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CASE REPORT

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KL-6 as an indicator for lymphocytic interstitial pneumonia (LIP) in a human T-lymphotrophic virus type 1 (HTLV-1) carrier

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Abstract A 59-year-old woman was admitted to our hospital complaining of a productive cough, dyspnea on effort, and low-grade fever. Although chest X-rays showed no marked abnormalities, her level of serum KL-6 was extremely high. We therefore suspected the presence of interstitial pneumonia. High-resolution computed tomography (CT) scan revealed infiltrative shadows in S6 of the right lung, and her serum was positive for antihuman T-lymphotropic virus type 1 (HTLV-1) antibodies. From the clinical symptoms, radiographic findings, and histological findings, the diagnosis was probable lymphocytic interstitial pneumonia (LIP). After high-dose corticosteroid therapy, the level of serum KL-6 decreased rapidly. We conclude that KL-6 is a convenient and reliable marker for evaluating the activity of pulmonary manifestations in HTLV-1 carriers and that it is especially useful in monitoring the effectiveness of treatments.

Keywords Human T-lymphotropic virus type-1 · Krebs der Lungen-6 · Lymphocytic interstitial pneumonia · Lactate dehydrogenase · High-resolution computed tomography

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Introduction

Human T-lymphotrophic virus type 1 (HTLV-1) is a retrovirus that has been causally linked to adult T-cell leukemia (ATL) [19]. Recently, HTLV-1 has also been recognized as a causative factor in many inflammatory and autoimmune diseases, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [2, 14], uveitis [13], and bronchoalveolar disorders. A number of reports have suggested that there may be associations between HTLV-1 and various bronchoalveolar disorders, including interstitial pneumonia (IP), bronchiectasis, and diffuse panbronchiolitis [12, 15, 18].

Krebs der Lungen-6 (KL-6) is a MUC1 mucin (molecular weight >1000 KDa) that has been classified in cluster 9 of lung tumor and differentiation antigens [7, 10, 16]. In addition, serum KL-6 has been reported to be a sensitive marker for many diffuse interstitial lung diseases such as idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, radiation pneumonitis, sarcoidosis, and interstitial pneumonitis associated with collagen vascular disease [8, 9, 11]. The serum levels of KL-6 are significantly higher in patients with active interstitial pneumonitis than in those with an inactive form of the disease [11, 20]. Furthermore, in a group of patients with rapidly progressive idiopathic pulmonary fibrosis who underwent high-dose corticosteroid therapy, a decrease in the level of KL-6 was significantly related to a favorable outcome of treatment**,** whereas the level of lactate dehydrogenase (LDH) was not [20].

In this case report, we describe an HTLV-1 carrier with lymphocytic interstitial pneumonia (LIP). We also evaluate the relationship between the effectiveness of high-dose corticosteroid therapy and changes in the levels of serum KL-6 and LDH.

Case report

A 59-year-old woman was referred to Hiroshima University Hospital in June 1999. She had been complaining of a productive

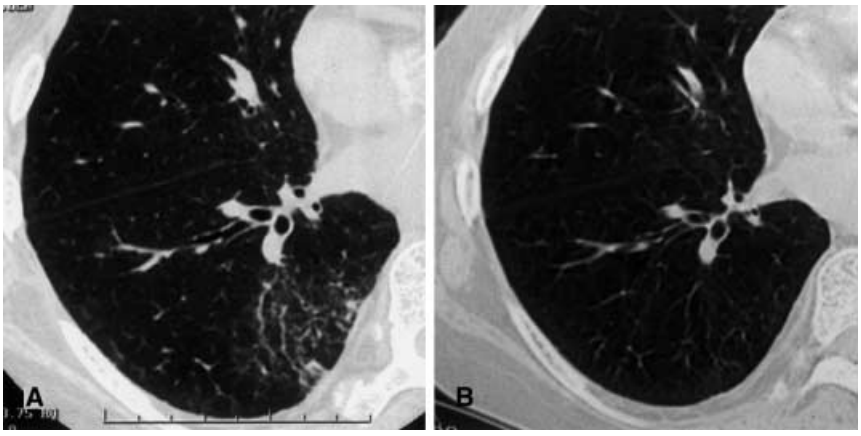

Fig. 1A, B High-resolution computed tomography (HRCT) of the chest. **A** on admission; **B** after steroid pulse therapy

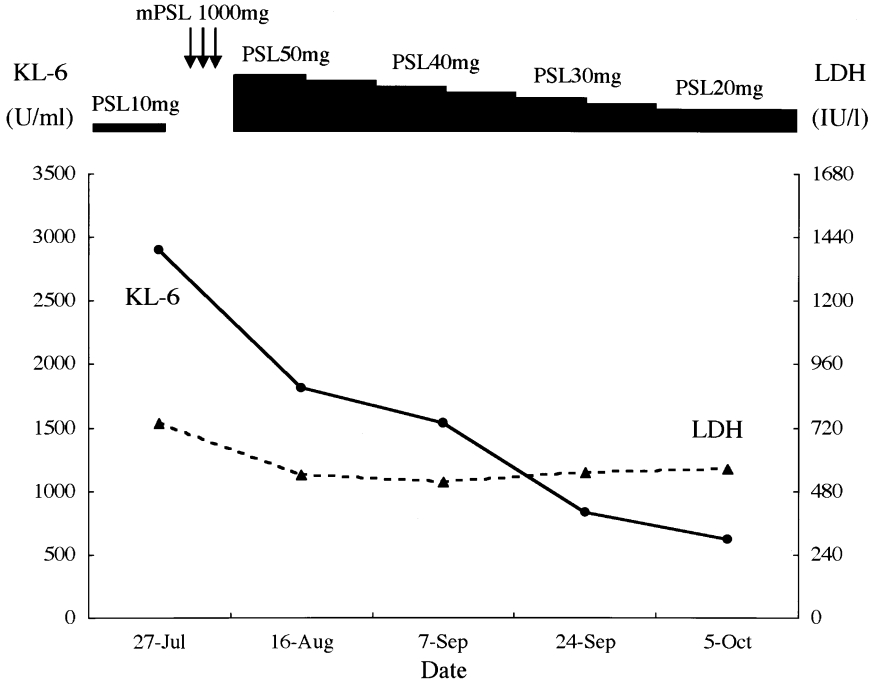

Fig. 2 **A** Transbronchial lung biopsy (TBLB) specimen obtained from the right B6 bronchus. Chronic interstitial pneumonia coupled with lymphocyte infiltrations can be seen in the alveolar septa (H&E, ×25). **B** The same biopsy specimen was assessed immunohistochemically using a monoclonal antibody against KL-6. Positive staining of regenerating type II pneumocytes or type II pneumocytes in air spaces was observed (×25)

cough, dyspnea on effort, and low-grade fever from May 1999. Her medical history revealed that she was born in Saga in the southern part of Japan and had been diagnosed as having nephrotic syndrome in 1972, systemic lupus erythematosus in 1985, bronchial asthma in 1997, and aortic stenosis in 1998.

On physical examination, she had a low-grade fever and a skin rash. Mild fine crackles were audible in both lower lung fields. Hematological examination, carried out soon after admission, showed a normal leukocyte count (6500/mm^3), with a normal differential white blood cell count, and a mild reduction in the red blood cell count ($311\times10^4/mm^3$) and in hemoglobin levels (10.6 g/dl). Laboratory examinations also showed moderate hepatic and renal dysfunction. Serum levels of KL-6 (2899 U/ml, standard range: <500 U/ml), LDH (996 IU/l), and C-reactive protein (1.9 mg/dl) were higher than normal. Tests for autoantibodies were negative. Serum levels of IgG (414 mg/dl), IgA (48 mg/dl), and IgM (<10 mg/dl) were remarkably decreased. Serum HTLV-1 antibody was detected by a particle agglutination assay. Blood gas analysis, conducted while the patient was breathing room air, revealed PaO_2 of 71.3 mmHg, $PaCO_2$ of 36.3 mmHg, and pH of 7.406.

Chest X-rays showed no remarkable abnormalities, but tests of pulmonary function revealed a reduced diffusing capacity for carbon monoxide (%DL: 28.8%). Since the level of serum KL-6 was extremely high, we suspected that the patient might have interstitial pneumonia. High-resolution computed tomography (HRCT) of the chest demonstrated diffuse increased opacity around the bronchioles, with reticular and small patchy infiltrative shadowing of the right middle and lower lobes (Fig. 1A). A gallium-67 citrate scintigram showed diffuse accumulation bilaterally in the entire lung, especially in the right lower lobe. Bronchoalveolar lavage (BAL) fluid obtained from the right lower lobe showed an increased total cell count (3.06×10^5/ml) and an increased lymphocyte ratio (94%), but was negative for microorganisms including *Pneumocystis carinii*. Flow cytometric analysis of BAL fluid lymphocytes revealed a high CD4/CD8 ratio (4.46). No monoclonal integrations of the HTLV-1 genome were detected with the Southern blot technique in the DNA from peripheral blood cells and BAL cells. Histological examination of a transbronchial lung biopsy (TBLB) obtained from the right B6 bronchus revealed the presence of chronic interstitial pneumonia with lymphocyte infiltrations into the alveolar septa (Fig. 2 A). This biopsy specimen was assessed immunohistochemically using monoclonal antibodies UCHL-1 (anti-CD45RO) against T lymphocytes and L26 (anti-CD20) against B lymphocytes. Lymphocytes in this specimen tested positive for UCHL-1, but negative for L26. Furthermore, the

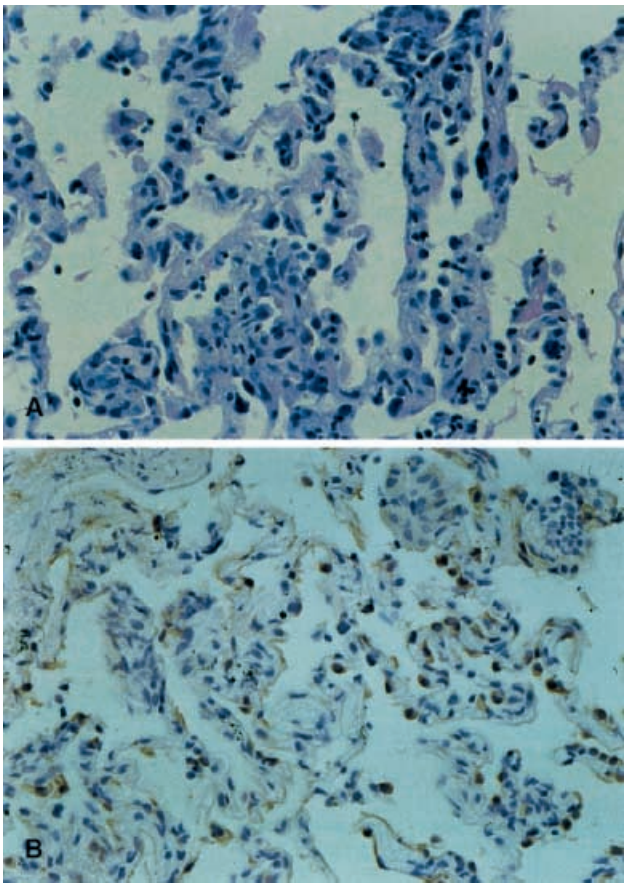

Fig. 3 Clinical course of treatment. The cutoff levels of KL-6 and LDH were 520 U/ml and 240 IU/l, respectively

biopsy specimen was also assessed immunohistologically using a monoclonal antibody for KL-6. This KL-6 antibody reacted positively with regenerating pneumocytes or type II pneumocytes in air spaces, but did not react with interstitial components (Fig. 2B). Taking these observations together with the clinical symptoms, radiographic findings, and histological findings, the patient was diagnosed as an HTLV-1 carrier with probable LIP.

As her symptoms did not resolve after daily oral administration of 20 mg prednisolone (PSL), we considered that the disease activity was high. Therefore, the patient was treated by high-dose corticosteroid therapy (1000 mg of methylprednisolone intravenously for 3 consecutive days), followed by 50 mg/day of PSL. On this treatment regimen she became asymptomatic, and so the PSL dose was tapered rapidly to 20 mg daily. The levels of the serum markers LDH and KL-6 are shown in Fig. 3. A decrease in serum levels of KL-6 but not LDH correlated well with both the disappearance of symptoms (productive cough, dyspnea on effort, and low-grade fever) and resolution of pulmonary consolidation, as observed by chest HRCT (Fig. 1B) and gallium-67 scintigram. In addition, the reduction in KL-6 levels correlated well with the recovery of pulmonary function.

Discussion

This is the first report to document the usefulness of KL-6 as a serum marker for the diagnosis of LIP in an HTLV-1 carrier. As the patient had a markedly elevated level of serum KL-6, we suspected that she might have interstitial pneumonia. It should be noted that there was a correlation between the improvement in LIP and a decrease in the level of serum KL-6.

LIP was initially described by Carrington and Liebow in 1966 [1]. It is characterized by the diffuse infiltrations of non-neoplastic lymphocytes and plasma cells into the alveolar septa. LIP has been reported in association with a variety of immunological disorders, such as Sjögren's syndrome, autoimmune thyroid disease, human immunodeficiency virus infection, HTLV-1 infection, and Castleman disease [12, 17]. In the current case, histological examination of a TBLB revealed the presence of chronic interstitial pneumonia with lymphocyte infiltrations into the alveolar septa. In general, open lung biopsy or video-assisted thoracoscopic surgery is the preferred method of diagnosing LIP; however, we could not perform these examinations because the patient was treated with anticoagulation therapy. Taking together the clinical symptoms, therefore, her disease was diagnosed as probable LIP in an HTLV-1 carrier.

In this case, the level of serum KL-6 was extremely high at the time of diagnosis and gradually decreased after high-dose corticosteroid therapy, and the level of KL-6 correlated positively with clinical and radiographic improvement whereas the level of LDH did not. Furthermore LDH activity has no specificity for IP, i.e., hepatic damage caused by the treatment of IP and hematological disease in the absence of IP frequency leads to increased LDH activity.

Although serum KL-6 level does not increase in bacterial pneumonia, it increases in fibrosing lung infections such as *Legionella* pneumonia, *Pneumocystis carinii* pneumonia, and tuberculosis with fibrosing widespread lesion [3, 11]. In the present case, we excluded the possibility of opportunistic infection and pulmonary infiltration of leukemic cells by cytological and molecular biological analysis of peripheral blood and BAL fluid. Immunohistochemical study showed that atypical and/or regenerating pneumocytes expressed high levels of KL-6, as we have described previously (Fig. 2) [8, 11]. KL-6 is consistently present in the epithelial lining fluid (ELF), which comprises alveolar fluid from the distal airways and alveoli lavaged by BAL. Because immunohistochemical studies have shown that atypical and/or regenerating pneumocytes in patients with institutional pneumonia express high levels of KL-6, the increased serum levels of KL-6 in the ELF may be related to regenerating pneumocytes in the peripheral lung tissue. In many lung diseases, evidence suggests that lung-specific epithelial proteins secreted at high levels into the ELF are transferred into the circulation across the air-blood barrier [4, 5]. Among patients with chronic beryllium disease, the serum level of KL-6 is correlated with the level of albumin in BAL fluid [6]. These results suggest that serum KL-6 is a useful marker of alveolar-capillary permeability, which results from damage to the alveolar epithelium [5, 11]. We speculate that the increased production of KL-6 by regenerating pneumocytes and for patients with IP, KL-6 is a useful marker of the permeability of the air-

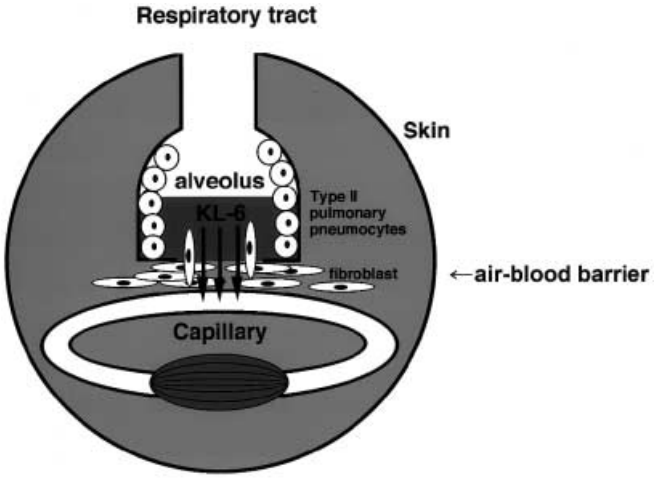

Fig. 4 Mechanism for blood uptake of KL-6

blood barrier, as shown in Fig. 4. In general, histological findings of LIP are characterized by diffuse infiltrations of lymphocytes and plasma cells; however, the existing pulmonary structure is maintained. We speculate that in LIP patients the markedly elevated levels of serum KL-6 are caused mainly by the increased production of KL-6 by regenerating pneumocytes and increased permeability of the alveolar capillaries.

We conclude that KL-6 is a convenient and reliable marker for evaluating the activity of pulmonary manifestations in HTLV-1 carriers and that it is especially useful in monitoring the effectiveness of treatments. However, the mechanisms underlying the production of KL-6 and the development of pulmonary manifestations in HTLV-1 carriers remain unclear. Further studies are necessary to determine whether serum KL-6 will be useful in the diagnosis of bronchoalveolar disorders, especially in HTLV-1 carriers.

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