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CASE REPORT

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A case of interstitial pneumonia caused by bucillamine: a study using serological markers

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Abstract The patient was a 61-year-old man diagnosed with rheumatoid arthritis (RA) in 2001. He initially received treatment at a nearby clinic, but his condition could not be satisfactorily controlled. He subsequently consulted our hospital during the same year. Although his symptoms improved in response to treatment at our hospital, slight fever, cough, and then high fever and dyspnea subsequently developed. A diagnosis of interstitial pneumonia was made on the basis of findings of diagnostic imaging. The time course of changes in serological markers, including surfactant protein A (SP-A), surfactant protein D (SP-D), and KL-6, as well as markers of inflammatory reaction and lactate dehydrogenase was examined to determine the clinical significance of serological markers in the management of interstitial pneumonia.

Key words Bucillamine · Interstitial pneumonia · KL-6 · Surfactant protein A (SP-A) · Surfactant protein D (SP-D)

Introduction

Rheumatoid arthritis (RA) can be complicated by various extra-articular symptoms during the course of treatment. Complication by lung disease requires particular care because it can have serious effects on patient prognosis and quality of life. However, diverse lung diseases (including infection, adverse drug effects, etc.) can complicate RA, and it is sometimes difficult to identify their cause.[1] Interstitial pneumonia (IP) is the most important lung disease that can complicate RA. Several serological markers have recently been used to assist the clinical diagnosis of IP.[2] We recently attempted to evaluate the usefulness of serological markers in a case of interstitial pneumonia in a patient with RA that appeared to have been caused by bucillamine.

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Case report

The patient was a 61-year-old man whose chief complaints were fever, cough, and dyspnea. He underwent amputation of the left toes due to trauma at the age of 32 years, and had spent 3 years as a coal mine worker beginning in 1957. His family history was noncontributory.

The patient was diagnosed with RA in 2001. He was treated at a nearby clinic, but his condition was poorly controlled. Bucillamine was prescribed (200 mg/day) at the end of September 2001. His symptoms were not alleviated by this treatment, and he visited our hospital on December 14, 2001. He was admitted to our hospital on February 10, 2002 for further investigation. At that time, no lung lesion was revealed by chest X-ray. His symptoms subsequently improved, and bucillamine therapy was continued at the same dosage.

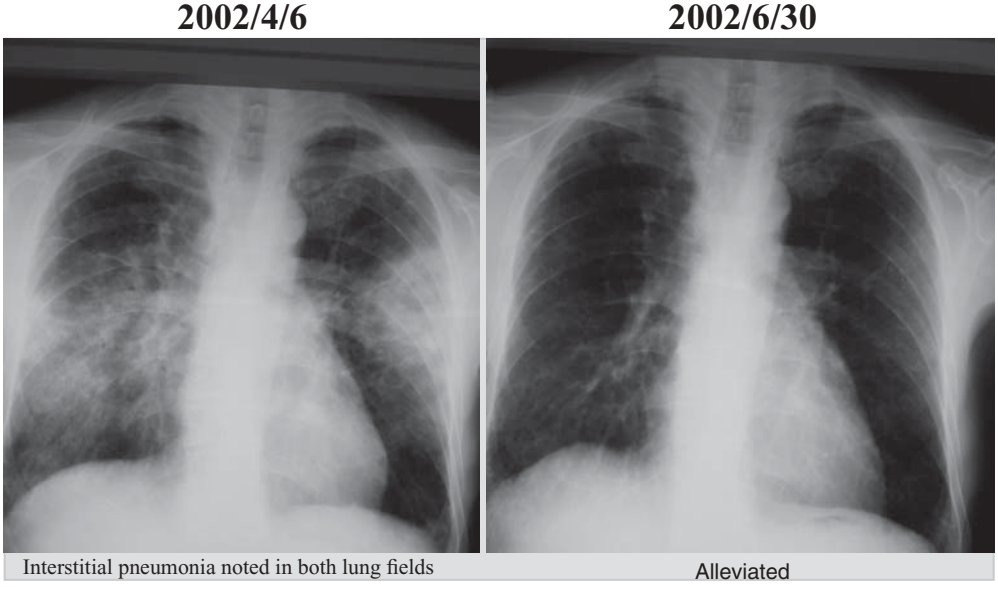
Early in April 2002, he developed slight fever, cough (primarily dry cough), and then high fever and dyspnea. At presentation, he had a body temperature of 38.1°C, blood pressure of 102/60 mmHg, and heart rate of 80 beats/min (regular). He was alert. His respiratory rate was increased, but he was not cyanotic. Chest auscultation revealed Velcro rales in the lower lung field. No abnormality was detected in the abdomen.

Laboratory test data are given in Table 1. Plain chest X-ray and chest computed tomography (CT) results are shown in Figs. 1 and 2, respectively. The patient's C-reactive protein (CRP) was positive, but no leukocytosis was noted. Sputum and blood cultures were negative. There was thus no laboratory evidence of infection. Diagnostic imaging disclosed interstitial shadows in both lungs, primarily in the dorsal region of each lung. A diagnosis of interstitial pneumonia was made on the basis of these findings. Because of

Table 1. Laboratory test data at onset of interstitial pneumonia

TP	5.7 g/dl	T-Cho	143 mg/dl	Hb	12.6 g/dl
ZTT	6.4 U	TG	67 mg/dl	Ht	36.9%
T-Bil	0.9 mg/dl	Glu	88 mg/dl	PL	33.4×10^4 μl
ALP	171 IU/l	UA	1.4 mg/dl	ESR	27 mm/h
GOT	20 IU/l	BUN	10.3 mg/dl	CRP	15.0 mg/dl
GPT	5 IU/l	Cr	0.7 mg/dl	RF	417 IU/ml
LDH	419 IU/l	Na	138 mEq/l	IgG-RF	4.2 (cutoff index)
LAP	87 IU/l	K	4.0 mEq/l	IgG	1540 mg/dl
γ-GTP	9 IU/l	C	104 mEq/l	IgA	478 mg/dl
CHE	207 IU/l	Ca	8.5 mEq/l	IgM	161 mg/dl
CPK	33 IU/l	WBC	9400/μl	KL-6	802 U/ml
AMY	86 IU/l	RBC	439×10^4/μl	SP-D	289 ng/ml
				SP-A	58.9 ng/ml

Fig. 1. Plain chest X-ray



the possibility that bucillamine was responsible for the patient's symptoms, this drug was discontinued and he was treated with oxygen and prednisolone (30 mg/day). His dyspnea (hypoxemia) worsened for a period of time, but inflammatory reaction (CRP, etc.), X-ray findings, and arterial partial pressure of oxygen improved, allowing his prednisolone dosage to be smoothly reduced. The drug lymphocyte stimulation test (DLST) using bucillamine, which was conducted after treatment with prednisolone, was positive.

Serological markers of IP, such as surfactant protein A (SP-A), surfactant protein D (SP-D), and KL-6, as well as markers of inflammatory reaction, lactate dehydrogenase (LDH), and certain other parameters were measured chronologically in this patient (Fig. 3). The time course of SP-D was followed for 1 year, as shown in Fig. 4.

Surfactant protein A, SP-D, and KL-6 all followed courses identical to that of IP. Surfactant protein D was elevated prior to the onset of symptoms. Lactate dehydrogenase, which has often been used as a marker of IP, changed little. C-reactive protein, an indicator of acute-phase reactions, rose only during the acute stage. Surfactant protein A, SP-D, and KL-6 were elevated after CRP became negative, i.e., when the plain chest X-ray had almost returned to normal. Towards the end of April, 4 weeks after the onset of symptoms, these serological markers decreased for a while, but later rose again, with subsequent slow decrease. The patient's dyspnea also worsened for a while, synchronously with the changes observed in laboratory data.

When diagnostic imaging was performed 2 months after disease onset, ground-glass opacity assuming a map-like form was noted in both lungs. The ground-glass opacity was less severe than on April 6. Air bronchogram was no longer observed. However, the extent of ground-glass opacity was slightly wider. Nodal/nodular shadows with irregular margins (linear or ring-shaped) persisted.

Surfactant protein D normalized very slowly as the time course of change in SP-D was followed for approximately 1 year. KL-6 followed a similar course, although it was measured at fewer time points.

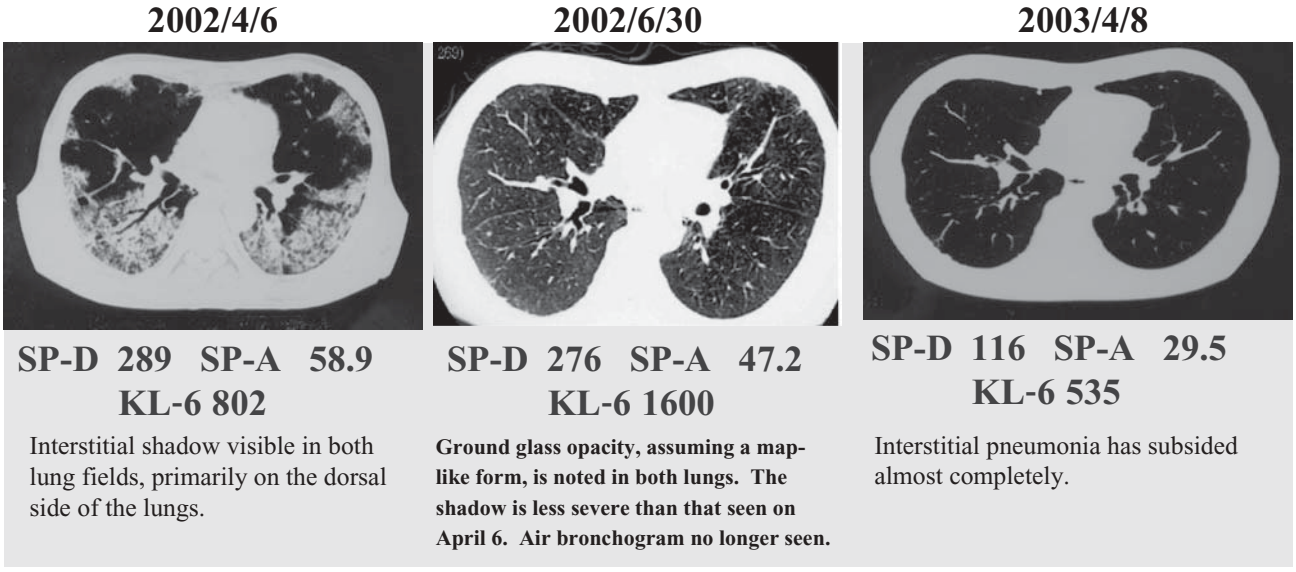


Fig. 2. Chest computed tomography scans. *SP-D*, surfactant protein D; *SP-A*, surfactant protein A

Discussion

Antirheumatic preparations such as those containing gold and methotrexate sometimes induce severe lung damage. Bucillamine has attracted attention because of the lung damage it causes, although the incidence of this side effect is lower than that of renal failure and most other reactions induced by it. Hamasaki and Inokuma[2] reported that bucillamine-induced lung damage has several characteristics: (1) it is induced in cases in which bucillamine is effective against the underlying disease; (2) the typical radiological appearance is a patchy invasive shadow along the bronchovascular bundle at the center of the lung field, often with air bronchogram (the peripheral lung fields remain clear except in advanced cases); (3) auscultation reveals few findings; and (4) marked reduction in blood immunoglobulin levels is noted. The present patient exhibited the first three of these characteristics. His IgG at the time of the first examination in December 2001 was 1840 mg/dl, and at hospitalization in February 2002 (before the onset of lung damage) it was 1540 mg/dl. These findings support the diagnosis of bucillamine-induced lung damage.

Conventionally, LDH and markers of inflammatory reaction (CRP, etc.) have been used for hematological diagnosis of IP. However, the sensitivity and specificity of these conventional methods are poor. In recent years, serological markers of IP have been developed, and their usefulness in the diagnosis of idiopathic interstitial pneumonia and IP complicated by collagen disease has been reported. Surfactant protein A and SP-D are primarily produced by alveolar type II epithelial cells and Clara cells, and probably play important roles in regulation of lung surfactant secretion and immune mechanisms.[4–6] KL-6 antigen is intensely expressed in alveolar type II epithelial cells, bronchiolar epithelial cells, bronchial gland serous cells, etc. In cases of interstitial pneumonia, KL-6 antigen expression is pronounced in proliferative alveolar type II epithelial cells. KL-6 is thought to serve as a chemotactic factor for fibroblasts. However, details of metabolism, etc. are unknown for surfactant protein and KL-6. The half-life of KL-6 in blood is reported to be considerably longer than that of surfactant protein. KL-6 has been used as a tumor marker (of lung adenocarcinoma). Patients exhibiting expression of this marker need to be checked for tumors.[7,8] These factors are known to be elevated in smokers.

Takahashi et al.[9] noted in their general discussion of lung surfactant protein that SP-A-positive and SP-D-positive rates in lungs affected with collagen disease were found to be 44% and 71%, respectively. When they compared the findings of high-resolution computed tomography with serum SP-A and SP-D levels in patients with idiopathic interstitial pneumonia, neither serum SP-A nor SP-D levels correlated with the severity of "honeycomb lung." They did, though, report a close correlation of SP-A level with the finding of ground-glass opacity. These results suggest that serum levels of these markers can vary depending on the features of IP.

Significant elevation of KL-6 level has also been reported for collagen disease patients with active pulmonary disease. In our study, the sensitivity and specificity of KL-6 were 69.2% and 100%, respectively, when calculated in relation to CT findings in patients with IP complicated by scleroderma.[10–12]

Among noninterstitial lung diseases, pulmonary tuberculosis is known to occasionally cause elevation of KL-6 levels. SP-A may be moderately elevated in patients with pneumoconiosis, bacterial pneumonia, tuberculosis, or diffuse panbronchiolitis. Surfactant protein D also increases in the presence of tuberculosis or sarcoidosis. These diseases

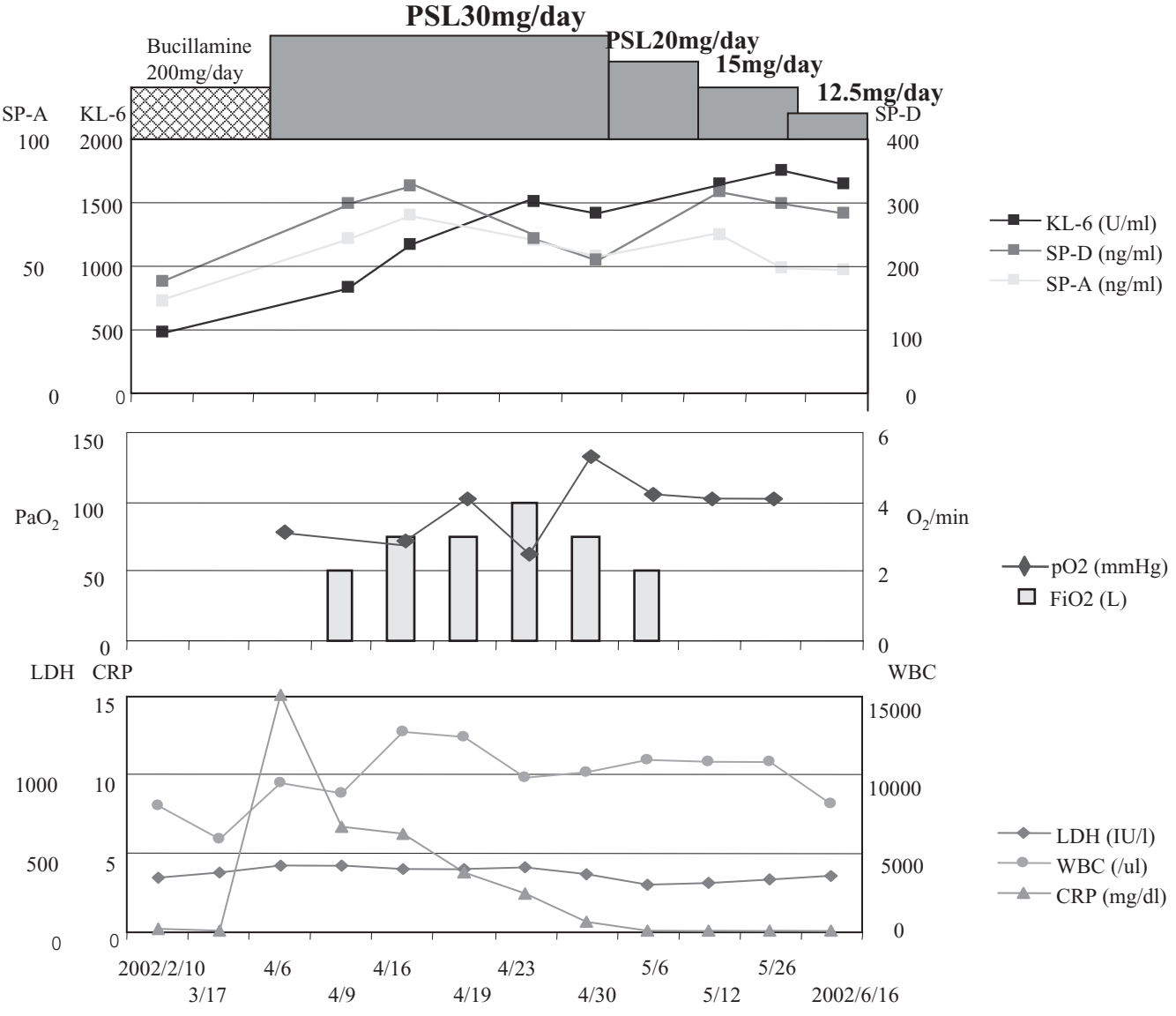


Fig. 3. Time course of various parameters in our patient with interstitial pneumonia. *SP-D*, surfactant protein D; *SP-A*, surfactant protein A; *PSL*, prednisolone; *LDH*, lactate dehydrogenase; *WBC*, white blood cells; *CRP*, C-reactive protein

need to be included in the differential diagnosis of IP. The sensitivity of testing of SP-A and SP-D is reported to be higher than that of plain X-ray, and tests of SP-A and SP-D are affordable. Notably, though, there are some restrictions to the use of these markers under the national health insurance system. When using them for the diagnosis of IP, it is important to bear in mind that the changes they exhibit vary depending upon the type of lesion.

In the present case, SP-A, SP-D, and KL-6 were measured, and all three exhibited changes consistent with the features of IP during the active phase of disease, although LDH changed little. The changes in inflammatory markers (CRP, etc.) differed from those in these serological markers. In the present case, serological markers remained elevated for a prolonged period of time despite improvements in the findings of diagnostic imaging. Inflammation of lung stroma appeared to have persisted in this case. In cases of drug-induced interstitial pneumonia, these serological markers sometimes normalize rapidly, depending on disease activity. Thus, interpretation of the measurement results of these markers requires particular care.

Conclusion

We experienced a case of IP in a patient with RA that appeared to have been caused by bucillamine, which showed characteristic findings in clinical conditions, physical examinations, and diagnostic imaging. It was suggested that serum SP-A, SP-D, and KL-6 are useful in the diagnosis of IP and evaluation of therapeutic effects during the

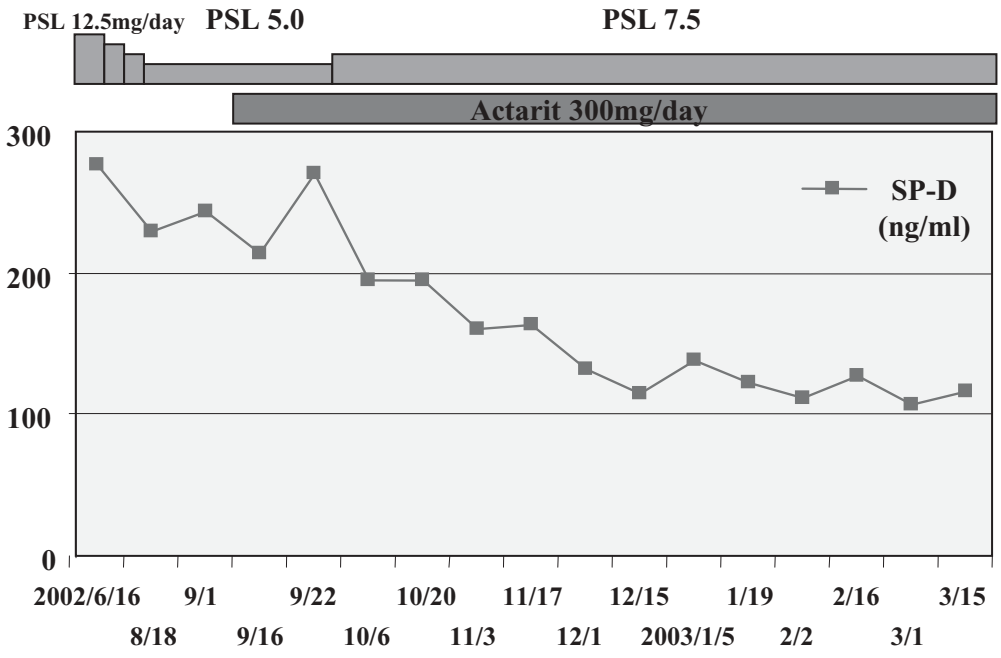


Fig. 4. Course after remission of interstitial pneumonia. *PSL*, prednisolone; *SP-D*, surfactant protein D

course of treatment. It is also important to monitor the time course of change in these markers from the early stage of treatment of RA, as the serum levels of these markers can vary depending on disease activity. Following the time course of change in these markers may thus enable necessary precautions in disease management to be taken before respiratory disease is revealed by diagnostic imaging.

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