Role of KL-6 in evaluating the disease severity of rheumatoid lung disease: comparison with HRCT

Fumiko Kinoshita*, Hidefumi Hamanoa, Hiromi Haradaa, Toshiyuki Kinoshitaa, Tadashi Igishib, Hiroshi Haginoc, Toshihide Ogawaa

aDepartment of Radiology, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8504, Japan
bThird Department of Internal Medicine, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8504, Japan
cDepartment of Orthopedic Surgery, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8504, Japan

Received 1 July 2003; accepted 12 April 2004

Summary Objective: To determine the role of KL-6 (Krebs von den Lungen-6) in evaluating the disease severity of pulmonary lesions in rheumatoid arthritis (RA) compared with high resolution computed tomography (HRCT) findings.

Methods: Fifty serum KL-6 levels and HRCT images were prospectively obtained from 47 RA patients. Eight HRCT findings were classified into five grades. Patients were also divided into two groups according to the KL-6 threshold level and HRCT findings were evaluated.

Results: There was a positive correlation between the serum KL-6 level and the total CT score ($r = 0.83$). Reticular opacity most closely related to the serum KL-6 levels ($r = 0.84$). In the high KL-6 group ($n = 10$), the average CT score was markedly increased (64.6 points) and severe honeycombing expanded into the whole lung. One case revealed diffuse ground glass opacity. In 12 of 40 cases in the normal KL-6 group, CT scores mildly increased compared with the other cases (over 20 points). The predominant finding of these cases could be classified into four types: (1) narrow spread honeycombing; (2) subtle fibrosis; (3) airway diseases; and (4) dense consolidation.

Conclusion: KL-6 is a useful marker to detect severe RA lung disease. It is also useful to distinguish non-fibrosis from fibrosis predominant cases. However, it sometimes could not detect early stage RA lung disease.

© 2004 Elsevier Ltd. All rights reserved.

KEYWORDS
Rheumatoid arthritis; Interstitial pneumonitis; KL-6; HRCT; Disease severity

Introduction

Pulmonary involvement, which can consist of a wide range of pathological changes including pulmonary fibrosis (PF), is frequently found in patients with rheumatoid arthritis (RA) and is called rheumatoid lung disease (RA lung). If it is not well controlled, respiratory failure follows and becomes ultimately fatal. Therefore, it is important to detect early stage disease and to precisely estimate its pattern and extent.
When evaluating the disease activity of RA lung, arterial gas analysis, clinical symptoms, chest radiograph, lactate dehydrogenase, and pulmonary function test have been used. However, these markers are not always sensitive and are sometimes nonspecific. KL-6 (Krebs von den Lungen-6), a new serum indicator for PF discovered by Kohno et al. in 1985, has been reported to correlate with clinical manifestation and has been investigated in RA lung. Oyama et al. reported that serum KL-6 levels showed no other significant correlation with parameters of disease activity such as erythrocyte sedimentation rate, C-reactive protein, IgM-rheumatoid factor, and IgG-rheumatoid factor in RA. Further, it was not influenced by extrapulmonary inflammation, and abnormal elevation of serum KL-6 levels strongly indicated the complication of active interstitial pneumonitis. They concluded that KL-6 was a valuable indicator in the management of the disease activity of RA lung.

On the other hand, high resolution computed tomography (HRCT) also provides useful information to assess the RA lung. Previous studies described its radiologic-pathologic correlation, and there is a general consensus that HRCT findings are highly correlated with pathological findings. Although some studies have investigated the relation between pulmonary function and chest radiographic findings in RA lung, correlation of KL-6 with HRCT has not been fully investigated. In this study, we compared serum KL-6 levels with HRCT findings in RA patients to determine a role for KL-6 in evaluating disease severity.

Subjects and methods

The subjects of this prospective study were 47 consecutive patients with RA (33 females and 14 males; aged 37–79 years; mean, 63.5), seen at our hospital between January and June 1999. All patients were clinically and serologically diagnosed as RA by an orthopedist and underwent treatment according to their symptoms over a period of 6 months. All fulfilled the revised criteria of the American Rheumatism Association for RA. Patients who had a clinical history of another lung disease, or had other complications like drug-induced pneumonitis as the side effects of treatment for RA were excluded from this study.

Fifty HRCT scans and KL-6 examinations were prospectively obtained from the 47 patients who gave informed consent prior to the examinations. Three patients had two HRCT scans and KL-6 examinations, each separated by intervals of 2–10 weeks. All KL-6 examinations were performed within 2 weeks before or after HRCT. Serum KL-6 levels were measured by a sandwich type of enzyme-linked immunosorbent assay using a KL-6 antibody kit (ED046; Eisai; Tokyo, Japan). The threshold level for serum KL-6 was determined at 520 unit/ml; level reported by Kohno et al. previously. On evaluation, patients were classified into two groups according to their serum KL-6 level; a normal KL-6 group: KL-6 < 520 U/ml and a high KL-6 group: KL-6 ≥ 520 U/ml.

HRCT evaluation

HRCT was performed using a Somatom Plus S CT unit (Siemens; Erlangen, Germany), with 2-mm collimation at 15-mm intervals at end inspiration from the lung apices to the bases. Expiratory HRCT scans at three selected levels were also obtained (aortic arch, hila, and lower lobes). All images were reconstructed with a high-spatial frequency algorithm, and photographed at window widths of −1500 H.U. and window levels of −600 H.U.

Six HRCT images at end inspiration, two slices each from the upper, middle and lower lung, were selected and analyzed. Two experienced chest radiologists, blinded to the clinical information, evaluated the HRCT images focusing on 8 findings: (1) nodular opacities, defined as well marginated nodules including micronodules, nodules and conglomerate masses; (2) bronchial dilatation and wall thickening, defined as abnormally dilated bronchial divisions with or without bronchial wall thickening including thickened bronchovascular bundle and traction bronchiectasis as well as tubular bronchiectasis; (3) pleural thickening; (4) reticular opacities, defined as reticular network of lines including intralobular reticular opacities and honeycombing; (5) linear opacities, defined as thin linear opacities of irregular thickness of 1–3 mm, including interlobular septal thickening, nonseptal line, subpleural curvilinear shadow, and band shadow; (6) increased lung opacities, defined as increased attenuation of lung parenchyma including ground glass opacities (GGO) and parenchymal opacification; (7) lung cysts, defined as thin-walled air spaces; and (8) emphysema, defined as diffusely decreased pulmonary attenuation. Air trapping on expiratory scans was also referred to when evaluating the findings numbers (2) and (8).

To determine the distribution of parenchymal abnormalities, we used a slight modification of the visual estimation method described by Davies et al. The findings were visually classified into five grades according to their extent. Each CT slice
level was divided into four areas according to a horizontal and a vertical line drawn by the first observer and scored in a semiquantitative manner as follows: 0 = absent; 1 = less than 25% involved; 2 = 25–50% involved; 3 = 50–75% involved; and 4 = greater than 75% involved. The final judgment was reached by consensus. Scores were added to obtain total scores for each patient and the cases were graded into three types according to their total CT scores: normal = 0–20 points; mildly abnormal = 21–40 points; remarkably abnormal >41 points.

Data were expressed as means ± standard deviation. The correlation between the CT scores and the serum KL-6 levels was calculated using Pearson’s correlation coefficients.

Results

The serum KL-6 levels ranged from 145 to 1863 U/ml, with a median value of 443.0 ± 34.5 U/ml. Total CT scores ranged from 0 to 84 with a median value of 23.6 ± 24.6 points. There was a positive correlation between total CT scores and serum KL-6 levels (r = 0.83, P < 0.001) (Fig. 1a).

Table 1 reveals the correlation coefficient between serum KL-6 levels and CT scores of the eight findings. Six findings, excepting nodular opacity and emphysema, had positive correlation. Especially reticular opacity (r = 0.84; Fig. 1b), pleural thickening (r = 0.79), increased lung opacity (r = 0.70; Fig. 1c), lung cyst (r = 0.67), and linear opacity (r = 0.60; Fig. 1d) had a high correlation with serum KL-6 levels.

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>Total CT score</th>
<th>Reticular opacity</th>
<th>Pleural thickening</th>
<th>Increased lung opacity</th>
<th>Lung cyst</th>
<th>Linear opacity</th>
<th>Bronchial dilatation, wall thickening</th>
<th>Emphysema</th>
<th>Nodular opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient</td>
<td>0.83*</td>
<td>0.84*</td>
<td>0.79*</td>
<td>0.70*</td>
<td>0.67*</td>
<td>0.60*</td>
<td>0.52*</td>
<td>0.12</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*P < 0.01

Figure 1 Plots of correlations between serum KL-6 levels and HRCT score. HRCT score has good correlation with serum KL-6: (a) total HRCT score (r = 0.83); (b) HRCT score of reticular opacity (r = 0.84); (c) increased lung opacity (r = 0.70); and (d) linear opacity (r = 0.60).
Ten cases were classified into the high KL-6 group (Table 2); with 9 of the 10 revealing remarkably abnormal CT findings having total CT scores over 60 points. The main abnormal HRCT finding of this group was honeycombing expanded into the whole lung and was mainly comprised of reticular opacities, pleural thickening, increased lung opacities, and linear opacities (Fig. 2). Only one case had diffusely distributed GGO and a mixture of honeycombing (Fig. 3).

Forty cases were classified into the normal KL-6 group; 28 had normal HRCT findings, whereas 12 had abnormal CT findings. Eleven cases revealed mildly abnormal CT findings with CT scores of 21 through 40 points, and one revealed remarkably abnormal CT findings with CT score of 41 points. In these cases, HRCT revealed four main abnormal patterns: narrow spread honeycombing with subpleural linear shadows (Fig. 4); subtle fibrosis consist of a nonseptal line, septal thickening, intralobular reticular opacities, and localized GGO (Fig. 5); airway disease such as bulla, emphysema, and bronchial dilatation and wall thickening (Fig. 6); and patchy air-space consolidation associated with GGO within a small area (Fig. 7).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Average serum KL-6 level and total HRCT score in each group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum KL-6 level (U/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>High KL-6 group ( (n=10) )</td>
<td>1102.4 ± 440.7</td>
</tr>
<tr>
<td>Normal KL-6 group ( (n=40) )</td>
<td>278.1 ± 106.5</td>
</tr>
</tbody>
</table>

Figure 2 A 48-year-old woman in the high KL-6 group (serum KL-6 level = 1092, total HRCT score = 65.5). HRCT shows bilateral extensive honeycombing with traction bronchiectasis. This finding expands into the whole lung.

Figure 3 A 56-year-old man in the high KL-6 group (serum KL-6 level = 1086, total HRCT score = 83.5). HRCT demonstrates bilateral diffuse ground glass opacities. Traction bronchiectasis and mild honeycombing are also present. This patient died one month after this examination.

Figure 4 A 65-year-old woman in the normal KL-6 group (serum KL-6 level = 479, total HRCT score = 41). HRCT demonstrates narrow spread honeycombing predominantly in subpleural region in the bilateral lung bases.
Discussion

RA lung is one of the major extraarticular complications in patients with RA, and shows various types of pulmonary lesions such as necrobiotic nodule, pleuritis, bronchiolitis obliterans organizing pneumonia (BOOP), bronchiolitis obliterans (BO), arteritis, lymphoid hyperplasia, and PF. Above all, bronchiectasis and interstitial lung involvement are the most common CT features. Though in previous reports the prevalence has been shown to vary according to the diagnostic criteria and method used, it is known from recent HRCT studies, that bronchiectasis is the most frequent abnormality, reaching up to 40% of cases. On the other hand, the frequency of PF is also reported to be as high as around 40%. Some patients with RA lung develop severe respiratory failure caused by extensive fibrosis; while it usually progresses slowly, accelerated deterioration also occurs. Therefore, it is necessary to precisely evaluate disease activity and to detect early stage lesions.

KL-6, a serum indicator of disease activity that has recently been utilized, is a mucinous high-molecular weight glycoprotein, which is strongly expressed on proliferated type 2 alveolar pneumocytes and epithelial cells. In alveolitis, inflammatory cells damage basement membrane and epithelial cells of the alveolar wall, followed by regenerated type 2 alveolar pneumocytes appearing over the basement membrane. KL-6 may be released into blood by the injured epithelial cells within the lung compartment. Measurements of these molecules in peripheral blood may reflect the degree of leakage from alveolus to the capillaries. Previous reports have revealed KL-6 to be a useful marker reflecting the severity of pulmonary fibroproductive lesions. It can be used to evaluate disease activity in various lung diseases besides idiopathic pulmonary fibrosis such as radiation pneumonitis and pneumocystis carinii pneumonia, which cause fibrotic lesions. KL-6 has also been reported to be useful for detecting active PF in RA lung. In this study, there was a positive correlation between serum KL-6 levels and total HRCT scores. Furthermore, 9 of the 10 cases with increased serum KL-6 levels had remarkably high CT scores of over 41 points. On the other hand, CT scores of 39 of the 40 cases with normal KL-6 level were under 40 points. As previous reports have mentioned, high serum KL-6 level is sufficient evidence to diagnose that there is severe fibrotic lesions of RA lung.

In clinical cases, when RA patient are seen to have a high serum KL-6 level, HRCT can reveal severe honeycombing or diffusely expanded GGO.

Figure 5 A 47-year-old woman in the normal KL-6 group (serum KL-6 level = 348, total HRCT score = 31.5). HRCT demonstrates bilateral increased interstitial markings, mainly nonseptal line, in the lower lung zone corresponding to subtle fibrosis.

Figure 6 A 55-year-old woman in the normal KL-6 group (serum KL-6 level = 258, total HRCT score = 28). There is marked bronchiolectasis and wall thickening.

Figure 7 A 71-year-old woman in the normal KL-6 group (serum KL-6 level = 202, total HRCT score = 29). There is localized ground-glass opacity with peripheral dense consolidation in the right lower lung.
In our study the HRCT finding that best correlated with serum KL-6 level was reticular opacity. And in four of the five cases with extremely high KL-6 levels (over 1000 U/ml), honeycombing involved the whole lung associated with pleural thickening and linear opacities. Reticular opacity reveals ongoing fibrotic process; while in early stage fibrosis, fine reticulation can be observed in the lower lung zones. As fibrosis develops, reticular opacities progress to peripheral honeycombing, which then expands from the periphery to the central lung. This process progresses slowly and is often irreversible; a high KL-6 level could reflect this slow progression.

On the other hand, increased lung opacity was the third most correlated HRCT findings with serum KL-6 level. In four of the five cases with extremely high KL-6 levels, it was observed as a mixed pattern with reticular opacities. In another case, GGO, which has been known to be a valuable indicator for disease activity, was recognized throughout the lung. In early stage fibrosis very fine fibrosis is often observed as localized GGO, and in the stage of accelerated deterioration diffuse GGO is observed reflecting active alveolitis. GGO is also reported to correlate with pathological disease activity or the response to treatment. In our study the patient with diffuse GGO died 1 month after examination and suggested to be in the condition of accelerated deterioration. High KL-6 level could also reflect rapid progression.

When a RA patient is seen to have a normal KL-6 level, HRCT generally will reveal normal findings, but sometimes abnormal findings can be revealed. In the present study, HRCT described four main abnormal patterns in normal KL-6 level patients. The presence of narrow spread honeycombing and subtle fibrosis suggested mild PF. Although the finding of early stage RA lung is not well described, it has been reported to resemble that of early stage PF. Thus, a mild PF pattern might correspond early stage RA lung. The presence of airway diseases suggested a BO lesion of RA lung, while dense consolidation within a small area suggested a BOOP lesion of RA lung. These two patterns correspond to nonfibrotic lesions of RA lung. Increases of the serum KL-6 level has been reported not only in PF but also in pulmonary alveolar proteinosis, sarcoidosis and pulmonary tuberculosis. Various lung diseases cause proliferation of type II alveolar pneumocytes, epithelial cell injury, and alveolar-capillary permeability changes, which cause an increase of the serum KL-6 level. In RA lung, the wide spectrum of pathologic patterns are recognized as reflecting the various types of pulmonary lesions, except fibrosis. However, HRCT findings representing those patterns had less correlation with the serum KL-6 level. This result suggests that KL-6 is useful to distinguish nonfibrosis predominant cases from fibrosis predominant cases.

Unfortunately, this study still remains an attempt to acquire preliminary data that will provide a foundation for future studies. For a better objective evaluation of the disease activity, it will be necessary to examine changes of CT findings within longer periods. In this study, due to our short research period, serial CT studies were obtained in just three patients in the high KL-6 group. In two of the three cases HRCT findings did not change even if KL-6 levels remained high. In the other case, serum KL-6 decreased as HRCT findings improved after treatment. There are many reports which have described that the serum KL-6 level decreased after successful treatment for accelerated deterioration. KL-6 measurement might be useful to follow-up the disease activity. Further study involving larger numbers of patients is necessary, which focuses on how the HRCT findings change after 1 to several years as KL-6 change.

Consequently, in cases with a high serum KL-6 level, HRCT reveals severe fibrotic changes at a high frequency. In cases with normal serum KL-6 levels, HRCT generally reveals normal findings, though sometimes narrow spread fibrosis, airway diseases, and BOOP can be revealed. KL-6 seems to be difficult to detect subtle fibrotic changes. However, KL-6 is useful to distinguish nonfibrosis from fibrosis predominant cases. KL-6 is a convenient, objective, and sensitive marker to estimate disease severity; nevertheless, it is an ancillary tool that can help screen the RA lung. These two examinations, KL-6 and HRCT, play supplemental roles in the evaluation of disease severity.

Acknowledgements

We are extremely grateful to Patrick J. Fultz, MD (Department of Radiology, University of Rochester, Rochester, NY) for his support with editing of the manuscript.

References


