KL-6 as a Possible Monitoring Marker for Hypersensitivity Pneumonitis

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Accepted for publication on July 9, 1998

ABSTRACT. A high level of serum KL-6 is known to exist in active pulmonary fibrosis, and KL-6 may be produced and secreted by type II pneumocytes. Herein, we describe a case of hypersensitivity pneumonitis with high serum KL-6 levels. The serum KL-6 level in this 57-year-old woman decreased after admission to our hospital, after avoidance of the causative antigen. It correlated with the severity of symptoms, and reversely correlated with her PaO_2 levels and chest x-ray findings. The findings suggest that the serum KL-6 level may increase in such allergic pneumonias as hypersensitivity pneumonitis and that its determination provides a useful indicator and/or monitoring marker of hypersensitivity pneumonitis.

Key words: KL-6 — hypersensitivity pneumonitis — *Trichosporon* — mucin — like glycoprotein

KL-6, a mucin-like glycoprotein which has now been classified as cluster 9 (MUC-1),[1] believed to reflect the disease activity of fibrosing processes in the lung.[2-4] Recently, however, we showed that increases in the serum KL-6 level in such cases may result from proliferation of type II pneumocytes with or without pulmonary fibrosis.[5,6]

Summer type hypersensitivity pneumonitis (HP) is caused by *Trichosporon asahii* and *Trichosporon mucoides*,[7-9] and histopathologically is characterized by the features of either lymphocytic interstitial pneumonitis or organizing pneumonia, or by those of bronchiolitis obliterans organizing pneumonia (BOOP), which of granulomas or of prominent type II pneumocytic hyperplasia, which are those caused by other organic antigens. Therefore, we assume that the proliferation of type II pneumocytes is responsible for the increase in serum KL-6 in HP. Herein, we describe an HP case with high serum KL-6 levels which decreased after avoidance of the causative antigen.

CASE REPORT

A-57-year-old woman with exertional dyspnea was admitted to our hospital in August 1995. She had been diagnosed as having schizophrenia and had been well medicated since 1978. Chest x-ray films and a chest CT scan revealed non-segmental diffuse ground glass opacities in both lung fields (Fig 1, 2). The patient indicated she neither drank alcohol nor smoked. After

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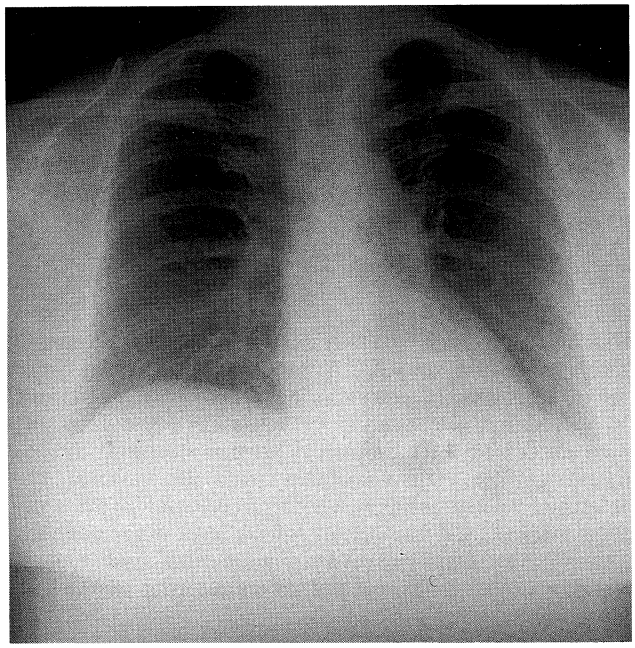

Fig 1. A chest x-ray film on admission revealing ground-glass opacities in both lung fields.

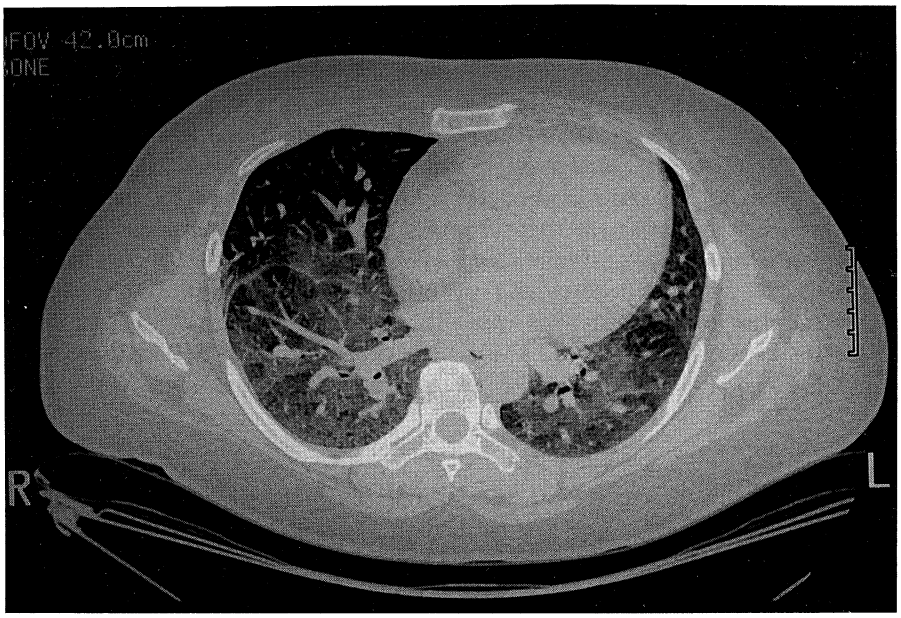

Fig 2. A chest CT scan on admission showing extensive ground-glass opacities and sparing in some regions in both lung fields.

admission, her fever, dyspnea and chest x-ray abnormality improved. Physical examination on admission was unremarkable except for fine crackles on chest ausculation. Her arterial blood gas values were PH 7.45 and PaO_2 57.3 mmHg in breathing room air. The diffusion capacity for carbon monoxide (DLco) was 7.95 ml/min/mmHg (44%), inspiratory vital capacity was 1.31 L (49%) and forced expiratory volume in 1 second ($FEV_{1.0}$) was 1.31 L (76%) on pulmonary function tests. Other laboratory data revealed hemoglobin of 12.5 g/dl, a white blood cell count of 9,800/μl (neutrophils : 81%, eosinophils : 1%, lymphocytes : 12%, monocytes : 6.0%), an erythrocyte sedimentation rate of 47 mm/h and C-reacted protein (CRP) of 6.3 mg/dl. Blood chemical analysis disclosed a high serum lactate dehydrogenase (LDH) level of 264 IU/l. Analysis of bronchoalveolar lavage fluid (BALF) revealed a total of 1.5 x 10^6 cells/ml. The percentages of macrophages, lymphocytes, neutrophils, eosinophils and basophils from the recovered cells were 22.2%, 66%, 8.0%, 4.0% and 0.6%, respectively. The value of CD 4/8 in BALF was 0.35. Transbronchial lung biopsy specimens demonstrated features of lymphocytic alveolitis, and organizing pneumonia, with a scattering of small granulomas. These findings were considered to be consistent with HP.

After the symptoms and abnormal laboratory data had improved, a provocation test was performed. Six hours after returning home, the patient developed fever and dyspnea. Her white blood cell count and CRP became high and her PaO_2 level was low, although her chest x-ray films did not disclose any opacities. Serum precipitins against *Trichosporon asahii* and *Trichosporon mucoides,* which are well known causative agents of HP were also present.

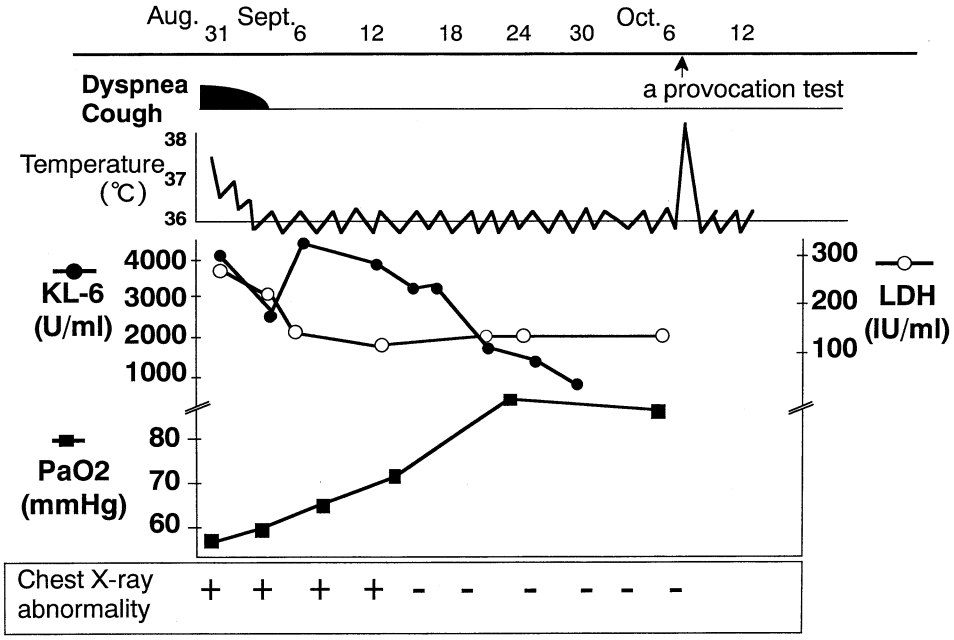

Fig 3. Clinical course. Cut off levels of KL-6, PaO_2 and LDH are 500U/ml, 80 mmHg and 125 IU/ml, respectively.

KL-6 levels were examined with a sandwich-type enzyme-linked immunosorbent assay (EIA) using KL-6 monoclonal antibody (IgG1) in sera. The levels were extremely high before admission, but gradually decreased to within normal range after avoidance of the possible causative antigen. During hospitalization, even when the opacities on the chest X-ray films had disappeared and the patient's PaO_2 level was low, her serum KL-6 levels remained high (Fig 3).

DISCUSSION

This patient was diagnosed as having HP caused by *Trichosporon*, based on the improvement of abnormal laboratory data, fever and symptoms after admission as a result of avoiding possible causative agents, a positive provocation test, and the presence of serum precipitin against *Trichosporon* (*T. asahii and mucoides*). HP is considered to be an allergic pneumonitis caused by the repeated inhalation of an antigen or antigens, and most studies in this field have focused on Type III (immune complex) and Type IV (cell-mediated) allergic responses. Morphologically, the acute stage of HP, including summer type HP due to *Trichosporon,* is characterized by lymphocytic alveolar infiltration, features of organizing pneumonia or BOOP, granulomas, and proliferation of type II pneumocytes.[7-10]

Serum KL-6 is known to be a valuable indicator of the disease activity in interstitial pulmonary fibrosis, radiation pneumonitis, and pulmonary sarcoidosis.[2-4,11] Serum KL-6 levels also be high in the acute stage of allergic pulmonary pneumonitis; namely HP. Recent studies have demonstrated that many growth factors and cytokines influence the growth of type II pneumocytes.[12,13] Therefore we speculate that type II pneumocytes stimulated by growth factors and cytokines produce KL-6 in some forms of allergic pneumonitis such as HP. However, the mechanisms regulating their production and secretion of KL-6 remain unclear and further studies are necessary.

Clinically, HP is usually characterized by abnormal data, such as ground-glass opacities on chest x-ray films, high serum LDH levels, and impairment of PaO_2 and DLco levels. Chest x-ray findings vary with the stage of HP. Early in the course of the acute stage of HP, they may be hardly discernible.[12] In our case, the level of serum KL-6 was correlated with the severity of symptoms and reversely with PaO_2 levels. Even when the opacities on chest x-ray films disappeared, the KL-6 level was high and that of PaO_2 was low. Therefore, elevation of serum KL-6 may be a useful monitoring marker of HP. The reason for the decrease of serum KL-6 level on the 3rd hospital day is unclear. However, we assume that bronchoalveolar lavage performed two days before the test might have something to do with his descent.

Some HP patients have been misdiagnosed as having mycoplasma pneumonia or a viral disease, and the correct diagnosis of HP has been recognized when there were repeated attacks and recurrence on return home or to the workplace.[14] Our previous data clearly showed that serum KL-6 levels were low in *Mycoplasma pneumoniae, Chlamydia psittaci, and Chlamydia pneumoniae* pneumonia and bacterial pneumonias.[15] Therefore, serum KL-6 may be a useful indicator of HP.

This case report was supported in Part by a Reserch Project Grant (No.

10-606) from Kawasaki Medical School.

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