ORIGINAL ARTICLE

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KL-6 as a novel marker for activities of interstitial pneumonia in connective tissue diseases

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Abstract The objective of this study was to determine the role of serum KL-6 levels as a marker for the activity of interstitial pneumonia in patients with connective tissue diseases. The serum concentrations of KL-6, a glycoprotein produced mainly by pulmonary type II epithelial cells, were measured in 21 patients with connective tissue disease. The activity of interstitial pneumonia was compared with the associated serum KL-6 concentrations. Serum KL-6 concentrations in patients with interstitial pneumonia were significantly higher than those in the controls. Among patients with active interstitial pneumonia, serum KL-6 concentrations following the treatment (after improvement) were significantly lower than the pretreatment values. The extent of the pulmonary fibrosis correlated positively with the serum KL-6 concentrations during the inactive phase of the interstitial pneumonia. These results suggest that sequential measurement of serum KL-6 levels is a new and useful means for the evaluation of interstitial pneumonia in patients with connective tissue diseases.

Key words Interstitial pneumonia · KL-6 · Corticosteroids · Marker

Introduction

Interstitial pneumonia is an interstitial inflammation of the lungs, mainly alveolitis, and is known as one of the major organ involvements in various connective tissue diseases [1, 2]. Interstitial pneumonia causes an increase in the volume of connective tissues and subsequently leads to the destruction of the pulmonary architecture and replaces the normal tissues with fibrotic tissues, i.e., leading to pulmonary fibrosis. These changes cause a functional failure of pulmonary gas exchange and render the prognosis poor. Corticosteroids and/or immunosuppressive agents have been used for treatments of interstitial pneumonia. These regimens, however, do not produce satisfactory therapeutic effects.

The evaluation of the activity of interstitial pneumonia is clinically relevant in the decision to either start or modify the treatment. Radiographs of the lungs and carbon monoxide diffusion capacity values in spirometry have been widely used for the evaluation. Recently, a computed tomography (CT) of the lungs is also being used. As serum markers, lactate dehydrogenase (LDH) levels and erythrocyte sedimentation rates (ESR) have been used. These methods, however, are clinically not satisfactorily sensitive and reliable due to their low sensitivity and specificity or the limited chances to perform these tests.

KL-6, a glycoprotein produced by type II epithelial cells of the lungs, has been measured in serum and is known as a marker for lung cancer [3] and idiopathic interstitial pneumonia [4]. In this study, we measured serum KL-6 concentrations and examined whether KL-6 levels could serve as a useful marker in evaluating the activities of interstitial pneumonia associated with connective tissue diseases.

Patients and methods

Subjects

Among patients with connective tissue diseases hospitalized in our department during the 3 years from February 1996, 21 had interstitial pneumonia diagnosed by chest radiographs and CT scans. These patients included 11 cases of systemic sclerosis (SSc), 6 cases of polymyositis/dermatomyositis (PM/DM), 2 cases of rheumatoid arthritis (RA), 1 case of systemic lupus erythematosus (SLE), and 1 case of overlap syndrome (SLE, PM, and SSc). Nine patients without interstitial pneumonia served as a control group (two cases...
each of RA, SLE, and PM/DM, and three cases of SSc). Diagnosis of each disease was made based on the American College of Rheumatology (ACR) preliminary criteria for SSc [5], the Bohan and Peter criteria for PM/DM [6], the 1987 revised diagnostic criteria of the ACR for RA [7], and the 1982 revised criteria for the classification of SLE for SLE [8].

Based on the activities of interstitial pneumonia, determined by changes in clinical symptoms and serial chest radiographs/CT scans, these patients with interstitial pneumonia were divided into two groups. One was an inactive group in which the above parameters remained stable for at least 6 months (14.5 ± 7.7 months), and included ten patients. The other was the active group (11 patients), which presented progression or deterioration of the interstitial pneumonia. In the active group, interstitial pneumonia in four patients responded and improved, as evaluated by clinical symptoms and chest radiographs, after treatment with corticosteroids (prednisolone 65.0 ± 10.0 mg/day) or immunosuppressive agents (azathioprine, methotrexate, or mizoribine).

Measurement of serum KL-6

Sera were stored at −80 °C. Serum KL-6 levels were determined by a commercially available kit (Eitest KL-6, Tokyo, Japan) based on the method reported by Kono et al. [3]. The kit is a sandwich-type enzyme immunoassay using an anti-KL-6 mouse monoclonal antibody. A total of 35 sera, including 26 from patients with interstitial pneumonia and 9 from the control group, were measured.

Statistical analysis

Values were expressed as the mean ± SD. The Mann–Whitney U-test for unpaired comparisons and the Wilcoxon Rank-Sum test for paired comparisons were used for comparisons of serum KL-6 levels between the two groups. Pearson’s correlation coefficients between serum KL-6 levels and the extent of pulmonary fibrosis were also determined. Statistical significance was defined as P < 0.05.

Results

Serum KL-6 concentrations were significantly higher in patients with interstitial pneumonia than in the control group (Fig. 1; 1517.5 ± 1347.1 vs 236.7 ± 78.2 U/ml, P < 0.01). Among patients with active interstitial pneumonia (the active group), serum KL-6 levels decreased after improvement (6.2 ± 5.4 months) following intensive treatments of the interstitial pneumonia as compared with the pretreatment values (Fig. 1; 695.6 ± 461.3 vs 2252.8 ± 1398.1 U/ml, P < 0.05). Serum LDH and C reactive protein (CRP) concentrations and ESR neither differed between patients with or without interstitial pneumonia (159.7 ± 52.6 vs 138.6 ± 40.5 mU/ml, P = 0.205; 1.89 ± 2.38 vs 1.30 ± 1.47 mg/dl, P = 0.903; 48.91 ± 38.52 vs 36.13 ± 35.49 mm/h; P = 0.655, respectively) nor varied markedly before and after treatment of interstitial pneumonia (175.6 ± 32.4 vs 173.8 ± 63.3 mU/ml, P = 0.946; 2.23 ± 2.97 vs 1.50 ± 2.30 mg/dl, P = 0.714; 47.75 ± 31.85 vs 44.80 ± 52.71 mm/h, P = 0.510, respectively). Figure 1 shows sequential changes in serum KL-6 concentrations in the same patient before and after the treatment. Serum KL-6 concentrations correlated well with the activity of interstitial pneumonia even in individual patients.

In patients with interstitial pneumonia remaining stable for more than 6 months (the inactive group), however, serum KL-6 concentrations varied widely between low (207 U/ml) and high (3726 U/ml) levels. Because KL-6 is also produced by regenerating epithelial cells in the lungs, we determined the extent of the pulmonary fibrosis on chest radiographs to estimate the amounts of regenerating epithelial cells in the lungs. Figure 2 shows the extent of pulmonary fibrosis expressed as the percentage in the inactive group positively correlated with serum KL-6 concentrations.

Discussion

Connective tissue diseases are often complicated by interstitial pneumonia, one of the most serious organ