Comparison of Pulmonary HRCT Findings and Serum KL-6 Levels in Patients with Sarcoidosis

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**Purpose**

KL-6 is a mucin-like high molecular weight glycoprotein that is expressed on type II pneumocytes and respiratory bronchiolar epithelial cells in the normal lung [1,2]. Serum levels of KL-6 are elevated in various respiratory and non-respiratory conditions including breast and pancreatic cancers [3,4], and diabetes mellitus [5]. This observation has led to a focus on the use of KL-6 as a diagnostic and prognostic tool in respiratory diseases.

Serum and bronchoalveolar lavage fluid levels of KL-6, first described by Kohno et al. in 1988 [6], were raised in patients with interstitial pneumonia [1,2,7]. Several investigators have also reported that KL-6 is a useful serum marker to confirm diagnosis and for long-term management in patients with diffuse pulmonary diseases, particularly interstitial lung diseases. Patients with idiopathic pulmonary fibrosis or non-specific interstitial pneumonia showed significantly elevated KL-6 levels [8-13].

Several studies indicate that serum KL-6 level is elevated in patients with sarcoidosis [14-16]. However, no studies describing radiologic findings comparing thin-section CT images between patients with elevated KL-6 levels and those with normal KL-6 levels have been published in English.

Thus, we aimed to retrospectively evaluate and compare pulmonary CT findings between patients with elevated KL-6 levels and those with normal KL-6 levels.
Methods and Materials

Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal KL-6 (n=75)</th>
<th>Elevated KL-6 (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>54.1 (19-82) years</td>
<td>54.3 (19-75) years</td>
</tr>
<tr>
<td>Men</td>
<td>23 patients</td>
<td>7 patients</td>
</tr>
<tr>
<td>Women</td>
<td>52 patients</td>
<td>19 patients</td>
</tr>
<tr>
<td>Mean KL-6 level</td>
<td>305.7 (152-499) U/ml</td>
<td>802.4 (521-2940) U/ml</td>
</tr>
</tbody>
</table>

One hundred and one patients with known serum KL-6 levels who underwent thin-section CT between December 2003 and November 2008 at our institutions, and in whom sarcoidosis was histologically and clinically diagnosed, were included.

Thin-section CT scans were performed within 3 days of KL-6 level measurements. Transbronchial lung biopsy and other tissue biopsies were performed within 2 weeks after CT scans.

Our study included 75 sarcoidosis patients (23 men, 52 women; age range, 19-82 years; mean age, 54.1 years) with normal KL-6 levels (152-499 U/ml; mean, 305.7 U/ml; Table 1), in whom transbronchial lung biopsy (n = 42), surgical lung biopsy (n = 1), lymph node biopsy (n = 12), muscle biopsy (n = 4), testis biopsy (n = 1), skin biopsy (n = 5) or clinical diagnosis (n = 10) had been performed. Twenty-six sarcoidosis patients (7 men, 19 women; age range, 19-75 years; mean age, 54.3 years) with elevated KL-6 levels (521-2940 U/ml; mean, 802.4 U/ml; Table 1), in whom transbronchial lung biopsy (n = 18), lymph node biopsy (n = 4), muscle biopsy (n = 1), liver biopsy (n = 1) or clinical diagnosis (n = 2) had been performed, were also included in this study. The ethical review boards of the institutions that contributed cases to this study did not require approval or informed consent for the retrospective review of patient records and images.

Patients with idiopathic interstitial pneumonia were excluded from the study. Moreover, patients with all other known cases of interstitial pneumonia (i.e. connective tissue disease, pneumoconiosis, hypersensitivity pneumonitis or drug-induced pneumonitis), those diagnosed with concurrent infectious diseases by serological tests and by clinical and pathologic findings, and those with malignancy or diabetes mellitus were excluded.
Sarcoidosis was diagnosed on the basis of histologic findings and clinical history. The clinical findings in all patients were subsequently reviewed by two chest radiologists to ensure that all cases fulfilled the diagnostic criteria recommended by the American Thoracic Society and the European Respiratory Society [17].

CT Examinations

Thin-section CT examinations were performed within 7 days of the chest radiographs. The CT examinations were performed with 1-mm collimation at 10-mm intervals from the apex of the lung to the diaphragm (n = 25; 19 with normal KL-6 levels and 6 with elevated KL-6 levels), or volumetrically with a multidetector CT system with 1-mm reconstruction (n = 76; 56 with normal KL-6 levels and 20 with elevated KL-6 levels). CT images were obtained at the end of inspiration and in a supine position. The scanning protocol consisted of the reconstruction of 1-mm collimation sections with a high-spatial frequency algorithm at 10-mm intervals. Images were captured at window settings allowing the viewing of the lung parenchyma (window level, -600 to -700 HU; window width, 1,200-1,500 HU), and the mediastinum (window level, 20-40 HU; window width, 400 HU). All initial scans were evaluated.

Radiographic Interpretation

Images were reviewed independently, in random order, by two chest radiologists (with 21 and 9 years of experience in chest image interpretation). The observers were unaware of KL-6 levels and clinical information.

Chest radiographs were used to classify the patients as being type 0 (normal chest radiograph), type I (bilateral hilar lymphadenopathy), type II (bilateral hilar lymphadenopathy with pulmonary infiltrates), and type III (pulmonary infiltrates without lymphadenopathy).

CT images were assessed for the following radiologic patterns: ground-glass opacity, consolidation, nodules, interlobular septal thickening, traction bronchiectasis, intralobular reticular opacity, architectural distortion, bronchial wall thickening, enlarged hilar/mediastinal lymph node(s) (> 1 cm in diameter of the short axis), and pleural effusion. Areas of ground-glass opacity were defined as hazy increases in attenuation without obscuration of vascular markings [18,19]. Areas of consolidation were defined as areas of increased attenuation causing obscuration of normal lung markings [18,19]. Interlobular septal thickening was defined as abnormal widening of interlobular septa [19]. Intralobular reticular opacity was considered present when interlacing line shadows were separated by a few millimeters [18,19]. Traction bronchiectasis was defined as irregular bronchial...
dilatation within the surrounding areas showing parenchymal abnormalities. Architectural distortion was considered present when bronchi, pulmonary vessels, or interlobular fissures or septa were abnormally displaced [19].

Serum KL-6 levels were measured within 3 days of the initial CT scans and before steroid treatment using a sandwich-type enzyme-linked electrochemiluminescence immunoassay kit (Picolumi KL-6; Sanko Junyaku Co, Tokyo). The recommended cut-off value was determined at 500 U/ml according to levels reported in healthy individuals [6]. The assay was performed by technicians unaware of the clinical information related to the samples.

**Measurement of KL-6 levels**

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**Statistical Analysis**

Statistical analyses of the incidence of symptoms and laboratory data were conducted using the Fisher exact test and the $\chi^2$ test. Mean age comparison was conducted using a Student’s $t$-test. $p < 0.05$ was considered to be statistically significant.
Results

<table>
<thead>
<tr>
<th>Finding</th>
<th>Normal KL-6 (n=75)</th>
<th>Elevated KL-6 (n=26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>3 (4)</td>
<td>2 (7.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td>3 (4)</td>
<td>16 (61.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodules</td>
<td>50 (66.7)</td>
<td>25 (96.2)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
<td>20 (26.7)</td>
<td>25 (96.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>7 (9.3)</td>
<td>25 (96.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interlobular reticular opacity</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>25 (33.3)</td>
<td>21 (80.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Architectural distortion</td>
<td>7 (9.3)</td>
<td>26 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node enlargement</td>
<td>70 (93.3)</td>
<td>21 (80.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thoracic CT findings in 101 patients with Sarcoidosis

CT Patterns

CT findings are summarized in Table 1. Of the 75 patients with normal KL-6 levels, nodules (n = 50, 66.7%) were observed most frequently, followed by bronchial wall thickening (n = 25, 33.3%), interlobular septal thickening (n = 20, 26.7%), ground-glass opacity (n = 10, 13.3%), architectural distortion (n = 7, 9.3%), traction bronchiectasis (n = 7, 9.3%), consolidation (n = 3, 4%) and intralobular reticular opacity (n = 3, 4%) (Figs. 1-8).

By contrast, of the 26 patients with elevated KL-6 levels, architectural distortion (Figs. 4 and 5) was observed in all cases, followed by nodules (Figs. 3, 5, 7 and 8), interlobular septal thickening and traction bronchiectasis (n = 25, 96.2%; Figs. 4 and 5), bronchial wall thickening (n = 21, 80.8%; Fig. 5), ground-glass opacity (n = 16, 61.5%; Fig. 1) and consolidation (n = 2, 7.7%, Fig. 7 and 8).
Ground-glass opacity, nodules, interlobular septal thickening, traction bronchiectasis, architectural distortion, and bronchial wall thickening were significantly more frequent in patients with elevated KL-6 levels than in those with normal KL-6 levels (p < 0.001, p < 0.005, p < 0.001, p < 0.001 and p <0.001, respectively).

**Lymph Nodes and Effusions**

In 70 of 75 patients with normal KL-6 levels (93.3%) and in 21 of 26 patients with elevated KL-6 levels (80.8%), enlarged lymph nodes were observed at the pretracheal, paratracheal, tracheobronchial, or subcarinal regions (Fig. 9). There was no significant difference in frequency of lymph node enlargement between the two groups.

Pleural effusions were not found in any patients in the study.

**Follow-up study**

Follow-up CT scans were obtained from 36 out of 101 patients at an interval of 1 to 61 months after initial CT examination (mean follow-up time, 7 months).

Of 14 patients with ground-glass attenuation (2 patients with normal KL-6 levels and 12 patients with elevated KL-6 levels), follow-up CT scans revealed complete clearing in 1 patient, a decrease in another patient, an increase in 1 patient, and no change in 11 patients. In the patients with complete clearing and decreased ground-glass opacity, elevated KL-6 levels improved to within normal limits (Fig. 2). In all of the patients with unchanged findings, initial KL-6 levels remained unchanged. By comparison, in the patient with an increase of ground-glass opacity, the KL-6 level worsened.

Of 19 patients with architectural distortion (2 with normal KL-6 levels and 17 with elevated KL-6 levels), follow-up CT scans showed a decrease in 4 patients, no change in 14 patients, and an increase in 1 patient. In all patients with improved findings, KL-6 levels improved (Fig. 6); in the patient with worsened findings, the KL-6 level increased (Fig. 4).

Of 33 patients with nodules (16 with a normal KL-6 level and 17 with elevated KL-6 levels), follow-up CT scans showed a decrease in 9 patients, no change in 19 patients, and an increase in 5 patients. Of the 9 patients with improved findings, KL-6 levels improved in 7 patients (Fig. 6) and remained unchanged in 2. Of the 19 patients with unchanged findings, KL-6 levels improved in 4 patients, remained unchanged in 14, and worsened in 1. By comparison, of the 5 patients with worsened findings, KL-6 levels remained unchanged in 4 and worsened in 1.
Of 22 patients with bronchial wall thickening (8 with normal KL-6 levels and 14 with elevated KL-6 levels), follow-up CT scans showed a decrease in wall thickening in 2 patients, no change in 19 patients and an increase in 1 patient. Of the patients with improved findings, KL-6 levels improved in 1 patient (Fig. 6) and remained unchanged in 1. In all of the 19 patients with unchanged findings, initial KL-6 levels remained unchanged. In the patient with an increase in bronchial wall thickening, the KL-6 level worsened.

Of 3 patients with consolidation (2 with normal KL-6 levels and 1 with an elevated KL-6 level), follow-up CT scans remained unchanged in 2 and worsened in 1. In all of the patients with unchanged findings or worsened findings (Fig. 8), the initial KL-6 level remained unchanged.

Of 28 patients with lymph node enlargement (15 with normal KL-6 levels and 13 with elevated KL-6 levels), follow-up CT scans showed a decrease in 1 patient and no change in 27 cases. In the patient with improved findings, KL-6 level improved. Of the 27 patients with unchanged findings, KL-6 levels improved in 13 patients with ameliorated parenchymal abnormalities, and worsened in 3 patients with exacerbated parenchymal findings. No change was observed in 11 patients with unchanged parenchymal abnormalities.
Fig. 0: Images in a 69-year-old woman Transverse CT scan (1-mm section thickness) obtained at the level of right upper lobe shows ground-grass appearance (arrows; KL-6, 2940 U/ml).

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Fig. 0: Transverse CT scan (1-mm section thickness) obtained, after surgical biopsy 4 years later from Fig.1, shows disappearance of ground-grass opacity (KL-6, 313 U/ml).

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Fig. 0: Image in a 69-year-old man Transverse CT scan (1-mm section thickness) obtained at the level of left lower lobe shows a nodule in the periphery (arrows; KL-6, 333 U/ml).

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**Fig. 0:** Transverse CT scan (1-mm section thickness) obtained 6 months later from Fig.3 shows architectural distortion (KL-6, 581 U/ml). Traction bronchiectasis is also present (arrows).

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Fig. 0: Images in a 35-year-old woman Transverse CT scan (1-mm section thickness) obtained at the level of upper lobes shows multiple small nodules (arrows) and architectural distortion (arrowheads; (KL-6, 1000 U/ml). Traction bronchiectasis and bronchial wall thickening are also present (white arrows).

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**Fig. 0:** Transverse CT scan (1-mm section thickness) obtained 6 months later from Fig.5 demonstrates disappearance of nodules, architectural distortion, traction bronchiectasis, and bronchial wall thickening (KL-6, 285 U/ml).

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Fig. 0: Images in a 65-year-old woman Transverse CT scan (1-mm section thickness) obtained at the level of division of right B6 shows consolidation in right middle lobe (arrow) and multiple nodules (arrowheads; KL-6, 400 U/ml).

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**Fig. 0:** Transverse CT scan (1-mm section thickness) obtained five months later from Fig.7 shows worsened consolidation and unchanged nodules, however, the KL-6 level is not elevated (KL-6, 397 U/ml).

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**Fig. 0:** Images in a 46-year-old man (KL-6, 239 U/ml) Transverse CT scan (1-mm section thickness) obtained at the level of the right pulmonary artery shows enlarged lymph nodes at subcarinal and bilateral hilar regions (arrows).

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**Fig. 0:** Images in a 46-year-old man (KL-6, 239 U/ml) Transverse CT scan (1-mm section thickness) obtained at the level of the right pulmonary artery shows no abnormal parenchymal lesions.

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Conclusion

CT findings of nodules, bronchial wall thickening, ground-glass opacity, traction bronchiectasis, and architectural distortion were associated with elevated serum KL-6 levels.

Serum KL-6 levels may be a useful marker for indicating the severity of parenchymal sarcoidosis.
References


