Lymphoid Interstitial Pneumonia as a Pulmonary Lesion of Idiopathic Plasmacytic Lymphadenopathy with Hyperimmunoglobulinemia

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A case of idiopathic plasmacytic lymphadenopathy with hyperimmunoglobulinemia is reported. A 71-year-old man was admitted to the hospital because of an abnormal shadow on chest roentgenogram. Chest X-ray taken on admission showed remarkable diffuse infiltration and pleural thickening. Laboratory examinations revealed an elevated total protein level of 10.1 g/dl, and a gammaglobulin level of 7.0 g/dl including 6,790 mg/dl IgG. Mediastinal lymphadenopathy was observed on a chest CT. The patient underwent open lung biopsy. Heavy infiltration of lymphocytes and plasma cells were seen in the moderately fibrotic pulmonary interstitium. LIP was diagnosed. Lymph node biopsy was also performed. Follicular hyperplasia with prominent germinal centers and plasma cell proliferation in the interfollicular area were seen. Treatment with prednisolone resulted in an improvement in the chest X-ray findings, as well as a diminished polyclonal hypergammaglobulin level.
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Key words: LIP, IPL, Castleman's disease, open lung biopsy

Introduction

Carrington and Liebow reported 5 cases of an entity that they called lymphocytic interstitial pneumonia (1). After their report, some of these cases were found to be associated with other immunologic disorders, such as Sjögren's syndrome (2), myasthenia gravis (3) and pseudolymphoma (4). It has also been reported that this disease is frequently associated with dysproteinemia, monoclonal or polyclonal hyperimmunoglobulinemia and hypoinmunoglobulinemia (3, 5-8). Liebow and Carrington have reviewed additional cases of the disease, which they later termed lymphoid interstitial pneumonia (LIP) (9). In Japan, a clinicopathological entity, idiopathic plasmacytic lymphadenopathy with hyperimmunoglobulinemia (IPL), in which a remarkable number of plasma cells infiltrate into systemic lymph nodes as well as lungs and skin, has been proposed (10). Although this disease is very similar to multicentric Castleman's disease, whether or not these two diseases are identical still remains uncertain. However, associa-

tion of pulmonary involvement in patients with Castleman's disease has not been reported. Here we describe a case of lymphoid interstitial pneumonia (LIP) associated with IPL. We confirmed LIP by open lung biopsy, followed by an immunohistochemical method. We have treated the patient with a moderate dose of prednisolone and observed apparent improvement on chest roentgenogram, and hypergammaglobulinemia and pulmonary function. This is the second report of LIP associated with IPL, confirmed by open lung biopsy; the first report is that of Akanuma's (11).

Case Report

The patient is a 71-year-old Japanese male who was admitted to Higashi Nagoya National Hospital on April 22, 1991 following a recent medical examination. Diffuse interstitial infiltration on both upper lung fields and pleural thickening were first pointed out on his X-ray findings in 1979. He was treated with isoniazid and ethambutol for 2 months, then

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isoniazid alone for 4 months following the 1979 checkup. His chest roentgenogram had not shown any remarkable changes for 5 years. No further follow-up was performed until 1989 at the time of his next medical checkup. On his chest X-ray, infiltration and pleural thickening appeared to have worsened compared with the 1979 film. Further examinations, however, were not performed at that time. Recently he felt slight exertional dyspnea. The chest roentgenogram taken on admission (Fig. 1) showed diffuse infiltration on both upper lung fields, pleural thickening and the loss of the lung volume compared with the 1979 film. Dry rales were slightly heard on the lower back. Clubbing of the fingers and cyanosis were absent. Liver and spleen were not palpable, and no skin rash nor superficial lymphadenopathy was observed. Laboratory findings on admission are presented in Table 1. Pulmonary function study revealed mild restrictive impairment, and arterial blood gas analysis showed mild hypoxemia. The erythrocyte count was 383 million and the sedimentation rate was 130 mm/h. Total protein was 10.1 g/dl, albumin 3.1 g/dl and globulin 7.0 g/dl. The electrophoretic pattern showed: albumin 35.7%, α_1 globulin 3.1%, α_2 globulin 7.2%, β globulin 6.5%, and γ globulin 47.5%. The immunoglobulin fraction showed a marked increase in IgG. Immunoelectrophoresis showed polyclonal gammopathy. Cutaneous reaction to PPD was positive

Fig. 1. Chest roentgenogram taken at admission. Marked infiltration, together with pleural thickening was seen on both lung fields.

Table 1. Laboratory Data

Blood gas analysis (room air)		Chemistry		Anti-nuclear antibody	
PaO ₂	76.5 torr	T.P.	10.1 g/dl	Homogenous	×80
PaCO ₂	42.6 torr	Alb	3.1 g/dl	Speckled	×80
SaO ₂	95.50%	A/G	0.44	Anti-DNA antibody	5.8 IU/ml
pH	7.427	Alp	210 IU/l	LE test	—
Spirogram	VC	ChE	363 IU/l	CH ₅₀	44 U/ml
		LAP	16.1 GR-U	ACE	20.6 IU/l
		ZTT	32.6 K-U	ADA	39.5 IU/l
		GOT	66 IU/l	ATLA	—
		GPT	53 IU/l	Coombs' test (EIA)	—
		γ-GTP	17 mU/ml	direct	—
FEV _{1.0}	1,870 ml	LDH	408 IU/l	indirect	—
FEV _{1.0} %	88.21%	UA	6.1 mg/dl	Anti-ENA antibody	—
Complete blood count		BUN	23 mg/dl	RNASE sensitive	—
RBC	383×10 ⁴ /mm ³	Cr	0.8 mg/dl	RNASE resistant	—
Hb	12.4 g/dl	T.C.	177 mg/dl	Thyroid test	—
Ht	37.2%	TG	178 mg/dl	Microsome test	—
Plt	29.8×10 ⁴ /mm ³	β-lipo	797 mg/dl	Paul-Bunnell test	7 (<112)
WBC	7,900/mm ³	Ca	8.8 mg/dl	Anti-RNP antibody	—
stab	4%	P	3.2 mg/dl	Anti-Sm antibody	—
seg	37%	Mg	1.9 mg/dl	Anti-mitochondria antibody	—
eosino	12%	Na	136 mEq/l	Anti-virus antibody	—
mono	8%	K	4 mEq/l	Herpes simplex (CF)	×16
lymp	39%	Cl	102 mEq/l	Cytomegalo (CF)	×32
		CRP	<0.25 mg/dl	Anti-toxoplasma antibody	—
Serum immunoglobulin		Tumor marker			
IgG	6,790 mg/dl (680–1,620)	CEA	3.6 ng/ml		
IgA	242 mg/dl (84–438)	AFP	2.8 ng/ml		
IgM	56 mg/dl (57–288)	CA19-9	28 U/ml		
IgD	0.6 mg/dl (<9)	NSE	6.4 ng/ml		
IgE	200 IU/ml (<250)	SCC	0.5 ng/ml		

Bone marrow aspiration

Section of the iliac bone marrow aspiration showed almost normal appearing bone marrow. Cellularity was estimated to be 40%. There was no evidence of malignancy nor lymphoma.

(15×15mm). Definite evidence suggesting viral infection or autoimmune disease was not found except for slightly elevated titers of anti-viral antibodies and anti-nuclear antibodies. On repeated urinalyses, no proteinuria could be detected and Bence Jones protein was negative. On chest computed tomography, mediastinal lymphadenopathy was observed. Transbronchial lung biopsy was performed 7 days after admission, which showed infiltration of inflammatory cells to alveolar septum and mild fibrotic changes. Bronchoalveolar lavage (BAL) was also performed. Analysis of BAL fluid cells on centrifuge preparations revealed an increased proportion of lymphocytes (17%). Thirty-four days after admission, open lung biopsy was performed. The upper portion of the left thoracic cavity exhibited fibrous adhesion, so S⁸ was chosen as the biopsy site. The biopsy specimen from left S⁸ showed patchy honeycombing, smooth muscle proliferation and diffuse infiltration of plasma cells and lymphocytes in the alveolar wall (Fig. 2a and 2b). Similar lymphoplasmacytic infiltration and fibrosis, together with local exudation of fibrin were presented in the visceral pleura (Fig. 3). The lung specimen was also examined

immunohistochemically using antisera against light chains of immunoglobulins (κ and λ), T lymphocytes and B lymphocytes (data not shown). Polyclonality of plasma cells and lymphocytes was observed. These findings were compatible to chronic fibrotic stage lymphoid interstitial pneumonia (LIP). Figure 4 shows a mediastinal lymph node taken at the open lung biopsy. Follicular hyperplasia with prominent germinal center and plasma cell proliferation in the interfollicular area were seen. To confirm implication of interleukin-6, IL-6 was measured using enzyme-linked immunosorbent assay (ELISA). Serum IL-6 level was, however, under the detection level. After establishment of the diagnosis, prednisolone was administered at an initial dosage of 40 mg/day, which was reduced gradually over a 10-week period. Chest roentgenogram taken on hospital day 154 revealed remarkable improvement of the pleural thickening and interstitial infiltration (Fig. 5). The serum total

Fig. 2. a) Various degrees and stages inflammatory changes in the lung and pleura (HE stain, ×20). b) Heavy infiltration of lymphocytes and plasma cells in the mildly fibrotic pulmonary interstitium (HE stain, ×400).

Fig. 3. Heavy diffuse infiltration of plasma cells and lymphocytes in the fibrotic pleura (HE stain, ×200).

Fig. 4. Mediastinal lymph node. Follicular hyperplasia with prominent germinal center was seen (HE stain, ×4). Plasma cells infiltration was observed in the interfollicular area (HE stain, ×400).

Fig. 5. Chest X-ray film taken after treatment. Improvement of the lung infiltration could be seen.

Table 2. Pulmonary Function Test and Blood Gas Analysis*

	before treatment (1991, 4, 23)	after treatment (1992, 10, 14)
Blood gas analysis		
PaO ₂ (torr)	76.5	73.6
PaCO ₂ (torr)	42.6	40.0
SaO ₂ (%)	95.5	95.1
pH	7.427	7.421
Spirogram		
VC (cm ³)	2,010	2,480
%VC (%)	66.78	83.22
FVC (cm ³)	2,120	2,500
FEV _{1.0} (cm ³)	1,870	2,310
FEV _{1.0} %	88.21	92.40

*Blood gas analyses were performed on room air.

protein level and IgG decreased to 6.4 g/dl and 2,050 mg/dl, respectively. He was discharged from the hospital when the prednisolone was tapered to 10 mg a day; he has been followed at this hospital without any symptoms. Pulmonary function test performed after treatment also revealed improvement (Table 2).

Discussion

Originally, LIP was reported as one type of chronic intersti-

tial pneumonia (12). But Colby and Carrington have reported that many cases previously regarded as LIP or pseudolymphoma, are actually malignant lymphomas (13). It is difficult to distinguish LIP from low grade malignant lymphoma. Therefore in order to obtain an accurate diagnosis, open lung biopsy specimens should be examined immunohistochemically. In this case, we performed open lung biopsy and confirmed the polyclonality of plasma cell and lymphocytes by immunohistochemistry. Association of dysproteinemia with LIP might indicate the existence of immunological disorders at the base of this disease. Upper lobe infiltration and pleural thickening were also improved by steroid therapy, so we thought these lesions were also LIP.

Recently, Mori and colleagues have proposed a new entity that they termed idiopathic plasmacytic lymphadenopathy with hyperimmunoglobulinemia, or, IPL (10). According to their criteria, the characteristic of IPL are as follows; 1) Existence of polyclonal hyperimmunoglobulinemia and serum IgG level higher than 4,500 mg/dl without M-peak. 2) Existence of systemic superficial lymphadenopathy. The largest lymph node should be more than the width of a thumb or 1.8 cm in diameter. Histologically, the lymph node is characterized by marked infiltration of plasma cells without destruction of architecture. 3) Absence of other diseases associated with hyperimmunoglobulinemia. They reviewed 10 cases of IPL. They found the similarity between IPL and plasma cell type of giant lymph node hyperplasia. The major difference between them they mentioned was the existence of systemic lymphadenopathy, which was observed in patients with IPL. Although there was no superficial lymphadenopathy in the present case, mediastinal lymphadenopathy was observed, the histopathologic findings of which were just the same as IPL. Moreover pulmonary involvement in the present case is similar to that of IPL. Therefore, we regard the present case as a variant type of IPL. These facts suggest that IPL might be a predisposing factor of LIP (14).

There have been no reports that describe association of LIP in patients with Castleman's disease. Castleman's disease was originally defined as a solitary intra-mediastinal lymphadenopathy and elevated serum immunoglobulin level. Removal of this lymph node results in the decrease of serum immunoglobulin. Castleman's disease is now regarded as a functioning tumor which produces interleukin-6 (IL-6) (15). IL-6, a cytokine released from T lymphocytes, activates immunoglobulin production by B lymphocytes. Therefore, IL-6 might also play some roles in the genesis of IPL. The serum level of IL-6, however, was not elevated in the present case.

Ohkubo and colleagues also reported a case of IPL (16). In their report, they summarized nineteen cases including their own, and found plasma cells to infiltrate into organs other than lymph nodes, mainly bone marrow and lungs. Most patients showed little or slight exacerbation in their clinical course. In our case, the onset of this disease is not clear and twelve years have passed since 1979 when an abnormality was first pointed out on chest X-ray findings. These facts suggest that IPL is a generalized benign lymphoproliferative disorder. The progres-

sion of symptoms after treatment is also very slow. As for the treatment of this disease, here prednisolone administration did reduce the serum total protein but interruption of the administration caused immunoglobulins to elevate. Because the incidence of LIP is rare, the present case appears to be of interest to many physicians.

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