Eur Respir J, 1995, 8, 689–696
DOI: 10.1183/09031936.95.08050689

European Respiratory Journal
ISSN 0903 - 1936

Elevation of tumour markers in serum and bronchoalveolar lavage fluid in pulmonary alveolar proteinosis

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ABSTRACT: It is unclear whether tumour markers are generally increased in the serum and bronchoalveolar lavage fluid (BALF) of patients with pulmonary alveolar proteinosis (PAP). To clarify this point, levels of tumour markers were measured in the serum and BALF of patients with PAP.

Squamous cell carcinoma (SCC) antigen, carcinoembryonic antigen (CEA), and carbohydrate antigens sialyl Lewis^a (CA 19-9) and sialyl SSEA-1 (SLX) were assayed with radioimmunoassay kits. Cytokeratin 19 fragments (CYFRA) were measured by enzyme-linked immunosorbent assay.

Values for the tumour markers in serum, except for SCC, exceeded cut-off values in some PAP patients. Levels of the markers were higher in BALF compared with those in serum, and were significantly elevated in PAP patients compared with control subjects. There was a significant inverse correlation between CA19-9 level in BALF and arterial oxygen tension (Pao_2) in PAP patients. A gradual elevation of CA19-9 and SLX was observed in a patient who showed a decrease in Pao_2 level during the study period.

In the light of these findings, it is possible that levels of tumour markers in BALF, especially levels of CA19-9 and SLX, may reflect the severity of the disease in PAP patients.

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Keywords: Bronchoalveolar lavage fluid
pulmonary alveolar proteinosis
tumour marker

Received: October 10 1994
Accepted after revision February 8 1995

Pulmonary alveolar proteinosis (PAP), a rare chronic pulmonary disease of unknown cause, is characterized by the accumulation of large amounts of pulmonary surfactant within the alveoli [1, 2]. It has been reported that biochemical analysis [3] and cytology [4] of bronchoalveolar lavage fluid (BALF) is useful for the diagnosis of PAP. Surfactant protein A (SP-A) is the predominant phospholipid-associated glycoprotein in pulmonary surfactant, and is specific to the lung [2, 5]. It has recently been reported that the measurement of SP-A in BALF and sputum with an enzyme-linked immunosorbent assay (ELISA) is valuable for the diagnosis of PAP [2, 6, 7].

There have been a few single case reports [8–10] describing patients with PAP in whom carcinoembryonic antigen (CEA) was elevated in BALF, and also a few reports of patients with PAP in whom CEA was elevated in serum [11]. Immunohistochemical study of the lung biopsy specimens obtained from these patients showed that CEA was localized in alveolar epithelial cells and in the material filling the alveoli [9–11].

However, it is not clear whether the high levels of CEA in the serum and BALF of patients with PAP are a general feature, since studies in larger PAP population samples have not yet been performed. It is also unknown whether other tumour markers are elevated in the serum or BALF of PAP patients. Accordingly, in this study, we examined the levels of various tumour markers in the serum and BALF of several PAP patients. We also studied the time course of changes in the levels of tumour markers in the serum and BALF in one PAP patient.

Materials and methods

Study subjects and design

Six patients with PAP (median age 43 yrs) were enrolled in this study (table 1). Four of the six were smokers. Cigarette consumption was expressed as Brinkman index (numbers of cigarettes smoked per day × years of smoking) [12]. Five patients complained of dyspnoea on exertion, but one had no symptoms. On chest radiographic films, bilateral alveolar-interstitial infiltrates were observed in all patients. The diagnosis of PAP was confirmed both by transbronchial lung biopsy (TBLB) and bronchoalveolar lavage (BAL) in three patients, and by BAL only in two patients. One patient, who showed no typical findings of PAP on either TBLB or BAL, was diagnosed by open lung biopsy.

Blood gas analysis data and the results of pulmonary function tests are summarized in table 1. The patients were carefully examined to rule out malignancy.

Levels of various tumour-markers in serum and BALF samples from PAP patients were measured and evaluated.

Table 1. – Characteristics of patients with pulmonary alveolar proteinosis

Pt No.	Age yrs	Sex	Brinkman Index	Symptom	Diagnosed by	Pa_{O_2} kPa (mmHg)	Pa_{CO_2}	VC % pred	FEV_1 % pred
1	50	M	600	Dyspnoea on exertion	BAL, TBLB	9.3 (70.0)	5.5 (41.5)	93	90
2	51	M	140	Dyspnoea on exertion	BAL	7.0 (52.8)	4.7 (35.2)	57	95
3	54	M	1360	Dyspnoea on exertion	BAL, TBLB	8.4 (62.8)	4.7 (35.1)	80	91
4	37	M	380	Dyspnoea on exertion	BAL, TBLB	7.9 (59.3)	5.0 (37.5)	87	89
5	46	M	0	CXR abnormal shadow	Open lung biopsy	12.9 (96.6)	5.4 (40.6)	99	80
6	17	F	0	Dyspnoea on exertion	BAL	5.8 (43.6)	4.3 (32.0)	60	93

Pt: patient; M: male; F: female; CXR: chest radiograph; BAL: bronchoalveolar lavage; TBLB: transbronchial lung biopsy; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted. Brinkman index: number of cigarettes smoked per day × years of smoking.

The findings for BALF from PAP patients were compared with two other groups: a group of eight patients with sarcoidosis (two males and six females; three smokers) and a control group of seven subjects (three males and four females; three smokers). All sarcoidosis patients showed typical BAL findings for sarcoidosis, such as an elevated lymphocyte rate and high CD4/CD8 ratio. Since samples from healthy volunteers could not been obtained, samples from seven patients who had uveitis were used as control. Pulmonary sarcoidosis and other pulmonary diseases were ruled out in these patients by lack of abnormal findings on chest radiographs, BAL analysis, and TBLB. Values for the mean total cell number, differential cell counts, and CD4/CD8 ratio in the BALF of the three groups are summarized in table 2.

Serum and BALF samples from patients with PAP

Serum. On admission, blood was obtained from the patients by venipuncture. The blood samples were centrifuged, and the serum was removed and stored at -70°C until studied.

BALF. BAL was performed as described previously with a total of 150 ml saline (3×50 ml aliquots) [2]. The recovered fluid was immediately passed through two layers of sterile gauze to remove mucus. The filtrates were centrifuged at 250×g for 15 min at 4°C to remove cells. The supernatants were obtained and stored until ready for use. BALF from the right eighth segment (subsegment a or b) was used for this study, since the first therapeutic BAL was performed in this segment.

Measurement of protein, albumin and SP-A

Total protein and albumin in BALF were assayed by a pyrogallol red-molybdenum complex method [13] and by latex turbidimetric immunoassay [14], respectively. SP-A in BALF was measured with an ELISA kit, using two monoclonal antibodies to human SP-A, PE10 and PC6 [2, 6]. The ELISA kit was a kind gift from Teijin Institute of Bio-Medicine, Hino, Japan.

Measurement of tumour markers

Levels of squamous cell carcinoma (SCC) antigen, carcinoembryonic antigen (CEA), carbohydrate antigen sialyl Lewis^a (CA19-9) and sialyl SSEA-1 (SLX) in serum and BALF were measured with radioimmunoassay kits. The cut-off levels of SCC antigen and CEA in serum with the relevant kits (Dinabot, Tokyo, Japan) were 1.5 $ng \cdot ml^{-1}$ (average, 0.97±0.25 $ng \cdot ml^{-1}$ in 59 healthy controls) [15] and 2.5 $ng \cdot ml^{-1}$ (2.5±1.0 $ng \cdot ml^{-1}$ in 48 healthy controls) [16], respectively. The cut-off level of CA19-9 with the relevant kit (Centcor, Malvern, PA, USA) was 37 $U \cdot ml^{-1}$, according to the finding that the average concentration of CA19-9 in serum of 1,020 healthy individuals was 8.4±7.4 $U \cdot ml^{-1}$ [17]. The cut-off level of SLX in the relevant kit (Otsuka Assay Laboratory, Tokushima, Japan) was 38 $U \cdot ml^{-1}$, corresponding to the mean +2SD calculated in 1,105 healthy subjects [18]. The

Table 2. – Total cell numbers and differential cell counts of the BALF in the three groups

Group	n	Total cell number $\times 10^7$	Differential cell count %				CD4/CD8 ratio
			Macrophages	Lymphocytes	Neutrophils	Others	
PAP	6	7.4±7.1	75.6±3.5	21.7±4.3	2.2±1.4	0.5±0.4	ND
Sarcoidosis	8	3.5±2.2	53.5±14.1	45.4±14.5	0.7±0.8	0.3±0.3	13.0±8.0
Control	7	2.3±0.7	93.6±2.0	5.3±2.1	0.7±0.9	0.4±0.4	1.4±0.7

The results were expressed as means±standard deviations. BALF: bronchoalveolar lavage fluid; PAP: pulmonary alveolar proteinosis; ND: not determined.

levels of cytokeratin 19 fragments (CYFRA) in the samples were kindly assayed by Boehringer Mannheim, Tokyo, Japan, using an ELISA [19, 20]. The cut-off level was 3.5 ng·ml^{-1}, based on the average concentration of CYFRA of 1.22±0.44 ng·ml^{-1} in 440 healthy individuals [19].

Statistics

All values were expressed as means±SD. The Mann-Whitney U-test was used for statistical comparisons of means. The correlation between two parameters was examined by regression analysis.

Results

Tumour marker concentration in serum of PAP patients

As shown in table 3, concentrations of SCC in serum were below the cut-off value in all patients with PAP. Serum CEA was elevated in three of five patients; the mean CEA level in serum was 7.8±10.8 ng·ml^{-1}. High levels of serum CA19-9 were found in two of five patients, the mean level of CA19-9 in serum being 30.4±28.8 U·ml^{-1}. SLX was high in only one patient. Elevated levels of CYFRA in serum were found in three of four patients. Positive (>cut-off value) percentages of SCC, CEA, CA19-9, SLX, and CYFRA in serum were 0, 60, 40, 20 and 75%, respectively. All tumour markers were within cut-off levels in patient No. 1 (smoker, Brinkman index=600), whilst all markers except for SCC were elevated in the serum of patient No. 6 (nonsmoker). Patient No. 2 had a high concentration of CA19-9 but normal levels of the other markers. Patients Nos. 3 and 4 showed high levels of CEA and CYFRA in serum. The effects of smoking on the levels of tumour-markers in serum were not significant.

Tumour marker concentration in BALF of PAP patients

Concentrations of tumour markers were high in the BALF of most patients (table 3). The ratio of the concentration of each marker in BALF to that in serum is also shown in table 3. Serum SCC levels were lower than the cut-off value, as noted above, whilst concentrations of SCC in the BALF of all patients were high. The ratio of the value in BALF to that in serum varied from 9.8 to 233.3. CEA was also elevated in BALF, even though the serum value was in the normal range, as in patient No. 2. CA19-9 and SLX were increased in the BALF of five of the six patients. Although CYFRA in BALF could be measured in only five patients, the concentrations of this tumour marker in BALF were high in all five. In patient No. 4, the ratio of the concentration of each marker in BALF to that in serum was very high, except for SCC. Levels of all tumour markers, except for SCC, were lower in the BALF of patient No. 5 than in other patients. The highest levels of CEA, SLX and CYFRA were shown in patient No. 6, who was a nonsmoker but had the highest total cell number in BALF. The effects of smoking on the levels of tumour-markers in BALF were not significant.

Total cell numbers and differential cell counts in the BALF of PAP patients, sarcoidosis patients and control subjects

Although there was no statistical significance, the total cell number in BALF of PAP patients was apparently higher than those of the other two groups, as shown in table 2. The percentage of neutrophils in BALF of PAP patients was significantly higher than those of the other groups (p=0.0481 and 0.0435 for sarcoidosis patients and control subjects, respectively). The percentage of lymphocytes in BALF of PAP patients was also significantly higher than that of control subjects (p=0.0045). Patient No. 6 showed the highest total cell count (1.92×10^8) with the highest percentage of lymphocytes (26.7%).

Concentrations of protein, albumin and SP-A in the BALF of PAP patients, sarcoidosis patients and control subjects

Mean total protein and albumin values in PAP patients were 132.7±149.6 and 66.6±88.3 mg·dl^{-1}, respectively,

Table 3. – Levels of tumour markers in the serum and BALF of patients with pulmonary alveolar proteinosis

Pt No.	SCC ng·ml^{-1}			CEA ng·ml^{-1}			CA19-9 U·ml^{-1}			SLX U·ml^{-1}			CYFRA ng·ml^{-1}		
	Serum	BALF	Ratio^{+}	Serum	BALF	Ratio	Serum	BALF	Ratio	Serum	BALF	Ratio	Serum	BALF	Ratio
1	1.0	64	64	2.0	8.6	4.3	7	47	6.7	18	180	10	ND	ND	-
2	0.6	120	200	1.2	11.0	9.2	65	1000	15.4	30	150	5	2.0	185.6	92.8
3	0.6	140	233.3	3.7	9.2	2.5	16	290	18.1	22	170	7.7	5.5	74.0	13.5
4	0.5	23	46	5.2	98.0	18.9	6	410	68.3	20	340	17	20.1	4000	199
5	ND	55	-	ND	2.8	-	ND	6	-	ND	30	-	ND	22.2	-
6	0.8	7.8	9.8	27.0	48.0	1.8	58	750	11.4	66	750	11.4	41.3	3773	91.4

SCC, CEA, CA19-9, and SLX levels in serum and BALF were determined by radioimmunoassay. CYFRA level was measured by ELISA. $^{+}$: concentration of tumour marker in BALF/concentration in serum. Pt: patient; SCC: squamous cell carcinoma antigen; CEA: carcinoembryonic antigen; CA19-9: sialyl Lewis^a antigen; SLX: sialyl SSEA-1 antigen; CYFRA: cytokeratin 19 fragments; BALF: bronchoalveolar lavage fluid; ELISA: enzyme-linked immunosorbent assay. ND: not determined (assay could not be performed as the sample volume was not sufficient).

(fig. 1). Total protein level was significantly higher in the BALF of PAP patients compared with the values in the two other groups. Mean albumin value in BALF of PAP patients was also significantly higher than that of control subjects. Although the difference was not statistically significant, total protein and albumin concentrations were higher in patients with pulmonary sarcoidosis than in the control subjects.

As shown in figure 2, the concentration of SP-A in the BALF of all patients with PAP was significantly higher than that in the other two groups, the mean values in PAP patients, sarcoidosis patients, and control subjects being 61.3±10.9, 3.2±0.8, and 3.8±0.7 $\mu g \cdot ml^{-1}$, respectively.

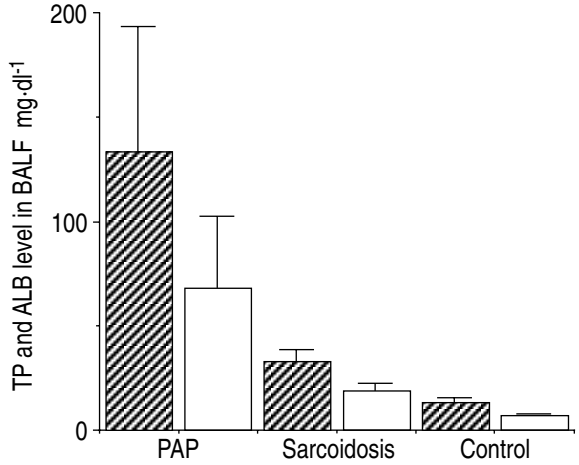

Fig. 1. – Total protein (TP) and albumin (ALB) levels in the BALF of PAP patients, sarcoidosis patients and control subjects. Total protein in BALF was significantly higher in PAP patients than in the other two groups (p=0.0389 and p=0.0066, to sarcoidosis patients and control subjects, respectively). Albumin in BALF was significantly higher in PAP patients than in the control subjects (p=0.0043). ▭: total protein; □: albumin. BALF: bronchoalveolar lavage fluid; PAP: pulmonary alveolar proteinosis. Bar = standard error.

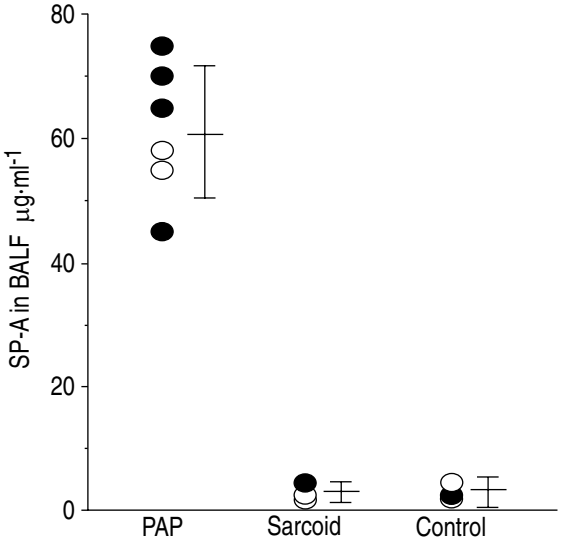

Fig. 2. – Concentration of surfactant protein A (SP-A) in the BALF of PAP patients, sarcoidosis patients and control subjects. ❍ : nonsmokers; ● : smokers. The concentration of surfactant protein A was significantly higher in the BALF of PAP patients than in the other two groups (p=0.0019 and p=0.0027, respectively). For abbreviations see legend to figure 1.

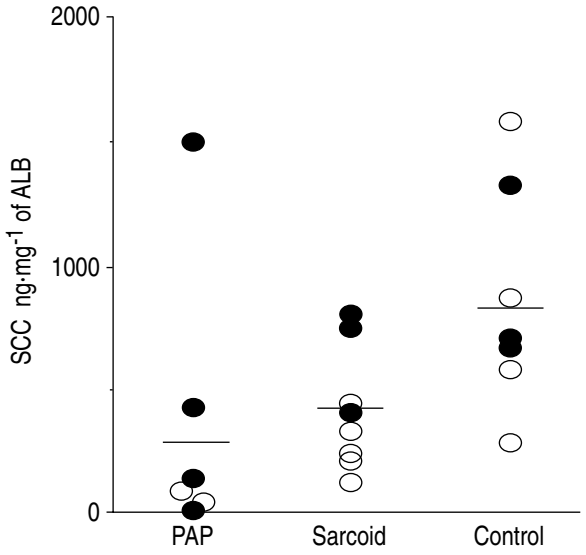

Fig. 3. – Ratio of SCC to albumin (ALB) in BALF. ❍ : nonsmokers; ● : smokers. There were no significant differences in the ratio of SCC to albumin among the three groups. SCC: squamous cell carcinoma antigen. For further abbreviations see legend to figure 1.

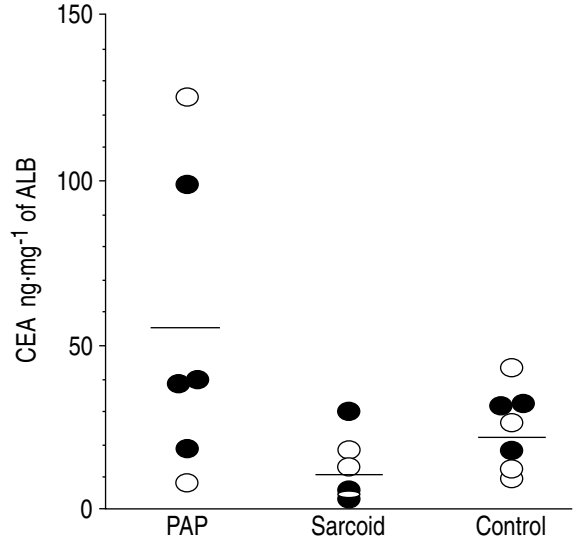

Fig. 4. – Ratio of CEA to albumin (ALB) in BALF. ❍ : nonsmokers; ● : smokers. The ratios of CEA to ALB were significantly higher in PAP patients than in sarcoidosis patients and control subjects (p=0.0098 and p=0.0455, respectively). CEA: carcinoembryonic antigen. For further abbreviations see legend to figure 1.

Comparison of tumour marker levels in the BALF of PAP patients, sarcoidosis patients and control subjects

The concentration of tumour markers in the BALF of PAP patients was compared with that in sarcoidosis patients and control subjects. Since there were significant differences in the concentrations of total protein and albumin among the three groups, the ratios of tumour markers to albumin were also evaluated.

There were no significant differences in the concentration and the ratio (fig. 3) of SCC in BALF among the three groups, although the levels of all the other tumour markers in the BALF of PAP patients were significantly higher than those in the other two groups (data not

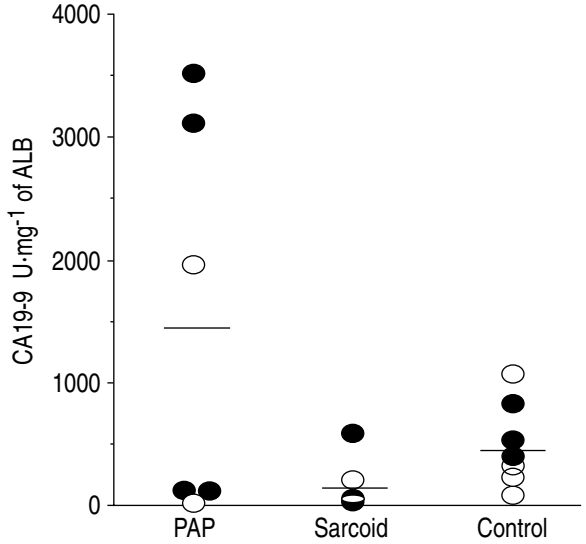

Fig. 5. – Ratio of CA19-9 to albumin (ALB) in BALF. ❍ : non-smokers; ● : smokers. Although there was no statistical significance, the ratios of CA19-9 to ALB were apparently higher in PAP patients than in sarcoidosis patients and control subjects. CA19-9: sialyl Lewis[a] antigen. For further abbreviations see legend to figure 1.

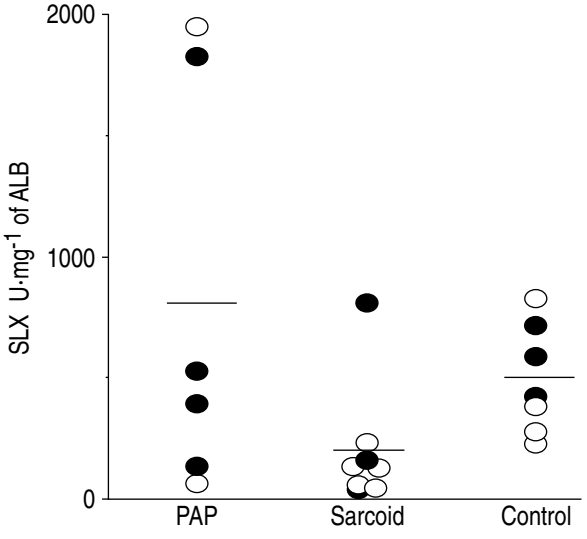

Fig. 6. – Ratio of SLX to albumin (ALB) in BALF. ❍ : non-smokers; ● : smokers. Although there was no statistical significance, the ratios of SLX to ALB were apparently higher in PAP patients than in sarcoidosis patients and control subjects. SLX: sialyl SSEA-1 antigen. For further abbreviations see legend to figure 1.

shown). The ratios of these tumour markers to albumin were also apparently higher in PAP patients than in the other two groups (figs. 4–7).

Correlation of arterial oxygen tension (Pa_{O_2}) and concentration of tumour markers in serum and BALF

As shown in figure 8, there was a significant inverse correlation between the Pa_{O_2} value and the concentration of CA19-9 in the BALF of PAP patients. No such correlation was found for the concentration of CA19-9 in serum. There was also no correlation between the Pa_{O_2} values and concentrations of the other tumour markers in serum or in BALF.

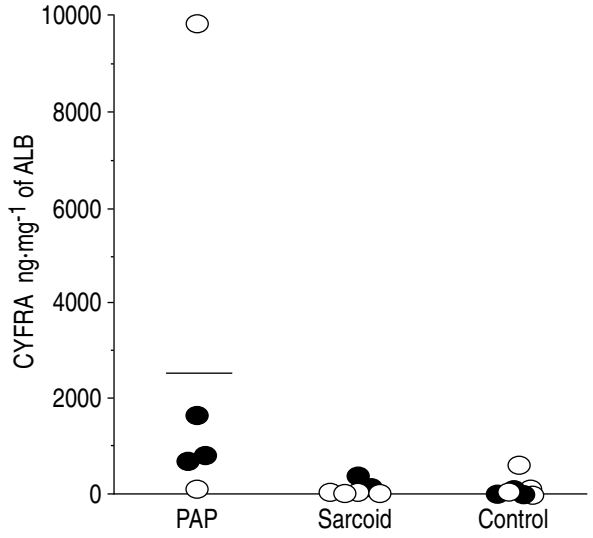

Fig. 7. – Ratio of CYFRA to albumin (ALB) in BALF. ❍ : non-smokers; ● : smokers. The ratios of CYFRA to ALB were also significantly higher in PAP patients than in sarcoidosis patients and control subjects (p=0.0045 and p=0.0074, respectively). CYFRA: cytokeratin 19 fragments. For further abbreviations see legend to figure 1.

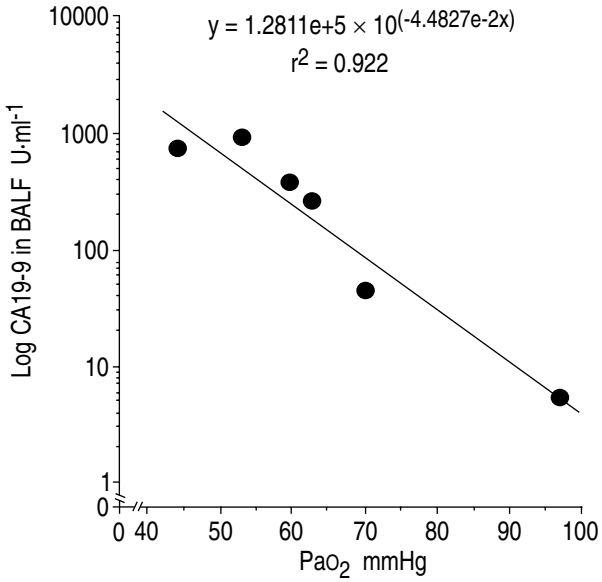

Fig. 8. – Correlation of CA19-9 levels in the BALF and Pa_{O_2} in PAP patients. There was a significant inverse correlation between CA19-9 levels in BALF and Pa_{O_2} in PAP patients. Pa_{O_2}: arterial oxygen tension. (1 mmHg=133.32 Pa). For further abbreviations see legend to figures 1 and 5.

Longitudinal changes in Pa_{O_2} and tumour marker concentration in serum and BALF in patient No. 2

Figure 9 shows the longitudinal changes in Pa_{O_2} and tumour markers in BALF obtained from the same subsegment. Pa_{O_2} declined from 10.5 to 8.2 kPa (78.6 to 61.3 mmHg) in 17 months. During this period, the concentrations of CA19-9 and SLX in BALF gradually increased. The other tumour markers in BALF did not change significantly, and none of the tumour markers in serum, including CA19-9 and SLX, changed significantly.

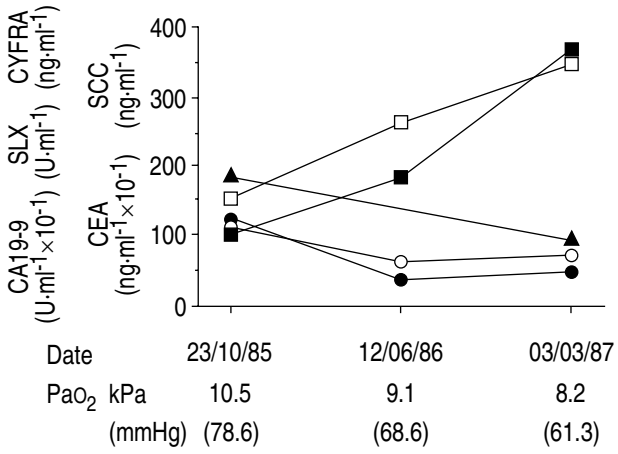

Fig. 9. – Time course of changes in Pa_{O_2} and levels of tumour markers in the BALF of a PAP patient (patient No. 2). The levels of CA19-9 and SLX in BALF increased with time in this patient, who showed a decrease of Pa_{O_2} from 10.5 to 8.2 kPa (78.6 to 61.3 mmHg) during this period. Other tumour markers did not show such time change. —■—: sialyl Lewis^a antigen (CA19-9 U·ml^{-1}×10^{-1}); —□—: sialyl SSEA-1 antigen (SLX U·ml^{-1}); —▲—: cytokeratin 19 fragments (CYFRA ng·ml^{-1}); —○—: carcinoembryonic antigen (CEA ng·ml^{-1}×10^{-1}); —●—: squamous cell carcinoma antigen (SCC ng·ml^{-1}). For further abbreviations see legends to figures 1 and 8.

Discussion

Concentrations of the tumour markers in serum, except for those of SCC, exceeded cut-off values in some PAP patients. Levels of the markers were increased in BALF compared with those in serum, and were significantly elevated in PAP patients compared with control subjects. There was a significant inverse correlation between CA19-9 level in BALF and Pa_{O_2} in PAP patients. A gradual elevation of CA19-9 and SLX was observed in patient No. 2, who showed a decrease in Pa_{O_2} level during the study period.

It has been suggested that biochemical and immunological tumour markers in serum are helpful in the diagnosis of cancer [21, 22]. The measurement of tumour markers in BALF is also useful in diagnosing lung cancer that is not visible endoscopically [22–24]. However, serum levels of some tumour markers are elevated in some benign lung diseases, healthy smokers, benign nonpulmonary diseases, and systemic diseases [25–28]. These tumour markers are also elevated in the BALF of smokers and patients with nonmalignant lung diseases [28–30]. MUKAE *et al.* [28] reported that tumour-associated carbohydrate antigens, such as CA19-9 and SLX, were high in the BALF of patients with diffuse panbronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, and interstitial pneumonia associated with collagen vascular diseases.

PAP, a chronic benign disease characterized by the accumulation of surfactant in alveoli, is diagnosed on the basis of invasive biopsy procedures [7]. It has recently been reported that PAP can be diagnosed cytologically on the basis of BAL material [4]. The biochemical analysis of BALF, in particular the measurement of SP-A level by ELISA, is also useful in the diagnosis of this disease [2, 3, 6, 7]. In this study the levels of SP-A in BALF were significantly high in all PAP patients. A few PAP patients with high levels of CEA in serum and/or BALF have been reported [8–11]. In this study, we measured five tumour markers in the serum and BALF of several patients with PAP, to determine whether CEA levels were generally high in these patients and to determine whether other tumour markers were also increased.

SCC was originally reported by KATO and TORIGOE [31] as a fraction derived from squamous cell carcinoma tissue of the uterine cervix. As well as being elevated in the serum of patients with uterine cervix carcinoma, this antigen is also elevated in patients with squamous cell carcinoma in other organs and regions, such as the lung, oesophagus, head, and neck, and it is used in the diagnosis of squamous cell carcinoma in these positions [15]. CEA is a cell surface glycoprotein, whose concentration is high in foetal tissues and in a variety of tumours, most commonly those of endodermal origin [32]. Tumour-associated carbohydrate antigen, CA19-9, is a useful marker for gastrointestinal malignancies, in particular pancreatic carcinoma [33]. SLX, also a carbohydrate antigen is elevated in the serum of patients with various types of carcinomas, in particular pulmonary adenocarcinoma [34]. CYFRA is a new tumour marker that detects soluble cytokeratin 19 fragments; it is used for the diagnosis of lung cancer [19, 20].

In the present study, we found that tumour markers other than SCC were elevated in the serum of the PAP patients. The positive pattern of serum tumour marker varied from patient to patient. Interestingly, all markers were relatively or absolutely increased in the BALF of all PAP patients. Although SCC levels were high in the BALF of PAP patients, it seems that this finding has no clinical significance, since the levels were also high in sarcoidosis patients and in control subjects. In contrast, the other tumour markers in BALF were apparently elevated in PAP patients compared with the levels in sarcoidosis patients and control subjects.

The mechanisms responsible for such high concentrations of tumour markers in the BALF of PAP patients may be that; 1) tumour markers produced locally in the lung leak into the circulation; or 2) tumour markers produced originally in other organs are concentrated in the lung. To elucidate the local production of the markers, further investigations, such as immunohistochemical studies, should be performed. In fact, CEA localization has been reported in the lungs of PAP patients [9–11], as has CA19-9 and SLX localization in patients with diffused panbronchiolitis [28]. Since CEA was localized in alveolar epithelial cells and in the material filling the alveoli [9–11], the levels of tumour markers in BALF may reflect the degree of alveolitis. The data of high total cell number and percentage of neutrophils and lymphocytes in BALF obtained from PAP patients may also suggest that the levels of tumour markers in BALF may correlate to lung inflammation.

Although it has been reported that some tumour markers are elevated in the BALF of smokers [27, 29], high levels of markers could also be detected in BALF of a patient who was a nonsmoker (patient No. 6).

We examined the correlation between Pa_{O_2} and the concentrations of tumour markers in sera and BALF, to determine whether the marker levels reflect the progression of the disease. In the PAP patients, there was a significant inverse correlation between CA19-9 level in BALF and Pa_{O_2}. The levels of tumour markers were low in patient No. 5, who showed normal level of Pa_{O_2} and no clinical symptoms or typical TBLB or BALF findings. We also performed longitudinal measurements of the markers in one patient. In this patient (patient No. 2), who showed a decrease of Pa_{O_2} during the study period, there was a gradual elevation of CA19-9 and SLX. Interestingly, none of the other tumour markers in BALF and none of the markers in serum in this patient showed such a change. These findings indicate that the levels of tumour markers in BALF, especially the levels of carbohydrate antigens CA19-9 and SLX, may reflect the severity of the disease in PAP patients. Further studies with larger samples of PAP patients are required. Since BAL and whole-lung lavage are usually performed in almost all PAP patients as a therapeutic procedure, obtaining BALF samples should not be difficult.

We reported here that several tumour markers increased in serum and BALF of most PAP patients. The results of this study, with regard to the clinical value of measurement of tumour markers in the BALF of PAP patients, are inconclusive. However, it is possible that levels of tumour markers in BALF, especially levels of CA19-9 and SLX, may reflect the severity of the disease in PAP patients.

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