Serum KL-6 Level as an Indicator of Active or Inactive Interstitial Pneumonitis Associated with Connective Tissue Diseases

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Abstract

Objective To elucidate the cut off levels of serum KL-6 indicating patients with interstitial pneumonitis (IP) and patients with active IP associated with connective tissue diseases (CTDs).

Methods CTD patients whose serum KL-6 level was measured were included. IP was diagnosed on the basis of medical records including XP/CT findings, and active IP was assumed in case that intervention for IP was newly added. The cut off levels were determined by receiver operating characteristic (ROC) curve analysis.

Results Among 240 (174 females) patients, 67 (42) had IP and 15 (9) had active IP. The ages of patients with and without IP, and with active IP and with inactive IP were 70.3±9.5 and 62.8±15.3, and 72.8±8.1 and 69.6±9.8, respectively. IP was significantly more prevalent in males and the elderly. The KL-6 levels were 990±90 and 301±12 U/mL in patients with and without IP, and 1,905±236 and 726±54 U/mL in those with active IP and with inactive IP, respectively. ROC curve analysis showed a cut off level of 509 U/mL for indicating IP, and that of 1,051-1,060 U/mL for indicating active IP.

Conclusion A serum KL-6 level of higher than 500 U/mL is a marker of the presence of IP, and a level of higher than 1,000 U/mL is a marker of the presence of active IP associated with CTDs.

Key words: KL-6, cut off level, interstitial pneumonitis, connective tissue diseases

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Introduction

Connective tissue diseases (CTDs) are characterized by multiple organ involvement including interstitial pneumonitis (IP) as one of the most critical illnesses. Although early diagnosis and treatment of IP is necessary, its development is sometimes masked by other organ involvement, and differentiation of active IP progression from preexisting stable IP is not very easy. Among a certain population of CTD patients having IP, many have it as an inactive fibrosis or chronic IP with very slow progression, in which case, massive doses of steroids or immunosuppressants should be avoided.

KL-6, krebs von den Lungen-6, a mucin-like high molecular weight glycoprotein preferentially expressed in regenerating type II pneumocytes, has been adopted as a serum marker of active IP (1), and the normal reference range when measured using a commercially available kit is set at less than 500 U/mL (2). However, in our clinical practice, some CTD patients showing a clearly higher KL-6 level than the upper normal range frequently have a quite stable IP.

In this study, we examined whether it is valid to regard a CTD patient showing a KL-6 level higher than the upper normal range as developing active IP. In addition, the cut off
levels for indicating cases of IP, and for discriminating cases with active IP from those with inactive IP were determined.

### Methods

Patients with CTDs who visited the Japanese Red Cross Medical Center between May, 2006 and July, 2009, and whose serum KL-6 level was measured were included. IP was diagnosed on the basis of medical records: diagnostic description by doctors in charge including subjective complaints, fine crackles, XP/CT findings, which were interpreted by radiologists, pulmonary function tests, and SpO2. Active IP was assumed mainly on the basis of newly added intervention for IP.

Serum KL-6 level was measured using LumipulsePrest KL-6 EIZAI (Sankojunyaku, Japan). For the patients in whom KL-6 level was measured twice or more, the peak level was adopted. KL-6 level was compared first between patient groups with and without IP, and then between the subgroups with active IP and with inactive IP. Cut off levels differentiating each pair of the patient groups were determined by receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, and diagnostic accuracy of the cut off levels were examined.

Statistical analysis was performed using Microsoft Office Excel 2007. The obtained data are presented as mean±standard deviation (SD). A p value of <0.05 was adopted for indicating a significant difference. Sequential changes in KL-6 level, before and after the newly introduced therapy for exacerbated IP, in a patient with the most available data were analyzed.

### Results

In total, 1,071 serum samples were measured for KL-6 level during the study period. These samples were obtained from 240 CTD patients. Among them, 123 patients had more than one measured KL-6 level. The underlying diseases were rheumatoid arthritis in 83, Sjögren’s syndrome in 42, systemic sclerosis in 22, polymyositis/dermatomyositis in 14, systemic lupus erythematosus in 7, and other diseases in 72. Among the 240 patients, 67 had IP and 173 did not. Among the 67 patients with IP, 15 were assumed to have actively progressing IP and 52 were assumed to have inactive stable IP (Table 1). During the study period, an 81-year-old female patient with ANCA-associated vasculitis, who showed a KL-6 level of 1,617 U/mL, eventually died of IP. No patient with inactive IP did not have therapy for their IP during the study period.

The numbers of females and males among all of the patients and in each subgroup are listed in Table 1. IP was significantly more prevalent in male patients (p=0.03 by the \( \chi^2 \) test), but no statistically significant gender difference was observed between patient groups with and without active IP (p=0.81). The ages of all the patients and of each patient group are listed in Table 1. The age was significantly higher in patients with IP than in patients without IP (p<0.001). Between the patient group with active IP and that with inactive IP, the age did not significantly differ (p>0.1).

Serum KL-6 levels are also listed in Table 1 and distribution of them is shown in Fig. 2. The patients having IP showed a higher KL-6 level than the patients without IP (p<0.001). When the patients having IP were divided into those with active IP and with inactive IP, the KL-6 level was significantly higher in patients with active IP (p<0.001).

ROC curve analysis for differentiating patients with IP from patients without IP showed a cut off level of 509 U/mL (sensitivity, 0.791; specificity, 0.93; diagnostic accuracy, 0.896) (Fig. 1A). The ROC curve analysis for differentiating patients with active IP from those with inactive IP showed a cut off level in the range of 1,051-1,060 U/mL (0.867; 0.865; 0.866) (Fig. 1B). The diagnostic accuracy for active IP was the highest at 1,400 U/mL. The ROC curves for differentiating patients with and without IP, and differentiating the subgroups with active IP and with inactive IP, are shown in Fig. 1C. Approximately 500 U/mL and 1,000 U/mL were the optimal levels.

Fig. 3 shows the changes in serum KL-6 level in a 62-year-old female patient with dermatomyositis who had had stable IP for over 4 years and was taking 5 mg of prednisolone. Her IP progressed after that. An intervention with 2 courses of pulsed methylprednisolone at 1 g for 3 days followed by a daily treatment with 30 mg of prednisolone and 150 mg of cyclosporine A was required. She responded adequately and her KL-6 level gradually decreased during convalescence.

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### Table 1. Age, Female/Male Ratio, and Serum KL-6 Level in Patients with Connective Tissue Diseases

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Age (mean±SD)</th>
<th>Female/Male</th>
<th>KL-6 (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>240</td>
<td>64.9±14.3</td>
<td>174/66</td>
<td>493±33</td>
</tr>
<tr>
<td>with IP</td>
<td>67</td>
<td>70.3±9.5</td>
<td>42/25</td>
<td>990±90</td>
</tr>
<tr>
<td>without IP</td>
<td>173</td>
<td>62.8±15.6</td>
<td>p&lt;0.001</td>
<td>301±12</td>
</tr>
<tr>
<td>with active IP</td>
<td>15</td>
<td>72.8±8.1</td>
<td>p&lt;0.05</td>
<td>1906±236</td>
</tr>
<tr>
<td>with inactive IP</td>
<td>52</td>
<td>69.6±9.8</td>
<td>p&gt;0.1</td>
<td>726±54</td>
</tr>
</tbody>
</table>

IP, interstitial pneumonia.
Discussion

KL-6, sialylated carbohydrate antigen KL-6, is one of the human MUC1 antigens expressed on type II pneumocytes and respiratory bronchiolar epithelial cells in early gestational age (3), and regenerating alveolar epithelial cells (4), and is detected in the circulation. Although a small amount of KL-6 appears on the surface coat of alveolar cells in normal lungs, the proliferation and regeneration of type II pneumocytes enhance KL-6 production. Staining showed KL-6 in a linear pattern in the surface of air spaces in CTD-associated IP (4). In cases where the alveolar lining cells and alveolar capillaries are involved, KL-6 is considered to more easily pass through the alveolar wall to the bloodstream. IP is the representative of such a case in that both production and transference is enhanced (1).

When comparing CTD-associated IP with idiopathic IP, the prognosis of the former might be better. However, because long-term use of steroids and/or immunosuppressants for underlying CTD induces severe susceptibility to infections or other adverse reactions, ineffectual and unnecessary therapy with these drugs must be avoided. In addition, the nature of multiple organ involvement makes it difficult to
evaluate IP precisely. A valid diagnosis of IP, particularly in determining whether it is active or inactive, is more necessary for CTD-associated IP than for idiopathic IP.

Studies of serum KL-6 level in CTD patients showed the increased levels in the patients with IP in general, when compared with healthy controls or CTD patients without IP (5-8). These studies showed diverse levels for different patient groups. A report indicated that a level of 1,000 U/mL discriminates nonsurvivors from survivors among idiopathic and CTD-related pulmonary fibrosis patients (9). However, the numbers of CTD patients are not mentioned. Another report showed a cut off level of 500 U/mL discriminating active IP from inactive IP associated with CTDs (10). Although a longitudinal analysis of serum KL-6 levels showed that its rapid increase is associated with the deterioration of pulmonary fibrosis (5), and another study showed a decrease in KL-6 level after cyclophosphamide therapy (11), a cut off level was not indicated. As a study of reference range of serum KL-6 level for the Japanese population showed an age-dependent increase and a higher level in males over 40 years of age, and this study revealed the predominance of IP in males and the elderly, the interpretation of the level demands careful consideration (12).

In this study, a KL-6 cut off level indicating IP, and a KL-6 cut off level indicating active IP were elucidated. This study would be the first to determine both levels for CTD patients. Although IP is one of the major complications of CTDs, stable, inactive, or very slowly progressing IP is prevalent in general, as was observed in this study. ROC curve analysis revealed the optimal cut off level of 500 U/mL for suspecting IP, which is just the normal upper limit level indicated in the instruction booklet. However, even when the level is higher than the limit of 500 U/mL, a level remaining at less than 1,000 U/mL suggests only the presence of IP, in this study. Actively progressive IP, which requires intervention, shows a level higher than 1,000 U/mL.

The diagnostic accuracy for active IP was the highest at 1,400 U/mL. A clear increase by a substantial extent would also suggest an active disease development, as is shown in Fig. 2.

Among active IP associated with CTD, acutely progressive IP with potentially fatal outcome is known. Although 1 patient with ANCA-associated IP died of it, our patients did not include a number of such severe cases. The KL-6 level that discriminates such patients would be better elucidated in the future.

In conclusion, a serum KL-6 level of higher than 500 U/mL is a marker of the presence of IP, and a level of higher than 1,000 U/mL is a marker of active IP associated with CTDs.

The authors state that they have no Conflict of Interest (COI).

References