KL-6 as a Serologic Indicator of *Pneumocystis carinii* Pneumonia in Immunocompromised Hosts

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KL-6, a serum marker for interstitial pneumonitis, was evaluated in patients with *Pneumocystis carinii* pneumonia (PCP). Patient 1 was a 56-year-old woman with rheumatoid arthritis treated with immunosuppressive drugs and corticosteroids. Patient 2 was a 59-year-old man with a glioblastoma who received anti-cancer drugs and corticosteroids. In both patients, serum KL-6 showed an abnormally high level due to the complication of PCP, and it decreased following successful treatment. These results indicate that PCP is one of the diseases in which serum KL-6 increases.

(Internal Medicine 37: 307-310, 1998)

**Key words:** pneumonitis, hyperplastic pneumocyte

**Introduction**

*Pneumocystis carinii* pneumonia (PCP) is a life-threatening opportunistic infection associated with suppressed cellular immunity in patients with acquired immunodeficiency syndrome (AIDS) and anti-cancer and immunosuppressive therapy (1, 2). Pulmonary infection with *P. carinii* is associated with histologic findings of interstitial pneumonitis and irreversible fibrotic changes (3, 4). KL-6, a human MUC1 mucin (5-7), has been reported to be a sensitive serum marker for interstitial pneumonitis (8-15). Here we evaluated the usefulness of serum KL-6 as a marker for the development of PCP in immunocompromised hosts.

**Case Report**

**Patient 1**

A 56-year-old woman was diagnosed with rheumatoid arthritis (RA) in March 1992. She was treated with prednisolone, methotrexate and azathioprine. She began to complain of progressive dyspnea on exertion in February 1996, and was admitted to Ehime University Hospital on May 24, 1996. On admission, her chest examination revealed fine crackles and bilateral interstitial shadows were observed on chest radiograph. Her leukocyte count was 3,100 cells/μl (18.3% lymphocytes; CD3: 64%; CD4: 49%, CD8: 9%). Serum levels of KL-6, C-reactive protein (CRP) and lactate dehydrogenase (LDH) activity were 1,900 (normal range ≤520) U/ml, 3.0 (normal range <0.5) mg/ml and 353 (normal range 200-425) IU/l, respectively. Her vital capacity was 98.8% of predicted, her %DLCO was 48.1% of predicted and her partial pressure of oxygen (PaO2) was 89.1 mmHg on room air. A transbronchial lung biopsy specimen showed interstitial pneumonitis with fibrosis. *P. carinii* and cells with inclusion bodies were not detected. Bacteriologic studies of lung tissue and bronchoalveolar lavage fluid (BALF) were negative. Her pulmonary disease was diagnosed as progressively deteriorating interstitial pneumonitis.

Two courses of steroid-pulse therapy (1 gram of methylprednisolone was intravenously administered for three consecutive days each week for two weeks) were administered. However, her dyspnea and chest radiographic findings worsened and arterial blood gas analysis showed hypoxemia with a PaO2 of 63.5 mmHg on room air on July 30, 1996. The leukocyte count was 3,400 cells/μl (7.0% lymphocytes). Serum CRP and LDH activity increased to 3.3 mg/dl and 523 IU/l, respectively. The serum KL-6 level increased markedly to 8,600 U/ml on August 23, 1996 (Fig. 1). This unexpected increase of serum KL-6 suggested that her interstitial pneumonitis was worse, possibly due to infection with *P. carinii* or *cytomegalovirus*. *P. carinii* was detected by the polymerase chain reaction (Sumitomo Bio Chemical Co., Ltd., Tokyo) in an induced sputum sample on August 7. Trimethoprim-
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Prednisolone 5 mg/d
Azathioprine 75 mg/d
Methotrexate 7.5 mg/week

TMP-SMX 8 g/d
Pentamidine (inhalation) 200 mg/d

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<th>1997</th>
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<td>PaO₂ (mmHg)</td>
<td>89.1</td>
<td>79.4</td>
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<tr>
<td>AaDO₂ (mmHg)</td>
<td>11.7</td>
<td>20.1</td>
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Methyl-prednisolone (1g/d)

Figure 1. Clinical course of patient 1, a 56-year-old woman, with rheumatoid arthritis. The horizontal line represents the upper limit of normal. TMP-SMX: trimethoprim-sulfamethoxazole, CRP: C-reactive protein, LDH: lactate dehydrogenase, AaDO₂: alveolar-arterial oxygen difference.

sulfamethoxazole (TMP-SMX; 8 g/day) was administered. Because of nausea and general fatigue, however, it was changed four days later to inhaled pentamidine isetionate at 4 mg/kg. Improvements of dyspnea, the chest radiograph, and hypoxemia were observed on day 14 of pentamidine isetionate. The alveolar-arterial oxygen difference (AaDO₂) normalized from 41.0 mmHg to 18.7 mmHg and the serum KL-6 level decreased to 2,200 U/ml on September 9.

Patient 2

A 59-year-old man was given 80 mg of nimustine hydrochloride (ACNU) for a glioblastoma. He complained of fever and dyspnea four weeks after receiving 3 mg per day of betamethasone to reduce his brain edema, and was admitted to National Kinki-Chuo Hospital for Chest Diseases on July 19, 1994. On admission, fine crackles were heard and a chest radiograph showed bilateral interstitial shadows. The leukocyte count was 2,900 cells/µl (24.0% lymphocytes). Serum KL-6, CRP and LDH levels were 2,000 U/ml, 3.2 mg/dl and 1,372 IU/l, respectively. Arterial blood gas analysis on room air showed a hypoxemia with PaO₂ of 48.0 mmHg. Anti-cytomegalovirus immunoglobulin M (IgM) antibody was not detectable, but P. carinii was detected cytologically in the BALF (Fig. 2A). The KL-6 level in BALF was 4,800 U/ml. Methylprednisolone and TMP-SMX were administered followed by the administration of pentamidine isetionate (intravenously and by inhalation) (Fig. 3). The serum KL-6 level increased to 6,600 U/ml until inhaled pentamidine isetionate was started, and then gradually decreased. His dyspnea and chest radiographic findings were improved remarkably and his AaDO₂ decreased from 80.9 mmHg to 18.1 mmHg.

Tissue specimens of the transbronchial lung biopsy performed on the day of admission showed interstitial pneumonitis. Immunohistochemical examination of the tissue revealed that KL-6 was produced by hyperplastic pneumocytes (Fig. 2B).

Discussion

The present patients showed a remarkably elevated level of KL-6, and suggest that KL-6 may be a useful serum marker in the evaluation of PCP in immunocompromised hosts. In patient
Figure 2. A) Pneumocystis carinii cysts (arrow) in bronchoalveolar lavage fluid from patient 2. Methenamine silver (×400). B) Immunohistochemical staining by anti-KL-6 antibody of biopsied lung tissue from patient 2. KL-6 exists diffusely in the thin epithelial lining fluid, but not in interstitial components. Hyperplastic pneumocytes have KL-6 on their cell membrane and in their cytoplasm (arrowhead) (×200).

<table>
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<tr>
<td>Betamethasone</td>
<td>3 mg/d</td>
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<tr>
<td>TMP-SMX</td>
<td>12 g/d</td>
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<tr>
<td>Pentamidine</td>
<td>200 mg/d</td>
</tr>
<tr>
<td>O₂ (l/min)</td>
<td>2</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
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<tr>
<td>AaDO₂ (mmHg)</td>
<td></td>
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<tr>
<td>Methyl-prednisolone</td>
<td>(500 mg/d)</td>
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Figure 3. Clinical course of patient 2, a 59-year-old man, with glioblastoma. The horizontal line represents the upper limit of normal.
1, the unexpected increase of serum KL-6 level following the administration of a high dose of corticosteroids raised the suspicion of PCP. In patient 2, the similar increase of serum KL-6 led to the diagnosis of PCP. In both patients, the KL-6 level decreased after successful treatment with pentamidine isetionate.

Though PCP occurred in patients receiving immunosuppressive drugs, Kawakami et al (16) have reported that KL-6 might be useful in the diagnosis of PCP in patients with AIDS. KL-6 was immunohistochemically expressed on hyperplastic pneumocytes in patient 2 and in the patient reported by Kawakami et al. This histologic finding is common in diseases in which serum KL-6 is increased (8, 9). KL-6 is not a specific marker for PCP, because serum KL-6 level is frequently increased in diseases such as idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, radiation pneumonitis, sarcoidosis with lung involvement, and interstitial pneumonitis in collagen vascular diseases. Serum KL-6 is not increased in patients with bacterial pneumonia (17). Since serum KL-6 is associated with alveolar-capillary permeability changes caused by alveolar epithelial cell injury in berylliosis (18), serum KL-6 levels might reflect the degree of epithelial cell injury also in interstitial lung diseases including PCP. Furthermore, KL-6 existing in pulmonary epithelial lining fluids might cause the intra-alveolar fibrosis in these diseases, because KL-6 is one of the chemotactic factors for human fibroblasts (19).

Further study is necessary to determine whether KL-6 is useful in the diagnosis of PCP, especially in patients with AIDS and in patients on immunosuppressive therapy.

Acknowledgements: This work was supported in part by Grant-in-Aid for Scientific Research (No. 08670665) from the Ministry of Education, Science, Sports and Culture, Japan.

References