/ml and 338 ng/ml, median) and chronic HP (1500 U/ml and 264 ng/ml, median) were significantly higher than in IPF, CVD-IP, and sarcoidosis. The area under the curve (AUC) values for serum KL-6 and SP-D between chronic HP and IPF were 0.771 and 0.729, respectively. Serum KL-6 levels in chronic HP were significantly higher during episodes of acute exacerbation than 1 month before acute exacerbation. The serum KL-6 levels had correlations with serum SP-D and the percentage of lymphocytes in bronchoalveolar lavage fluid.
Conclusions: Serum KL-6 and SP-D levels are useful for the diagnosis and management of chronic HP.

1. Introduction

Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease induced by inhalation of antigens contained in various organic dusts. HP is usually classified into acute, subacute, and chronic forms, though the subacute form might be a variant of acute HP [1]. Chronic HP is thought to be influenced by persistent or recurrent exposure to an antigen. The clinical features of chronic HP, namely, the physical symptoms, the radiological and pathological abnormalities, and the prognosis, are similar to those of idiopathic pulmonary fibrosis (IPF). The early recognition of chronic HP is important, because antigen avoidance is the mainstay of therapy and differentiation from IPF is difficult in the advanced stage [2]. Careful disease monitoring and vigilant efforts to predict disease course are essential in the management of chronic HP.

Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) are useful biomarkers for the diagnosis of various types of interstitial lung disease (ILD) [3–5]. Measurement of serum KL-6 and SP-D is widely accepted, particularly in Japan, as a diagnostic test for ILDs and as a marker of disease activity [6–8]. Ohnishi et al. tested serum KL-6 and SP-D levels in patients with various ILDs, but no

Abbreviations: AE, acute exacerbation; ATS, American thoracic society; BAL, bronchoalveolar lavage; CRP, C-reactive protein; CVD-IP, interstitial pneumonia associated with collagen vascular diseases; ERS, European respiratory society; HP, hypersensitivity pneumonitis; IIPs, idiopathic interstitial pneumonias; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PaO_2, partial pressure of arterial oxygen; ROC, receiver operating characteristics; SP-D, surfactant protein D; UIP, usual interstitial pneumonia; %DLco, percentage predicted diffusing lung capacity for carbon monoxide; %VC, percentage predicted vital capacity.

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patients with HP were included in their population [9]. Some reports have shown elevations in serum KL-6 and SP-D in HP, but none of them compared serum KL-6 and SP-D levels among chronic HP, IPF, and other ILDs [10–13]. In this study, we sought to clarify the utility of serum KL-6 and SP-D measurements in the diagnosis and management of HP.

2. Patients and methods

2.1. Study population

Our subjects were patients with chronic HP, acute HP, IPF, collagen vascular disease-associated interstitial pneumonia (CVD-IP), and sarcoidosis, diagnosed between 1995 and 2011 at our institution. Patients complicated with lung cancer or treated for ILDs at initial measurements of serum KL-6 and SP-D were excluded. These patients were followed at our institution after diagnosis. The HP diagnosis was based on clinical, radiologic, and histologic criteria, as described previously [14]. The diagnostic criteria for chronic HP included reproduction of symptoms by an environmental provocation or laboratory-controlled inhalation of a causative antigen and/or antibodies or lymphocyte proliferation to the presumptive antigens, evidence of pulmonary fibrosis on a pathological examination, and respiratory symptoms related to HP for 6 months or longer. Chronic HP can be further subgrouped into a recurrent type and insidious type [15,16]. Patients with the recurrent type experience repeated acute episodes accompanied by fever. The insidious type has a slowly progressive course without acute episodes. The diagnosis of IPF was established using the criteria defined in the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement [17,18]. The patients diagnosed with CVD-IP were clinically classified as having rheumatoid arthritis, polymyositis and dermatomyositis, systemic sclerosis, or Sjögren's syndrome, according to the criteria for each disease. The diagnosis of sarcoidosis was established based on the guidelines of the ATS/ERS/World Association of sarcoidosis and other Granulomatous Disorders [19]. The criteria for acute exacerbations (AE) was described previously [20]. In brief, patients presented with unexpected worsening of dyspnea within 30 days and newly developed bilateral ground glass abnormalities on high-resolution computed tomography without evidence of pulmonary infection or heart disease. All patients with chronic HP underwent surgical lung biopsy. We collected the data at diagnosis including gender, age of onset, serum C-reactive protein (CRP), lactate dehydrogenase (LDH), KL-6, SP-D levels, partial pressure of arterial oxygen (PaO_2), percentage predicted vital capacity (%VC), percentage predicted diffusing lung capacity for carbon monoxide (% DLco), and percentage of lymphocytes in bronchoalveolar lavage (BAL) fluid.

2.2. Assessments of serum KL-6 and SP-D levels

We began by retrospectively comparing serum KL-6 and SP-D levels among several ILDs. Commercially available ELISA kits were used to determine the serum levels of both KL-6 (Eisai Co., Tokyo, Japan) and SP-D (Yamasa, Chiba, Japan). Serum KL-6 and SP-D levels are routinely measured monthly for the management of ILDs. The serum cut-off levels were 500 U/ml (KL-6) and 110 ng/ml (SP-D). Next, we focused on chronic HP. Differences of serum KL-6 and SP-D levels were analyzed by genders, causative antigens, histology in surgical lung specimens, clinical type, the treatment of prednisolone, and the occurrences of AE in chronic HP. The correlations of each serum marker with laboratory data, pulmonary function test measures, and BAL fluid profiles in chronic HP were also analyzed. This study conformed to the Declaration of Helsinki and was approved by the institutional review board (approval date: June 27 2012, approval number: 1253).

2.3. Histological assessment

Lung tissues were obtained from 57 cases with chronic HP, 8 cases with CVD-IP, 4 cases with IPF by video-assisted thoracoscopic surgery. Autopsy lungs were obtained from 1 case with IPF. All cases with sarcoidosis were performed transbronchial lung biopsies. Histological patterns were evaluated by two pulmonary pathology specialists. The background histological patterns of chronic HP were classified into usual interstitial pneumonia (UIP)-like, fibrotic nonspecific interstitial pneumonia (NSIP)-like, cellular NSIP-like, and organizing pneumonia (OP)-like patterns according to the ATS/ERS international consensus classification [18,21,22].

2.4. Statistical analysis

All analyses were performed using Prism 6 (GraphPad Software, Inc., San Diego, CA, USA). Data were expressed as medians and interquartile ranges. The Kruskal–Wallis test was used to compare the values of different groups. When significant differences between groups were observed, intergroup comparisons were assessed using the Mann–Whitney U test. The significance of differences among frequency data was evaluated using the χ^2 test. In the analyses of serum levels of KL-6 and SP-D, receiver operating characteristic (ROC) curves were used to find the cut-off values for optimal diagnostic accuracy. Cut-off levels were set as the points closest to 100% sensitivity and 100% specificity. The Wilcoxon matched-pairs test was used to compare serum KL-6 and SP-D levels among the episodes of AE, 1 month before, and 2 months before AE and among 1 month before prednisolone treatment, the start of the treatment, and 1 month after the treatment. Correlation coefficients were obtained using Spearman's rank order correlation. Significance was defined as $p < 0.05$. The significance level for multiple comparisons was controlled by applying the Bonferroni correction for multiple comparisons.

3. Results

3.1. Patient characteristics

The patient characteristics are shown in Table 1. We collected 35 patients with acute HP, 57 with chronic HP, 54 with IPF, 67 with CVD-IP, and 47 with sarcoidosis. The causative antigens of chronic HP included avian antigen in 41 patients, fungi in 2 patients, and unknown antigens in 14 patients. We identified 32 patients with UIP-like pattern, 16 with fibrotic NSIP-like pattern, 8 with cellular NSIP-like pattern, and 1 with OP-like pattern in chronic HP. Clinical types of chronic HP included 46 patients with recurrent type and 11 with insidious type. The 67 patients with CVD-IP included 30 with rheumatoid arthritis, 21 with systemic sclerosis, 11 with Sjögren's syndrome, and 5 with dermatomyositis. The 47 patients with sarcoidosis included 1 with stage 0, 11 with stage I, 24 with stage II, 8 with stage III, and 3 with stage IV according to chest X-ray staging. In all cases with sarcoidosis, we found noncaseating granulomas in the lung tissues obtained by transbronchial lung bipopsies.

A predominance of male patients was observed in chronic HP and IPF. A female predominance was observed in acute HP, CVD-IP, and sarcoidosis. Acute and chronic HP patients were diagnosed at a significantly younger age than IPF. Sarcoidosis patients were diagnosed at a significantly younger age than chronic HP, IPF, or CVD-IP. Serum CRP levels were significantly higher in acute HP than in chronic HP, IPF, and sarcoidosis. CRP levels were significantly higher in CVD-IP than in sarcoidosis. Serum LDH levels were significantly