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Serum KL-6 in fibrotic NSIP: Correlations with physiologic and radiologic parameters☆

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Summary
Backgrounds: Fibrotic nonspecific interstitial pneumonia (f-NSIP) has been recognized as a distinct disease entity. KL-6 has been reported to be a useful serum marker in interstitial lung diseases. However, few previous reports evaluated the value of serum KL-6 exclusively in f-NSIP, as distinct from other subtypes of idiopathic interstitial pneumonia, therefore the associations of serum KL-6 with clinical and radiologic findings in this population remain unclear.
Methods: Serum KL-6 levels were measured in twenty-six consecutive patients with f-NSIP diagnosed by surgical lung biopsy. Pulmonary function testing, bronchoalveolar lavage, subjective measurement of dyspnea using baseline dyspnea index (BDI), and HRCT were performed in parallel. Two radiologists conducted independent visual examinations of the pattern and extent of abnormalities on HRCT.
Results: Serum KL-6 levels were elevated above the cut-off level in all patients. In univariate analysis serum KL-6 levels showed negative correlations with BDI (rho $= -0.52$; $p < 0.01$). Serum KL-6 had positive correlations with the extent of several patterns of opacities (rho $= 0.56$–0.62; $p < 0.01$). Among them, only the extent of traction bronchiectasis in HRCT showed significant association with serum KL-6 in multivariate analysis (β-coefficient $= 0.043$; $p < 0.01$).

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Conclusions: Serum levels of KL-6 were elevated in f-NSIP, and were correlated with the extent of fibrotic abnormalities on HRCT, suggesting a value of serum KL-6 as a marker for fibrosis in f-NSIP.

Introduction

Fibrotic nonspecific interstitial pneumonia (f-NSIP) has been recognized as one of the major types of chronic idiopathic interstitial pneumonia, along with usual interstitial pneumonia/idiopathic pulmonary fibrosis (IPF).[1–3] Recently, f-NSIP has become recognized as a distinct disease entity with characteristic clinical, radiologic, and pathologic features that differ from other idiopathic interstitial pneumonias.[3] However, long-term prognosis and optimal therapeutic strategy remains largely unclear. Hence, the identification of useful biomarkers for f-NSIP is anticipated.

KL-6, one of potent candidates of serum markers for idiopathic interstitial pneumonias, is a high molecular weight, mucin-like glycoprotein classified as human MUC1 mucin. KL-6 was strongly expressed by atypical and/or regenerating type II pneumocytes in tissue sections from patients with interstitial lung diseases.[4] Serum levels of KL-6 have been reported to be elevated in various interstitial lung diseases such as idiopathic pulmonary fibrosis, collagen vascular disease associated interstitial pneumonias, and other interstitial lung disorders.[5–9]

Several reports have reported the role of KL-6 in patients with idiopathic interstitial pneumonias (IIPs),[10,11] Little study has, however, evaluated the value of serum KL-6 exclusively in patients with f-NSIP, distinct from other subtypes of IIPs. Moreover multidimensional evaluation including serum marker, clinical symptom, pulmonary function, bronchoalveolar lavage and high resolution CT findings is scarce in this population.

To assess whether serum KL-6 reflects clinical and radiological findings and is valid for serum marker in patients with f-NSIP, we hereby conducted a comprehensive study on the correlations between serum levels of KL-6 and other disease parameters including pulmonary function, severity of dyspnea, BAL findings, and high resolution CT findings in patients with idiopathic f-NSIP, the diagnosis of which was confirmed by surgical lung biopsy.

Materials and methods

Study subjects

The study was approved by the Ethics Committee of Tosei General Hospital. Consecutive patients with idiopathic nonspecific interstitial pneumonia diagnosed at Tosei General Hospital between April 2000 and March 2007 were retrospectively reviewed. All patients underwent surgical lung biopsy (SLB), and the diagnosis of f-NSIP was confirmed by two lung pathologists. Patients with clinically evident collagen vascular diseases were excluded. No patients had received medical treatment such as corticosteroid and immunosuppressants prior to SLB.

Shortly before the SLB, all patients underwent the following evaluations: (1) measurement of serum levels of KL-6, LDH, and C reactive protein (CRP); (2) arterial blood gas analysis while breathing room air; (3) pulmonary function testing; (4) bronchoalveolar lavage; (5) subjective measurement of dyspnea with baseline dyspnea index (BDI)(14); and (6) high resolution CT. Measurements of serum KL-6 were performed using an electrochemiluminescence immunoassay kit (Sanko Junyaku; Kobe, Japan; reference range $<$500 U/mL) following the instructions of the manufacturer. Serum LDH and CRP levels were measured using commercially available kits (for LDH: Sika-liquid LDH-J, Kantoh Kagaku, Tokyo, Japan, reference range 119-229 U/L; for CRP: Iatro-CRP, Mitsubishi Chemical Medience, Tokyo, reference range $<$0.301 mg/dL). We adopted the upper limits of the reference levels as the cut-off points in order to assess the diagnostic sensitivities of KL-6, LDH, and CRP.

Analysis of high resolution CT findings

CT scans were obtained with 2 mm collimation at 10–15 mm intervals through the chest. The images were reconstructed using a high spatial frequency algorithm. Two radiologists independently interpreted patterns and extents of pulmonary parenchymal abnormalities on CT scans. They were blind to patients' information including serum concentration of KL-6. The patterns of parenchymal abnormalities were subcategorized into areas of ground-glass opacity, air-space consolidation, irregular linear opacity, and honeycombing. Presence of traction bronchiectasis was also assessed. Extents of abnormalities were semi-quantitatively scored according to a previous report.[12] The images were visually assessed at the following five levels: aortic arch, azygos arch, distal portion of the bronchus intermedius, right inferior pulmonary vein, and liver dome. The extent of each pattern of parenchymal abnormality was scored to the nearest 5% level. The overall extent of lung involvement was calculated by combining the figures of visual estimation at each level with correction factors of 1.1, 1.2, 1.4, 1.3, and 1.0 at each corresponding level for lung volume. We also defined the extent of traction bronchiectasis as the number of lung segments which were involved with traction bronchiestasis. Averaged scores of the two observers were used for the statistical analysis.

Statistical analysis

Binomial exact 95% confidence intervals (CIs) were calculated for the sensitivities of serum markers. The correlations between serum KL-6 and continuous variables were assessed using Pearson's correlation analysis. As the distribution of serum KL-6 levels was not normal, a natural logarithmic transformation was made to achieve normality.