The purpose of the present study was to evaluate the clinical utility of serum KL-6 level as a prognostic marker for DAH.

Methods

Study subjects

Consecutive patients who were admitted to the ICU and diagnosed as DAH between 2004 and 2011 were retrospectively studied. Patients' characteristics including age, sex, laboratory findings, radiological findings, ventilatory modes or therapeutic regimens were extracted from the medical records. The vital status of the patients was determined by reviewing medical records, death certificates, as well as by phone interviews.

Serum KL-6 and lactate dehydrogenase (LDH), prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time, D-dimer and hemoglobin levels and platelet counts were included as variables for analysis when taking routine blood tests and performing BAL.

Baseline KL-6 was defined as serum KL-6 level at admission, and peak KL-6 was defined as the highest serum KL-6 level during the follow-up. KL-6 was measured once-weekly. The etiologies of DAH were grouped into 5 categories: pulmonary infection, excessive anticoagulation, vasculitis, interstitial pneumonia or idiopathic based on the different pathogenesis in our patients. The diagnosis of vasculitis was defined by histological evidence, high titers of anti-neutrophil cytoplasmic antibodies, anti- deoxyribonucleic acid antibodies or anti-basement membrane antibodies [10,11]. Correlations between survival and clinical variables were evaluated.

Definition of DAH

Clinical diagnosis of DAH was based on the findings of diffuse ground glass or airspace-filling opacities on chest radiograph and computed tomography, and BAL fluid showing progressively bloodier returns and the presence of 20% or more hemosiderin-laden macrophages [12]. Exclusion criteria were apparent deterioration of left heart failure and contact bleeding with bronchoscope.

BAL

The procedure of BAL was done as previously described [13]. In brief, a flexible bronchoscope was wedged into a segmental bronchus of the middle lobe or the lingula. Sterile isotonic saline at 37°C was instilled in three 50 ml aliquots up to a total volume of 150 ml, with immediate aspiration by gentle suction after each aliquot. The total of recovered BAL fluid fractions were mixed and immediately filtered through two layers of gauze, and centrifuged at 500 g for 10 min at room temperature. Slides were stained with Prussian blue to detect haemosiderin-laden macrophages [12]. After incubation of the slides with 1% hydrochloric acid and 2% potassium ferricyanide (Katayama Medical Co. Ltd., Osaka, Japan) for 20 minutes, slides were counterstained with Kernechtrot stain (Tokyo Chemical Industry Co. Ltd., Tokyo, Japan). A total of 200 or more macrophages were examined for calculating a percentage of Prussian blue positive cells. The BAL fluid samples also underwent routine microbiologic testing for detecting bacteria and viruses.

Statistical analysis

Data are expressed as mean ± standard deviation. Comparison of non-normally distributed variables between groups was done with the Mann-Whitney's *U* test or Fisher's PLSD test. Analysis of changes in non-normally distributed variables between groups was done with the Wilcoxon's rank test or repeated measures of analysis of variance. Comparison of categorical variables between two groups was done with the χ^2 test. The probability of survival was estimated with the Kaplan-Meier method, and the differences in survival rates were evaluated by log-rank test. Multivariate analysis of prognostic factors was done using the Cox regression model. All statistical analyses were done using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL). Differences were considered statistically significant when the p value was <0.05.

Results and discussion

Patient characteristics

There were 25 males and 16 females with a median age of 69 (range, 16–83) years. There were 27 never smokers, 12 former smokers, 2 current smokers, respectively. The etiologies of DAH were pulmonary infection (n=19), excessive anticoagulation (n=9), vasculitis (n=6), interstitial pneumonia (n=2) and idiopathic (n=5). Thirteen patients survived, and 28 died. The ICU mortality was 54% (22/41), the in-hospital mortality was 68% (28/41), and the 28-day mortality was 32% (13/41), respectively. No significant differences were observed in age, sex, smoking status, radiological findings, use of mechanical ventilation, baseline P/F ratio, and laboratory markers at admission between the groups (Table 1). Use of methylprednisolone pulse after admission was more frequent, prothrombin time-international normalized ratio and activated partial thromboplastin time were higher, and duration of ICU stay was significantly longer in non-survivors than survivors (p=0.038, 0.043, 0.029, 0.005, respectively). Meanwhile, P/F ratio 48 hrs after admission was significantly lower in non-survivors than survivors (p=0.023). There was no difference in the frequency of etiologies of DAH between survivors and non-survivors.

Table 1 Differences in clinical characteristics between survivors and non-survivors with DAH

Variables	Survivors, n(%) (n=13)	Non-survivors, n(%) (n=28)	p-value
Age ≥70(yrs)	3 (23)	16 (57)	0.052*
Male sex	8 (62)	17 (61)	>0.99*
Never smoker	7 (54)	19 (70)	0.48*
Bilateral pulmonary involvement	9 (69)	24 (86)	0.24*
Consolidation on chest x-ray	7 (54)	15 (54)	>0.99*
GGA on chest x-ray	9 (69)	22 (79)	0.70*
Use of mechanical ventilation	10 (77)	26 (93)	0.30*
Mode of mechanical ventilation			0.28*
SIMV	5 (12)	9 (22)	
APRV	3 (7)	8 (20)	
HFOV	0 (0)	6 (15)	
CPAP/ PSV	2 (5)	1 (2)	
O_2 mask/ NIPPV	3 (7)	4 (10)	
Preceding interstitial pneumonia	0 (0)	3 (11)	0.54*
Treatment			
Methylprednisolone pulse	5 (38)	21 (75)	0.038*
Immunosupressant	2 (15)	5 (18)	>0.99*
Plasema exchange	1 (8)	4 (14)	>0.99*
Baseline PaO_2/F_IO_2 ratio	207±80	185±70	0.47#
P/F ratio 48 hrs after admission	314±86	250±114	0.023#
Laboratory markers at admission			
PT-INR	1.2±0.3	1.8±1.4	0.043#
APTT (sec)	29.6±4.7	42.0±18.0	0.029#
D-dimer	17.4±29.0	18.8±20.5	0.46#
Platelet ($x10^3$/mL)	185±88	142±103	0.09#
Hemoglobin (g/mL)	10.1±2.3	9.3±2.3	0.26#
LDH (IU/L)	567±399	736±1045	0.88#
Duration of ICU stay (days)	15±15	28±20	0.005#

*Fisher's exact test; # Mann-Whitney's *U* test.
GGA, ground glass attenuation; SIMV, synchronized intermittent mandatory ventilation.
APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation.
CPAP, continuous positive airway pressure; PSV, pressure support ventilation.
NIPPV, non-invasive positive pressure ventilation.
PT-INR, prothrombin time-international normalized ration.
APTT, acivated partial thromboplastin time; LDH, lactate dehydrogenase.
ICU, intensive care unit.

Baseline and peak serum KL-6 levels

The baseline and peak serum KL-6 levels in 41 patients are shown in Figure 1. The median duration before serum KL-6 level reached the peak level was 11±10 days. The median duration from the time of peak serum KL-6 level to death was 23±23 days. Baseline and peak serum KL-6 levels were significantly higher in non-survivors than in survivors (baseline levels, 845±831 vs 492±606 U/mL, p=0.01; peak levels, 1471±1648 vs 659±813 U/mL, p=0.004, respectively).

Correlation between serum KL-6 levels and the use of mechanical ventilation

In our cohort, 34 patients were intubated, whereas the remaining 7 patients were treated without mechanical ventilation. Mean serum KL-6 levels increased during the follow-up in both groups (p=0.01; Ventilated patients, baseline 703±799 U/mL, peak 1,189±1,567 U/mL; Non-ventilated patients, baseline 881±694 U/mL, peak 1,330±995 U/mL; Figure 2). There was no difference in serum KL-6 levels according to the use of mechanical ventilation (p=0.72).

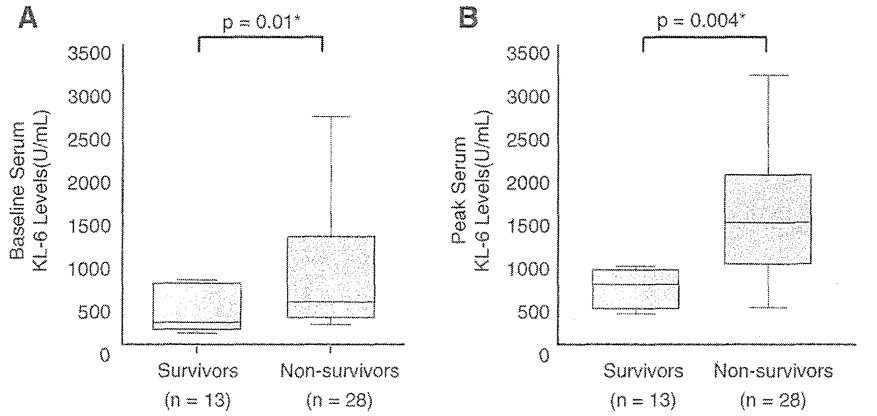

Figure 1 Box plot graphs showing the range of serum KL-6 levels in diffuse alveolar hemorrhage syndrome. (A) baseline and (B) peak serum KL-6 levels in survivors and non-survivors.

Serial changes in serum KL-6 in association with P/F ratio or oxygenation index

Serial changes in serum KL-6 in patients with DAH are shown in Figure 3. Patients who showed a decrease in P/F ratio (n=13, Figure 3A) or an increase in oxygenation index (n=16, Figure 3B) during the initial week showed a significant increase in serum KL-6 levels (p=0.002, p=0.003, respectively). In Figure 3A, two subjects appear to have extremely high levels of KL-6 one week after admission. When they were excluded to avoid statistical error, the increase in serum KL-6 levels during the initial week was still significant (p=0.003).

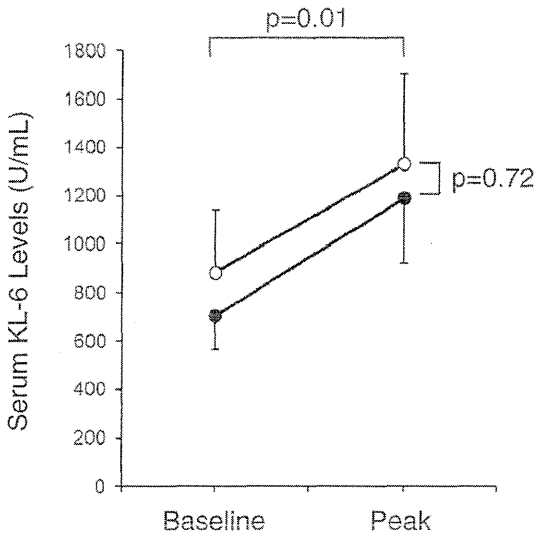

Figure 2 Baseline and peak serum KL-6 levels in patients treated with mechanical ventilation (n=34, closed circles) and without mechanical ventilation (n=7, open circles). Data are expressed as mean ± standard error of mean. Mean serum KL-6 levels increased in both groups (p=0.01). There was no difference in serum KL-6 levels according to the use of mechanical ventilation (p=0.72).

Receiver operating characteristic curve analysis

Receiver operating characteristic curve analysis was used to evaluate the sensitivity, specificity and accuracy of baseline and peak serum KL-6 levels in relation to non-survival (Figure 4). The larger area under the curve which is associated with non-survival was found for peak KL-6 with 0.78 (95% confidence interval (CI), 0.61 to 0.96) compared with baseline KL-6 with 0.74 (95% CI, 0.56 to 0.93). When the cut-off levels were set at the closest point to 100% sensitivity and 100% specificity, the levels in the prediction of non-survival were 700 U/mL for peak KL-6 (sensitivity, 75%; specificity, 85%; accuracy, 78%, respectively) and 240 U/mL for baseline KL-6 (sensitivity, 86%; specificity, 69%; accuracy, 81%, respectively).

Correlation between serum KL-6 levels and overall survival

The Kaplan-Meier analysis showed that higher baseline KL-6 levels were associated with a shorter median survival period (p=0.002) (Figure 5A). The same was true for higher peak KL-6 levels (p=0.0006) (Figure 5B).

In the univariate survival analysis, P/F ratios <200 48 hours after admission (Hazard ratio, 2.58, 95% CI, 1.17-5.68; p=0.018), baseline serum KL-6 levels ≥240 U/mL (Hazard ratio, 4.72, 95% CI, 1.63-13.7; p=0.004) and peak serum KL-6 levels ≥700 U/mL (Hazard ratio, 4.43, 95% CI, 1.76-11.1; p=0.002) were associated with non-survival, whereas no correlations were found between survival and age, sex, smoking status, radiological findings, baseline P/F ratio prothrombin time-international normalized ratio levels and activated partial thromboplastin time (Table 2). In the multivariate survival

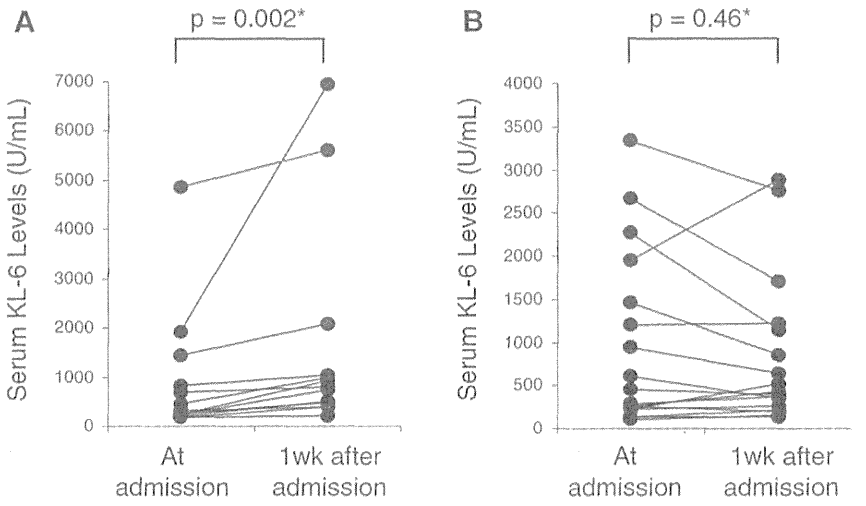

Figure 3 Serial changes in serum KL-6 levels at admission and one week after admission. (**A**) Patients who showed a decrease in PaO_2/F_iO_2 ratio during the initial week (n=13). (**B**) Patients who showed an increase in oxygenation index during the initial week (n=16).

analysis only peak serum KL-6 levels ≥700 U/mL were associated with non-survival (Hazard ratio, 3.95, 95% CI, 1.14-13.7; p=0.031), after adjustment for age, sex, smoking status, extent of pulmonary involvement and P/F ratio 48 hrs after admission.

Discussion

This study showed that baseline and peak serum KL-6 levels are significantly higher in non-survivors compared with survivors of DAH. The increase in serum KL-6 levels during the initial week was associated with a subsequent deterioration in P/F ratio or oxygenation index. With a cut-off level of 700 U/mL for peak serum KL-6, the sensitivity, specificity and accuracy for non-survival were 75%, 85% and 78%, respectively. In the multivariate analysis, peak serum KL-6 ≥700 U/mL was a significant prognostic factor for poor outcome in DAH.

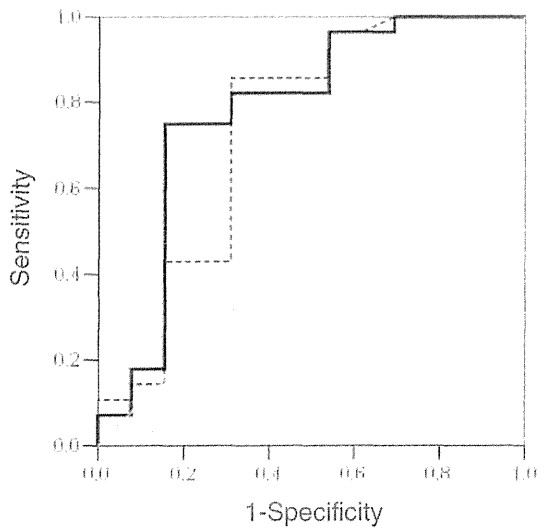

Figure 4 Receiver operating characteristic curve analysis. The curves show the diagnostic power of baseline and peak serum KL-6 levels for the detection of non-survival in diffuse alveolar hemorrhage syndrome. Narrow dotted line indicates baseline serum KL-6 levels; heavy continuous line indicates peak serum KL-6 levels.

Previous studies have shown several factors associated with mortality in DAH. Holguin *et al.* demonstrated that mechanical ventilation, admission to ICU and blood transfusion were associated with increased mortality within 28 days after admission in patients with ANCA-related pulmonary vasculitis [14]. Afessa *et al.* demonstrated in a retrospective study of 48 hematopoietic stem cell transplant recipients that autologous transplant and early-onset DAH were associated with good prognosis [15]. To date, no single serum marker has been shown to be related to the prognosis of DAH, and most of the previous studies focused on immunologically mediated DAH such as vasculitis [16]. The patient population in our study, however, included severe pulmonary infection and excessive anticoagulation as major etiologies of DAH, and this population has not been well investigated.

The mechanisms of the increase in serum KL-6 levels in various fibrotic lung diseases are thought to be due to an overexpression of KL-6 by regenerating alveolar type II pneumocytes, and/or due to an increased permeability following disintegration of the alveolar-vessel barrier [17,18]. The alveolar epithelial damage and the following excessive fibroblast accumulation in DAH appear to be associated with the increment in serum KL-6. As shown

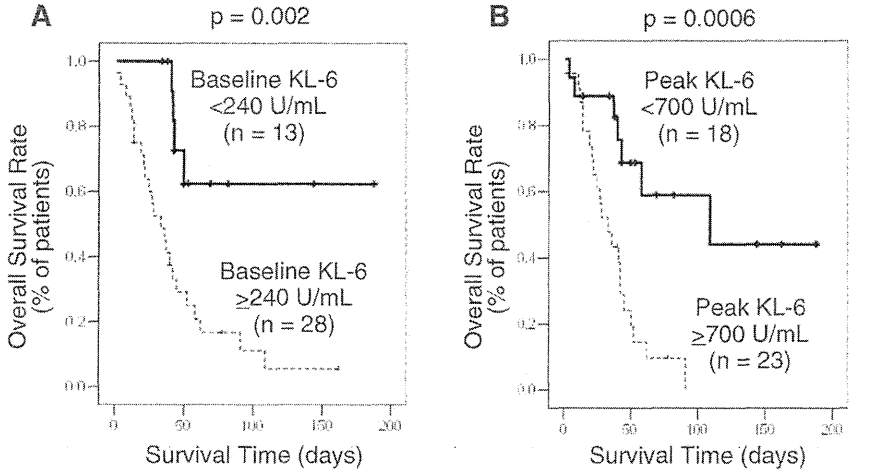

Figure 5 Kaplan-Meier analysis. The graph shows overall survival in patients with diffuse alveolar hemorrhage syndrome in relation to their (**A**) baseline and (**B**) peak serum KL-6 levels.

in Figure 1, 2 and 3, the range of both baseline and peak serum KL-6 levels are wide, indicating the individual variation. This variation might be attributed to the delay of first admission after the onset of DAH. Although both baseline and peak serum KL-6 levels were prognostic markers for poor outcome in the survival analysis, peak serum KL-6 levels had a stronger predictive value, suggesting that the advanced alveolar epithelial damage is likely the most important factor for death in DAH.

Mechanical ventilation itself may potentially cause acute alveolar damage and a resultant DAH. Previous studies have demonstrated that plasma level of KL-6 was increased with injurious ventilator settings, and may serve as a biomarker of ventilator-associated lung injury (VALI) [19]. All patients intubated in our study were treated with lung-protective ventilatory modalities to avoid VALI as much as possible, and no significant differences were observed in the use and modes of mechanical ventilation (Table 1). As a result, no significant difference was observed in serum KL-6 levels according to the use of mechanical ventilation (Figure 2).

Table 2 Cox's proportional analysis of the overall survival

Variable	Unfavorable/Favorable	β	HR (95%CI)	p-value*
Univariate analysis				
Age(yrs)	<70/ ≥70	0.34	1.40 (0.66-2.97)	0.38
Sex	female/ male	0.18	1.99 (0.56-2.58)	0.64
Smoking status	never/ smoker	0.43	1.54 (0.67-3.55)	0.31
Pulmonary involvement	bilateral/ unilateral	0.70	2.02 (0.68-6.02)	0.21
Baseline P/F ratio	<200/ ≥200	0.47	1.60 (0.74-3.45)	0.23
P/F ratio 48 hrs after admission	<200/ ≥200	0.95	2.58 (1.17-5.68)	0.018
PT-INR	≥2/ <2	0.10	1.11 (0.38-3.23)	0.85
APTT (sec)	≥30/ <30	0.28	1.33 (0.56-3.17)	0.52
Baseline KL-6 level (U/mL)	≥240/ <240	1.55	4.72 (1.63-13.7)	0.004
Maximum KL-6 level (U/mL)	≥700/ <700	1.49	4.43 (1.76-11.1)	0.002
Multivariate analysis *				
Baseline KL-6 level (U/mL)	≥240/ <240	0.99	2.70 (0.75-9.67)	0.13
Maximum KL-6 level (U/mL)	≥700/ <700	1.37	3.95 (1.14-13.7)	0.031

HR, hazard ratio; CI, confidence interval; GGA, ground glass attenuation; P/F, PaO_2/F_IO_2.
PT-INR, prothrombin time-international normalized ratio.
APTT, activated partial thromboplastin time.
* Adjusted for age, sex, smoking status, extent of pulmonary involvement and P/F ratio 48 hrs after admission.

A recent study has clarified that the epitope of KL-6 monoclonal antibody involved sulfate and sialic acid residues, which may be regulated by Gal6ST gene [20]. We have previously shown that the purified KL-6 molecule has chemotactic, proliferative and anti-apoptotic effects on fibroblasts *in vitro*, and that the proliferative and anti-apoptotic effects of KL-6 are additive to those of transforming growth factor-β [21,22].The increment of KL-6 in the alveolar space may be initially a resultant epiphenomenon of epithelial damage in DAH. Subsequently, however, through specific receptors, KL-6 may be able to accelerate epithelial damage and lead to fibrosis in DAH. Further *in vitro* studies are necessary to support the role of KL-6 in the development of DAH.

A potential limitation of our study is its retrospective design and the relatively limited number of patients enrolled. Because of the lack of separate disease controls such as acute exacerbation of idiopathic pulmonary fibrosis in our study, the specificity of KL-6 as a prognostic marker in DAH has not been shown. KL-6 is likely to increase in various types of lung injury resulting in epithelial damage, and may not be unique for DAH. Because the concentrations of KL-6 in the blood and BAL fluid were not simultaneously evaluated in our study, the interaction of systemic and local changes in DAH could not be investigated. Another potential limitation is the selection bias of the patients. The enrolled patients presented heterogeneous etiologies resulting in DAH. In addition, the enrolled patients had severe DAH, because we exclusively studied patients who were referred to the ICU unit. Therefore, our result may not be valid for patients with the milder forms of DAH which are clinically more common.

In conclusion, peak serum KL-6 level ≥700 U/ml may become a clinically useful marker of poor prognosis for DAH. Further longitudinal studies with a larger number of patients are required to support our findings.

Ethical standards

The experiments in this study comply with the current laws of Japan and Germany.

Abbreviations

BAL: Bronchoalveolar lavage; CI: Confidence interval; DAH: Diffuse alveolar hemorrhage; ICU: Intensive care unit; P/F: PaO_2/F_iO_2; VALI: Ventilator-associated lung injury.

Competing interests

Kohno has a royalty income concerning the discovery and the clinical application of KL-6. However, he has no significant conflicts of interest on the theme discussed in this article. Other authors have no financial support. No significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Authors' contributions

YK carried out the patient collection, made the database, carried out the statistical analyses and drafted the manuscript. SO conceived of the study, carried out the statistical analyses and helped to draft the manuscript. KO, TT, TO, KU and TS carried out the patient treatment and collected the data. YI, NH, NH, NK and KT participated in the design of the study and coordination, and helped to draft the manuscript. FB, JG and UC participated in the design of the study, carried out the statistical analyses and helped to draft the manuscript. All authors read and approved the final manuscript.

Author details

[1]Department of Emergency and Critical Care Medicine, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. [2]Department of Pneumology/Allergy, Ruhrlandklinik, University Hospital, Essen, Germany. [3]Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan. [4]General and Experimental Pathology, Ruhr-University, Bochum, Germany.

Received: 28 August 2012 Accepted: 11 December 2012
Published: 17 December 2012

References

1. Collard HR, Schwarz MI: Diffuse alveolar hemorrhage. *Clin Chest Med* 2004, 25:583–592.
2. Schwarz MI, Mortenson RL, Colby TV, Waldron JA, Lynch DA, Hutt MP, Chemiack RM, King TE Jr: Pulmonary capillaritis. The association with progressive irreversible airflow limitation and hyperinflation. *Am Rev Respir Dis* 1993, 148:507–511.
3. Rabe C, Appenrodt B, Hoff C, Ewig S, Klehr HU, Sauerbruch T, Nickenig G, Tasci S: Severe respiratory failure due to diffuse alveolar hemorrhage: clinical characteristics and outcome of intensive care. *J Crit Care* 2010, 25:230–235.
4. Stahel RA, Gilks WR, Lehmann HP, Schenker T: Third International Workshop on lung tumor and differentiation antigens: overview of the results of the central data analysis. *Int J Cancer Suppl* 1994, 8:6–26.
5. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M: New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. *Chest* 1989, 96:68–73.
6. Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, Naka T, Hamada H, Abe M, Nishimura K, Higaki J, Ikezoe J, Kohno N: Circulating KL-6 levels in patients with drug induced pneumonitis. *Thorax* 2003, 58:872–875.
7. Ohshimo S, Bonella F, Grammann N, Starke K, Cui A, Bauer PC, Teschler H, Kohno N, Guzman J, Costabel U: Serum KL-6 as a novel disease marker in adolescent and adult cystic fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2009, 26:47–53.
8. Yokoyama A, Kohno N, Hamada H, Sakatani M, Ueda E, Kondo K, Hirasawa Y, Hiwada K: Circulating KL-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998, 158:1680–1684.
9. Yokoyama A, Kondo K, Nakajima M, Matsushima T, Takahashi T, Nishimura M, Bando M, Sugiyama Y, Totani Y, Ishizaki T, Ichiyasu H, Suga M, Hamada H, Kohno N: Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. *Respirology* 2006, 11:164–168.
10. Burkhardt O, Kohnlein T, Wrenger E, Lux A, Neumann KH, Welte T: Predicting outcome and survival in patients with Wegener's granulomatosis treated on the intensive care unit. *Scand J Rheumatol* 2007, 36:119–124.
11. Khan SA, Subia MR, Behl D, Specks U, Afessa B: Outcome of patients with small-vessel vasculitis admitted to a medical ICU. *Chest* 2007, 131:972–976.
12. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C: Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. *Am J Respir Crit Care Med* 1995, 151:157–163.
13. European Society of Pneumology Task Group: Technical recommendations and guidelines for bronchoalveolar lavage (BAL). *Eur Respir J* 1989, 2:561–585.
14. Hoguin T, Ramadan B, Gal AA, Roman J: Prognostic factors for hospital mortality and ICU admission in patients with ANCA-related pulmonary vasculitis. *Am J Med Sci* 2008, 336:321–326.
15. Afessa B, Tefferi A, Litzow MR, Peters SG: Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med* 2002, 166:1364–1368.
16. Specks U: Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol* 2001, 13:12–17.

17. Kohno N, Awaya Y, Oyama T, Yamakido M, Akiyama M, Inoue Y, Yokoyama A, Hamada H, Fujioka S, Hiwada K: **KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease.** *Am Rev Respir Dis* 1993, **148**:637–642.
18. Inoue Y, Barker E, Daniloff E, Kohno N, Hiwada K, Newman LS: **Pulmonary epithelial cell injury and alveolar-capillary permeability in berylliosis.** *Am J Respir Crit Care Med* 1997, **156**:109–115.
19. Determann RM, Royakkers AA, Haitsma JJ, Zhang H, Slutsky AS, Ranieri VM, Schultz MJ: **Plasma levels of surfactant protein D and KL-6 for evaluation of lung injury in critically ill mechanically ventilated patients.** *BMC Pulm Med* 2010, **10**:6.
20. Seko A, Ohkura T, Ideo H, Yamashita K: **Novel O-linked glycans containing 6/sulfo-Gal/GalNAc of MUC1 secreted from human breast cancer YMBS cells: possible carbohydrate epitopes of KL-6 (MUC1) monoclonal antibody.** *Glycobiology* 2011, **22**:181–195.
21. Ohshimo S, Yokoyama A, Hattori N, Ishikawa N, Hirasawa Y, Kohno N: **KL-6, a human MUC1 mucin, promotes proliferation and survival of lung fibroblasts.** *Biochem Biophys Res Commun* 2005, **338**:1845–1852.
22. Hirasawa Y, Kohno N, Yokoyama A, Inoue Y, Abe M, Hiwada K: **KL-6, a human MUC1 mucin, is chemotactic for human fibroblasts.** *Am J Respir Cell Mol Biol* 1997, **17**:501–507.

doi:10.1186/1750-1172-7-99
Cite this article as: Kida *et al.*: KL-6, a Human MUC1 Mucin, as a prognostic marker for diffuse alveolar hemorrhage syndrome. *Orphanet Journal of Rare Diseases* 2012 **7**:99.

RESPIRATORY INVESTIGATION 50 (2012) 88–97

Contents lists available at SciVerse ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Rapid decrease in forced vital capacity in patients with idiopathic pulmonary upper lobe fibrosis

Kentaro Watanabe[a,*], *Nobuhiko Nagata*[b,1], *Yasuhiko Kitasato*[c], *Kentaro Wakamatsu*[b], *Kazuki Nabeshima*[d], *Taishi Harada*[a], *Takako Hirota*[a], *Motokimi Shiraishi*[a], *Masaki Fujita*[a]

[a]*Department of Respiratory Medicine, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan*
[b]*Department of Respiratory Medicine, National Hospital Organization, Omuta National Hospital, Omuta 837-0911, Japan*
[c]*Department of Respiratory Medicine, National Hospital Organization, Fukuoka Higashi Medical Center, Koga 811-3195, Japan*
[d]*Department of Pathology, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan*

ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form
17 May 2012
Accepted 27 June 2012
Available online 1 August 2012

Keywords:
Idiopathic interstitial pneumonia (IIP)
Pulmonary upper lobe fibrosis
Idiopathic pleuroparenchymal fibroelastosis
Respiratory function
Forced vital capacity (FVC)

ABSTRACT

Background: We are occasionally presented with patients with unclassifiable interstitial pneumonia of unknown etiology. Idiopathic pulmonary upper lobe fibrosis (IPUF) does not fit any of the currently defined subsets of idiopathic interstitial pneumonias (IIPs). This study was performed to examine clinical, functional, and pathological characteristics of IPUF.

Methods: We present 9 cases of histologically confirmed IPUF. The clinical and histological characteristics of the 9 patients were evaluated. The baseline respiratory function of all patients was measured. There were 7 patients whose forced vital capacity (FVC) had been monitored for at least a year who were selected to quantify the yearly decline in FVC.

Results: All patients were slender, with a body mass index of 16.0–19.8 kg/m^2. Seven patients had a history of pneumothorax. Six patients died 1.8 to 5.7 years after the onset of the first symptoms. Fundamental histological features were intraalveolar collagen deposition and densely packed elastic fibers in the subpleural areas. These findings are the same as those seen in pleuroparenchymal fibroelastosis. However, the visceral pleura was thickened with dense collagen in only 2 patients, and pleural thickening was localized, if present, in the remaining 7 patients. Ventilatory impairment was also a characteristic. The time course decline of FVC was rapid and almost linear. The median yearly decline in FVC was −20.3% (range, −7.7% to −26.5%), which was more rapid than that reported for chronic fibrosing interstitial pneumonias such as idiopathic pulmonary fibrosis.

Conclusions: IPUF is a unique pulmonary fibrosis that results in rapid deterioration of ventilatory function and poor prognosis.

Abbreviations: BMI, body mass index; DLco, diffusing capacity of carbon monoxide; FVC, forced vital capacity; FRC, functional reserve capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; IPUF, idiopathic pulmonary upper lobe fibrosis; IPPFE, idiopathic pleuroparenchymal fibroelastosis; IPF, diopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; RV, residual volume; SP-A, surfactant protein A; SP-D, surfactant protein D; TLC, total lung capacity; UIP, usual interstitial pneumonia

*Corresponding author. Tel.: +81 92 801 1011; fax: +81 92 865 6220.
E-mail address: watanabe@fukuoka-u.ac.jp (K. Watanabe).
[1] Present address: Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Fukuoka 814-0180, Japan.

2212-5345/$ - see front matter © 2012 The Japanese Respiratory Society. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.resinv.2012.06.003

1. Introduction

We occasionally encounter patients with pulmonary fibrosis/interstitial pneumonia of unknown etiology that does not fit any of the currently defined subsets of idiopathic interstitial pneumonia (IIP) [1].

Although pulmonary upper lobe fibrosis of unknown etiology has been reported in the past, it is not recognized by current classification systems as a discrete class of IIP. The condition has been described by a variety of terms, including idiopathic progressive pulmonary fibrosis [2], pulmonary upper lobe fibrocystic changes [3], pulmonary apical fibrocystic disease [4], idiopathic progressive pleuropulmonary fibrosis [5], idiopathic pulmonary upper lobe fibrosis (IPUF) [6–11], marked pulmonary fibrosis in the upper lobe [12], marked pulmonary fibrosis in the upper lung field [13], (idiopathic) pleuroparenchymal fibroelastosis (IPPFE, PPFE) [14–17], and upper lobe-dominant pulmonary fibrosis [18]. The clinical and pathological characteristics of the cases reported by these authors include upper lobe-predominant pulmonary fibrosis with a chronic progressive course and no known cause for the fibrosis [2–18], a history of recurrent pneumothorax [6–10,12,13,15], and marked weight loss [2,5–13]. Although not all the patients described in previous reports had identical conditions, they had many pathological and clinical variables in common.

Of the reports mentioned above, those of Amitani et al. [6] and Frankel et al. [14] are key studies of the clinical and histological characteristics of pulmonary upper lobe fibrosis of unknown etiology. The patients in these 2 studies had similar clinical and histological characteristics, but there were some differences, which will be discussed in a subsequent section.

In this report, we adopt the term "idiopathic pulmonary upper lobe fibrosis" (IPUF), which was first used by Amitani et al. [6], and present 9 cases of IPUF with clinical and pathological characteristics and long-term follow-up data on respiratory function, which may be helpful for understanding the natural course of the disease.

2. Materials and methods

2.1. *Patient selection*

We reviewed the medical files of all patients admitted to the departments of respiratory medicine at Fukuoka University Hospital, Fukuoka University Chikushi Hospital, National Hospital Organization Omuta National Hospital, and National Hospital Organization Fukuoka Higashi Medical Center from 2000 to 2010, and selected records of patients who had undergone a surgical lung biopsy or an autopsy. After reviewing the pathological and clinical information on these patients, we identified 9 patients with IPUF.

2.2. *Clinical data*

Clinical data including age, sex, smoking status, history of pneumothorax, steroid treatment, and body mass index (BMI) were reviewed. The follow-up interval from the onset of symptoms or the first recognition of abnormal findings on a chest radiograph to the date of the last follow-up consultation was determined, and information on the prognosis of the patients was recorded. The results of analyses for levels of Krebs von den Lungen-6 (KL-6), surfactant protein A (SP-A), and surfactant protein D (SP-D) were also recorded.

2.3. *Imaging and histological findings*

Chest radiographs and conventional and high-resolution computed tomography (HRCT) images of the 9 patients were reviewed and compared with those of patients whose cases were previously reported in the literature. Pathological specimens were obtained from surgical lung biopsies (patients 1–4 and 6–9) and autopsies (patients 5 and 9). Slides stained with hematoxylin and eosin or with elastica van Gieson (EVG) were reviewed.

2.4. *Respiratory function parameters*

Forced vital capacity (FVC) was measured using spirometry with the patient in a seated position. Results are expressed as absolute values (mL) and as percentages of predicted values (% pred), which were calculated using the formulas of the Japanese Respiratory Society and adjusted according to sex, height, and age [19]. Total lung capacity (TLC), functional reserve capacity (FRC), and residual volume (RV) were measured using the helium gas dilution method, and the diffusing capacity of carbon monoxide (DLco) was measured using the single-breath-holding method [20]. Predicted values for each lung volume parameter were estimated using Grimby's formula [21], and predicted values for DLco were estimated using Burrows' formula [22].

2.5. *Baseline and follow-up data on respiratory function*

Baseline respiratory function was estimated from the first measurements conducted at our hospitals on patients 2–9. Baseline data for patient 1 were obtained from another hospital.

To estimate the annual change in respiratory function, we used data from patients whose respiratory function parameters had been monitored for at least a year. Annual changes in respiratory function were estimated using linear regression, assuming time dependency and linearity. The annual percentage decrease or increase in respiratory function relative to baseline (Δ) was estimated from the linear equation [23].

The institutional review board at Fukuoka University Hospital approved this retrospective study (#10–127).

3. Results

3.1. *Patient characteristics*

Enrolled patients consisted of 5 females and 4 males. Their age at the first visit to our hospital ranged from 43 to 81 years. Seven of the patients (patients 2–6, 8, and 9) had never smoked, and patients 1 and 7 had stopped smoking 3 and 7 years previously. Seven of the 9 patients had a history of pneumothorax, and 3 of the 7 patients with pneumothorax had a recurrent pneumothorax that had been treated by tube

Table 1 – Clinical characteristics and laboratory data.

Patients	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age at first visit	43	48	56	79	81	55	59	60	69
Gender	Female	Female	Female	Female	Female	Male	Male	Male	Male
Smoking status (pack-years)	Ex-smoker	Never-smoker	Never-smoker	Never-smoker	Never-smoker	Never-smoker	Ex-smoker (16)	Never-smoker	Never-smoker
History of pneumothorax	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Recurrence of penumothorax	Yes	Yes	No	No	No	Yes	No	No	No
Administration of steroids	Yes	No	No	No	Yes	Yes	Yes	Yes	No
Medical history other than penumomthorax					Herpes Zoster, goiter	Hemorrhagic colitis by *E. coli* O157	Lung transplantation[a]		
Comorbidities in the course of the disease		MAC[b]					Pneumo-mediastinum		
Body mass index (kg/m^2)	16.0	16.6	16.2	17.1	17.9	17.4	16.2	19.8	15.6
First symptoms	Dry cough	Exertional dyspnea	Dry cough	Exertinal dyspnea	Weight loss	Chest pain	Exertional dyspnea	Exertional dyspnea	Chest pain
Crackles	Audible	Not audible	Audible	Audible	Audible	Not audible	Not audible	Audible	Audible
KL-6 (U/mL)	550	412	460	909	1060	293	260	558	1117
SP-A (ng/mL)		35.5		72.3	56.3			54	
SP-D (ng/mL)		71.7		255	153	268	156	107	
Period from the first onset[c] to the last follow-up (years)	5.1	5.5	6.3	1.8	2.9	12.2	7.3	3.3	4.2
Period from the first symptom to the last follow-up (years)	5.1	5.5	1	1.8	2.9	5.7	5.4	3.3	4.2
Prognosis	Died	Alive	Alive	Died	Died	Died	Died	Alive	Died

KL-6, Krebs von den Lungen-6; SP-A, surfactant protein A; SP-D, surfactant protein D.

[a] Lung transplatation was performed after 3.5 years of the onset of the symptom.

[b] Pulmonary mycobacterium avium complex diesase.

[c] First onset means the time of the first recognition of abnormal findings on chest radiograph.

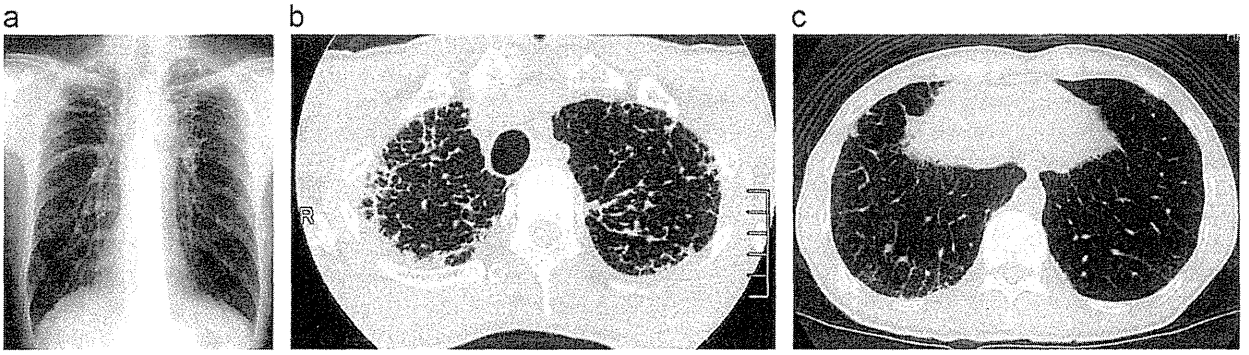

Fig. 1 – Chest radiograph and CT scan of patient 6. (a) Chest radiograph; (b) HRCT of the upper lung fields; (c) CT of the lower lung fields.

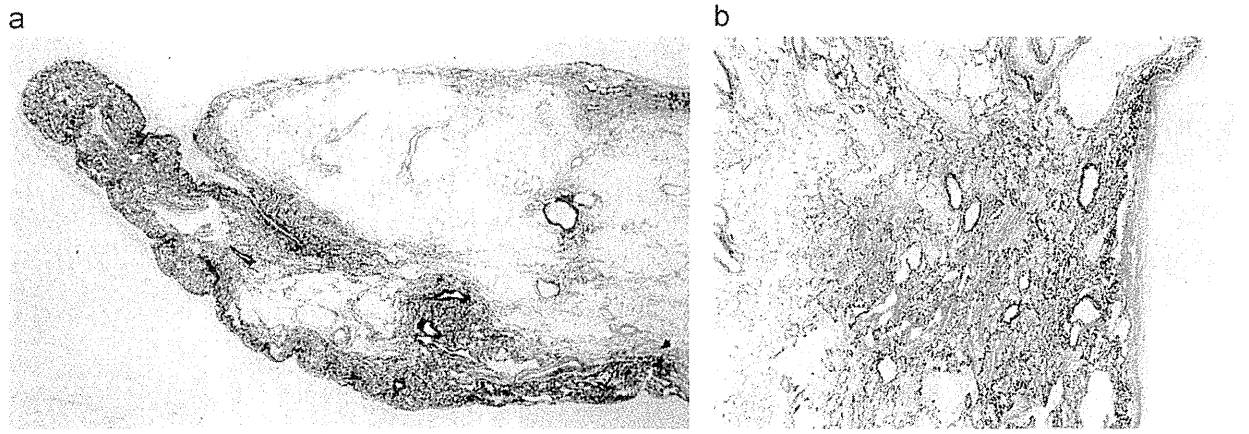

Fig. 2 – Biopsy specimens of patient 6. (a) Low-magnification view of a biopsy specimen (EVG). (b) Higher magnification view of the biopsy specimen (EVG).

thoracostomy. Steroids were administered to 5 patients, but without benefit. All patients were slender, with BMIs varying between 16.0 kg/m^2 and 19.8 kg/m^2. Six patients had audible crackles. The serum SP-D level (normal <110 ng/mL) was elevated in 4 of the 6 patients for whom data on this variable were available. The KL-6 level (normal <500 U/mL) at admission to our hospitals was elevated in patients 1, 4, 5, 8, and 9, and increased to above the normal range in patients 2 and 6 during the course of the disease (data not shown). The follow-up periods from the first recognition of abnormal findings on chest radiographs varied from 1.8 to 12.2 years. The follow-up periods from the first symptoms varied from 1.0 to 5.7 years. Six patients died within 1.8 to 5.7 years of the onset of the first symptom (Table 1).

3.2. *Imaging findings*

Fig. 1a shows a chest radiograph from patient 6. Bilateral apical pleural thickening and elevated hilar shadows were associated with a bilateral loss of volume of the upper lobes. A HRCT scan of the upper lobes of this patient (Fig. 1b) shows irregularly shaped nodular and reticular opacities with thickened subpleural parenchyma. This was associated with interlobular septal thickening. In contrast with the upper lobes, there were minimal changes in the lower lobes; scattered nodular opacities were evident (Fig. 1c). All patients had upper lobe-predominant lesions, and in patients 4 and 8, reticular or honeycomb opacities appeared in the bilateral basal areas during follow-up.

3.3. *Histological findings*

In patient 6, the marked band-like subpleural deposition of elastin extended along the visceral pleura, which was partially thickened, contained hyalinized collagen. The border between the band of elastic fibers and the less-involved lung parenchyma was sharply demarcated (Fig. 2a). At higher magnification, it was evident that the alveolar lumens were filled with mature collagen in the subpleural areas. At the border between normal lung and intra-alveolar fibrosis, there were alveoli filled with a proliferation of fibroblasts. Toward the pleural surface, collagen-filled alveoli were gradually replaced by densely packed elastic fibers resulting from the collapse of the alveoli (Fig. 2b). Isolated areas of fibrosis in which mature collagen filled the alveolar lumens were observed distant to the subpleural fibroelastosis. Inflammatory cell infiltration was minimal.

Histological findings for other patients were similar to those for patient 6. Subpleural intraalveolar collagen deposits with preserved alveolar structures and the condensation of

compressed alveoli with minimal deposition of collagen were dominant histological features. The fibrosis was dissimilar to usual interstitial pneumonia (UIP).

The pleura was remarkably thickened by dense collagen in patients 5 and 9 (Fig. 3). In the remaining patients, pleural thickening, if present, was not as remarkable (Fig. 4).

Imaging and microscopic findings of all 9 patients are summarized in Table 2. Intraalveolar collagen deposition and subpleural elastosis are core and common microscopic findings.

3.4. *Baseline values and yearly decline in respiratory function parameters*

The baseline levels of FVC (% pred) were low for all patients. The baseline levels of TLC, FRC, RV, and DLco varied among patients (Table 3), and may have been influenced by the time of their first visit. There was a marked decline in FVC (ΔFVC) in all patients over time that was almost linear (median, −20.3%; range, −7.7% to −26.5%) (Table 4 and Fig. 5). TLC, FRC, and DLco also declined sharply (Table 4).

In patients 1, 5, and 7, steroid treatment was started at 3, 1.44, and 1.92 years, respectively, after the onset of the first symptoms. In patient 8, steroid treatment had been started more than 1 year before the onset of the first symptom. Patient 6 received steroids after the last FVC measurement. Steroids did not appear to slow the decline in FVC.

4. Discussion

We present 9 patients with IPUF. By examining the biopsy or autopsy specimens obtained from the patients, we have identified the following common pathological findings: (1) densely packed elastic fibers, a result of the gathering of collapsed alveoli in the subpleural areas of the upper lobes (elastosis), associated with the deposition of mature collagen filling the alveolar lumens (intraalveolar fibrosis); (2) abrupt transitions from the subpleural fibrotic areas to less-involved pulmonary parenchyma; (3) isolated fibrotic areas in which mature collagen-filled alveolar lumens occasionally observed in lung parenchyma distant from the subpleural fibroelastosis; (4) minimal degrees of destruction of the lung architecture and inflammatory infiltration; and (5) occasionally thickened visceral pleura containing hyalinized collagen fibers.

IPUF has been described previously [2–18], and various terms have been adopted to describe pulmonary upper lobe fibrosis of unknown etiology. There are no standard criteria

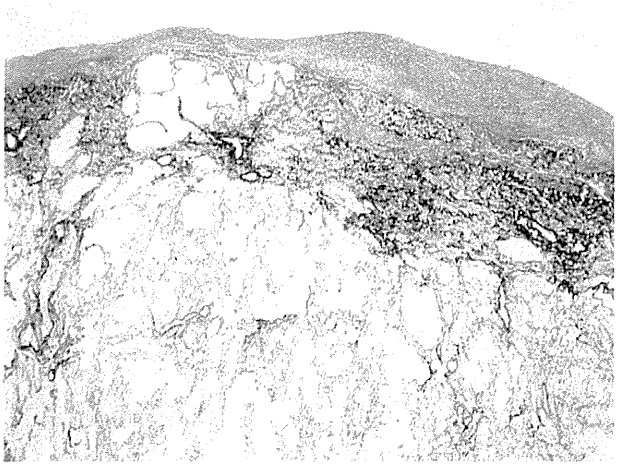

Fig. 3 – Low-magnification view of an autopsy specimen from patient 9. Pleural thickening with dense collagen is associated with subpleural elastosis and intraalveolar fibrosis (EVG).

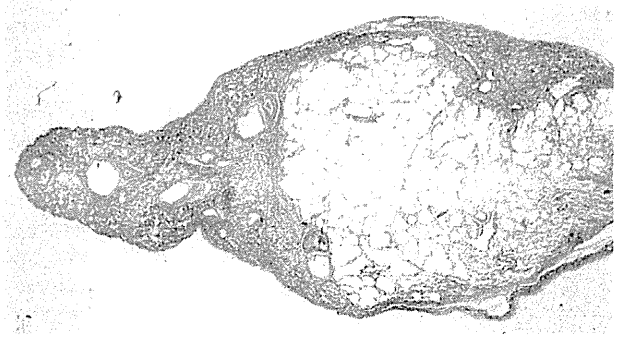

Fig. 4 – Low-magnification view of a biopsy specimen from patient 7. Subpleural elastosis is prominent without pleural thickening (EVG).

Table 2 – Summary of CT and microscopic findings of nine cases.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
CT findings									
Upper lobe involvement	+	+	+	+	+	+	+	+	+
Middle and/or lower lobe involvement at first visit	+	+	+	+	+	+	+	+	±
Middle and/or lower lobe involvement at the last follow-up	+	+	+	+	+	+	+	+	+
Honeycombing or reticular opacities in lower lobes	−	−	−	+	−	−	−	+	−
Microscopic findings									
Alveolar structures in upper lobes, preserved or destroyed	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved
Intra-alveolar collagen deposition	+	+	+	+	+	+	+	+	+
Subpleural elastosis	+	+	+	+	+	+	+	+	+
Pleural thickening with fibrosis	+	+	+	−	‡	+	−	−	‡

for its diagnosis and there is no consensus as to its entity as a disease. However, in Japan in 1992, Amitani et al. [6] reported 13 patients with IPUF, including 5 surgically biopsied or autopsied cases and presented their clinical and histological characteristics, i.e., (1) slender stature; (2) progressive bilateral subpleural fibrosis in the upper lobes with bullae but without honeycombing; (3) recurrent pneumothorax; (4) no extrathoracic lesions; (5) no acid-fast bacilli identified, and no effect of antituberculous drugs; (6) aspergillus infection may be superimposed; and (7) slowly progressive and fatal with 10–20 years of presentation. Since then, there have been many other Japanese case reports [7–13,18]. Although Amitani did not mention the pleural thickening that Frankel et al. [14] and Becker et al. [15] later described, upper lobe-dominant intraalveolar fibrosis and elastosis in the subpleural area are common and are fundamental histological findings in these papers.

Patients in Amitani's report appeared to survive longer than our patients. However, survival time is based on the time of initiation of follow up. In our patient 6, subtle abnormal shadows were first seen on a chest radiograph at an annual health check-up, and he died 12.2 years after the check-up. Thus, the subclinical stage of the disease might be longer, and the disease might progress rapidly only after the first symptoms appear.

The clinical characteristics of this disorder are also distinct from those of other IIPs. It seems to be unrelated to smoking status. In our study, 7 of the 9 patients had never smoked, and 2 were ex-smokers. Smoking status in the study of Frankel et al. [14] was similar to that of our group. All of our patients were slender. Patients mentioned in previous reports of similar cases [2,5–13] experienced weight loss. History of pneumothorax is another clinical characteristic of this condition. Seven of our 9 patients had a history of pneumothorax. Amitani et al. [6] reported that 7 of their 13 patients had histories of recurrent or bilateral pneumothorax. Other previous reports also mentioned patients with pneumothorax [2,7–10,12,13,15].

IPUF appears to start with upper lobe-dominant fibrosis. Initially, there is minimal involvement of the lower lobes, but the fibrosis extends to the lower lobes as the disease progresses. All of the patients in our study had lesions in both upper and lower lobes. Pure upper lobe fibrosis was found only in 1 patient (patient 9) at the start of the follow up. However, as the disease progressed, lower lobe lesions appeared. Subtle lower lobe lesions on chest CT that were not identified by chest radiograph were also found in patient 6 (Fig. 1). Although Amitani et al. [6] emphasize the importance of upper lobe-localized fibrosis, they do not entirely deny the existence of middle/lower lobe fibrosis. In their paper, they defined the lesions of middle/lower lobes as "almost normal." Moreover, CT images were not available for Amitani's research.

The main lesions are located in the subpleural pulmonary parenchyma, with or without involvement of the visceral pleura, and the remaining lung parenchyma appears almost normal. This progression and pathology is unique. However, the existence of bilateral basal reticular or honeycomb opacities (Patients 4 and 8) raises the possibility that this disorder could overlap with other idiopathic interstitial

Table 3 – Baseline values of respiratory function parameters.

Patients	#1	#2	#3	#4	#5	#6	#7	#8	#9
FVC (mL)	1680	2030	1400	1400	1830	3030	1160	2580	2530
FVC % pred	56	68	54	64	80	77	28	75	80
TLC (mL)	3560	3750	3160		3730	4360	1890		
TLC % pred	83	94	80		96	76	32		
FRC (mL)	2730	2550	2350		2700	2970	1180		
FRC % pred	120	105	91		99	90	35		
RV (mL)	2080	1560	1860		1900	1280	680		
RV % pred	139	116	121		107	68	34		
RV/TLC (%)	58	42	59		51	29	36		
DLco (mL/min/mmHg)	13.5	18.4	11.8		9.8	14.3	10.3		
DLco % pred	65	115	83		79	84	59		

FVC, forced vital capacity; TLC, total lung capacity; FRC, functional reserve capacity; RV, residual volume; DLco, diffusing capacity of carbon monoxide.

Table 4 – Change per year of respiratory function parameters.

Patients	#1	#2	#3	#4	#5	#6	#7	#8	#9
ΔFVC (mL)	−323	−284	[a]	[b]	−416	−650	−94	−494	−588
ΔFVC (%)	−20.3	−13.0			−22.9	−22.0	−7.7	−18.9	−26.5
ΔTLC (mL)	−862	−493			−1109	−821			
ΔTLC (%)	−24.2	−12.9			−30.3	−18.2			
ΔFRC (mL)	−692	−305			−863	−550			
ΔFRC (%)	−25.3	−11.7			−32.9	−17.7			
ΔRV (mL)	−723	−198			−707	+11			
ΔRV (%)	−34.8	−12.7			−40.4	+0.82			
ΔDLco (mL/min/mmHg)	−1.07	−2.60			−2.65	−3.90			
ΔDLco (%)	−8.0	−13.6			−26.8	−26.7			
Follow-up periods of FVC (years)	3.58	3.42	0.39	0	2.25	4.67	1.58	2.95	3.15

Δ, percent change per year from baseline; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional reserve capacity; RV, residual volume; DLco, diffusing capacity of carbon monoxide.

[a] In patient 3, FVC was measured two times with an interval of 0.39 years (1400 mL at baseline and 1220 mL at 2nd measurement), and

[b] FVC was measured only one time in patient 4.

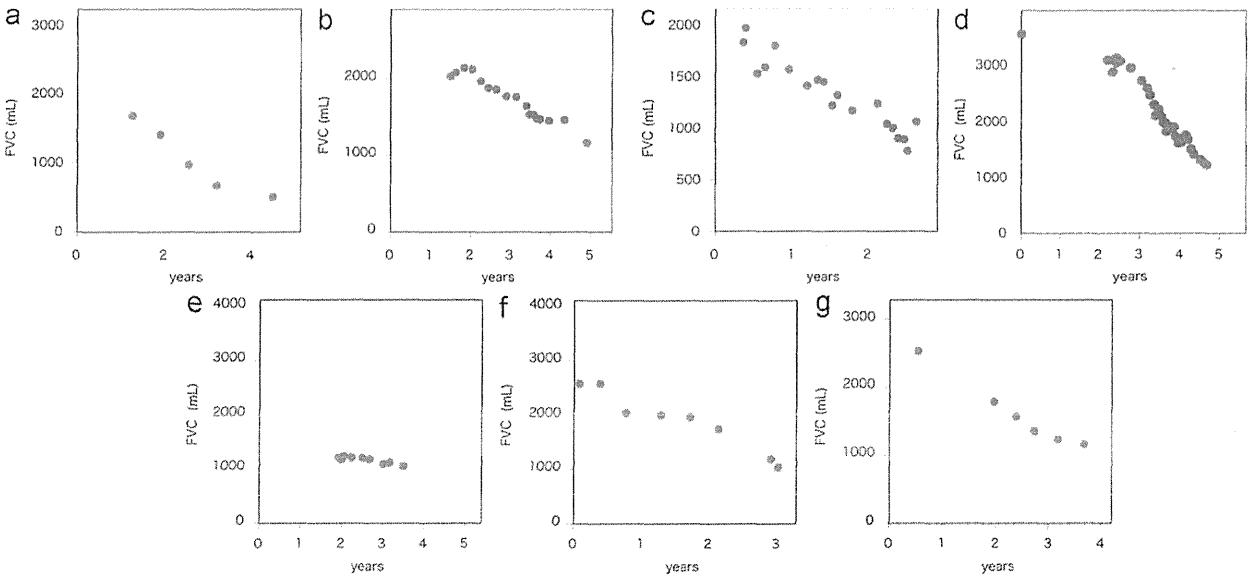

Fig. 5 – In each graph, the top of the vertical axis shows 100% of FVC as predicted for each patient at the first measurement, and the horizontal axis shows the time when the first symptom appeared (year 0, left) to the time of the last follow-up (right). Panels a, b, c, d, e, f, and g represent patients 1, 2, 5, 6, 7, 8, and 9, respectively. Declines in FVC (ΔFVC) with time were large and almost linear.

Table 5 – Summary of imaging and microscopic findings, and prognosis in previous papers and ours.

Authors [reference no.], year	Imaging findings		Microscopic findings				Prognosis dead/alive
	Lower lobe involvement	Honeycombing or reticular opacitites in the basal areas	Pleural thickening with fibrosis	Alveolar structures in the upper lobes, preserved or destroyed	Subpleural elastosis	Intra-alveolar collagen deposition	
Davies et al. [2], 1975	Yes	Yes (Case 1)	Yes	Preserved			2/5
Amitani et al. [6], 1992	Minimal	No	No	Preserved	Yes	Yes	5/8
Kobayashi et al. [7], 1999	Yes	Yes	Mild	Preserved	Yes	Yes	0/1
Shiota et al. [12], 1999	Yes	Yes	Mild	Preserved	Yes	Yes	3/4
Jingu et al. [13], 1999	1 Yes, 1 no		No	Preserved			0/2
Kobashi et al. [8], 2000	No	No	No	Preserved	Yes	Yes	1/0
Iwama et al. [9], 2000	Yes	No	Mild	Preserved	Yes	Yes	1/0
Frankel et al. [14], 2004	Absent or less marked		Yes	Preserved	Yes	Yes	2/3
Becker et al. [15], 2008		No	Yes	Preserved	Yes		1/1
Nei et al. [10], 2009	Yes	No	Yes	Preserved	Yes	Yes	1/0
Morimoto et al. [11], 2010	Minimal	No	No	Preserved	Yes	Yes	0/1
Kaneko et al. [18], 2010	Yes	No	Yes	Preserved	Yes	Yes	0/1
von den Thusen et al. [27], 2011	Yes		Yes	Preserved	Yes	Yes	2/2
Reddy et al. [17], 2012	Yes	Yes	11 Yes, 1 no	Preserved	Yes	Yes	5/6
Our study	Yes	Yes (Cases 4 and 8)	6 Yes, 3 no	Preserved	Yes	Yes	6/3

pneumonias such as IPF. Table 5 is a summary of imaging and microscopic findings for our patients and those from previously reported literature. Core pathologic findings (intra-alveolar fibrosis and subpleural elastosis) were noted in almost all reports, and were also found in our patients with IPF-like changes (patients 4 and 8). As we assert that these core pathologic findings are fundamental for a diagnosis of IPUF, patients who had pathologic IPUF and imaging features of UIP are categorized as those in 1 of the 3 subsets of IPUF that we tentatively propose (Table 6), although we did not confirm UIP lesions histologically in these 2 patients. Upper-lobe localized fibrosis might be an initial stage of idiopathic pulmonary upper lobe fibrosis, later deteriorating with multiple lobe involvement. We sometimes encounter a combination of UIP and NSIP when multiple lobes are biopsied. The 2 subsets of chronic pulmonary fibrosis of unknown etiology may coexist as UIP and NSIP. Reddy et al. [17] also mentioned a coexistent fibrosis in the lower lobes of PPFE patients.

What do the alveoli filled with mature collagen signify? These give the tissue the appearance of the obsolete condition of organizing pneumonia without resolution. It is probable that the foci of organizing pneumonia with incomplete resolution become chronically compressed in the subpleural area, causing elastosis. However, elastosis is not a specific feature of IPUF. It is also found in UIP as a gathering of compressed alveoli in the walls between honeycomb cysts. Organizing pneumonia without resolution in IPUF might be the initial lesion that progresses to subpleural fibroelastosis, as is the case with fibroblastic foci in UIP.

IPUF and IPPFE [14–17] may belong to the same disease spectrum, but there are some differences. Pleural fibrosis is not a dominant histological feature in IPUF. Among 9 reports from Japan, including ours [6–13,18], microscopic pleural fibrosis was documented by only 3 investigators [10,18], although "minimal" pleural fibrosis was noted in 3 reports [7,9,12]. In our series, pleural thickening with dense collagen was prominent in patients 5 and 9, present but localized in patients 1, 2, 3, and 6, was absent in patients 4, 7, and 8. Pleural thickening-like findings on CT were largely due to the subpleural parenchymal fibrosis. However, previous reports mention a spectrum of pleuroparenchymal fibroses, from cryptogenic pleural fibrosis [24,25] to pure cryptogenic pulmonary fibrosis. Reddy et al. [17] reported 12 cases of PPFE. Their report included patients with PPFE without pleural thickening of fibrosis, who were categorized as not "definite" but "consistent" with PPFE.

Another difference is comorbidities or complicating conditions. In the study of Frankel et al. [14], 2 patients had received anticancer chemotherapy and chemoradiotherapy for breast cancer, 1 patient had Charcot–Marie–Tooth disease, and the remaining 2 patients were twin sisters. Similarly, in the study of Becker et al. [15], 1 patient had received extensive chemotherapy and autologous stem cell transplant because of follicular center cell lymphoma, and the other patient had emphysema with severe obstructive ventilatory impairment that was inconsistent with pleuroparenchymal fibrotic disease. In the study of Piciucchi et al. [16], 1 patient had a suspected exposure to asbestos with calcified plaques on CT.

Upper-lobe fibrosis with pleural fibrosis occurs in clinical situations such as asbestos exposure, collagen vascular

Table 6 – Idiopathic pulmonary upper lobe fibrosis.

		CT findings			Microscopic findings		
		Upper lobe involvement	Middle and/or lower lobe involvement	Reticular or honeycomb opacities in lower lobes	Intra-alveolar fibrosis	Subpleural elastosis	Pleural thickening with fibrosis
Idiopathic pulmonary upper lobe fibrosis	Upper lobe-localized fibrosis	+	−	−	+	+	+ or −
	Upper lobe-predominant fibrosis	+	+	−	+	+	+ or −
	Upper lobe-predominant fibrosis associated with UIP-like lesions in lower lobes	+	+	+	+	+	+ or −

diseases, irradiation, exposure to drugs and anticancer chemotherapy, and as a complication after lung transplantation [26] or bone marrow transplantation [27]. Reddy et al. [17] emphasized recurrent infections, autoimmunity, and genetic predisposition in terms of the etiology of PPFE. The secondary form of this disorder should be differentiated from the idiopathic form.

Five of the 9 patients in our series had elevated levels of KL-6 at the initial measurement, and 2 of the remaining 4 patients developed elevated levels of KL-6 during the course of the disease. Three of the 4 patients had elevated levels of SP-D. These data suggest that alveolar epithelial cells are likely to be involved in the fibrotic process of the disease, as in fibrosing or cellular IIP [28].

The yearly decline in respiratory function in IPUF was remarkable, irrespective of the administration of steroids, and was more rapid than that observed for chronic fibrosing interstitial pneumonias such as UIP and fibrotic nonspecific interstitial pneumonia. The annual decline in FVC relative to baseline levels of the 7 patients in our study was greater than that in our previous report [22] and in other reports [29,30]. In our study, all respiratory function tests were performed after symptoms appeared. As mentioned above, as was seen in this study, it is possible that a subclinical stage without symptoms but with an abnormal chest radiograph occurs, but when our patients entered the symptomatic period of IPUF respiratory function deteriorated rapidly.

In conclusion, we have presented 9 cases of IPUF as a rare but distinct form of pulmonary fibrosis that has an upper lobe-dominant distribution. In IPUF, ventilatory function deteriorates rapidly and the prognosis is poor. Steroid treatment does not seem to change the course of this disease. The number of patients in our study was small. Larger-scale studies will be needed to support our findings and to establish a category for this disorder.

Conflict of interest

Authors have no potential conflict of interest.

Acknowledgments

This study was partly supported by a Grant to the Diffuse Lung Diseases Research Group from the Ministry of Health, Labor and Welfare, Japan.

REFERENCES

[1] Travis WD, King TE, Batemas ED, et al. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002;165:277–304.
[2] Davies D, Crowther JS, MacFariane A. Idiopathic progressive pulmonary fibrosis. Thorax 1975;30:316–25.
[3] Kentala E, Repo UK, Lehtipuu A-L, et al. HLA-antigen and pulmonary upper lobe fibrocystic changes with and without ankylosing spondylitis. a report of seven cases. Scand J Respir Dis 1978;59:8–12.
[4] Repo UK, Kentala E, Koistinen J. Pulmonary apical fibrocystic disease. A serology study. Eur J Respir Dis 1981;62:46–51.
[5] Fraisse P, Vandevenne FA, Ducolone A, et al. Idiopathic progressive pleuropulmonary fibrosis. Apropos of 2 cases. Rev Pneumol Clin 1984;40:139–43.
[6] Amitani R, Niimi A, Kuze F. Idiopathic pulmonary upper lobe fibrosis. Kokyu 1992;11:693–9.
[7] Kobayshi Y, Sakurai M, Kushiya M, et al. Idiopathic pulmonary fibrosis of the upper lobe: a case report. Nihon Kokyuki Gakkai Zasshi 1999;37:812–16.
[8] Kobashi Y, Ohba H, Yoneyama H, et al. A case of so-called "idiopathic pulmonary upper lobe fibrosis" complicated by both mediastinal emphysema and bilateral pneumothorax at different rimes. Kokyu 2000;19:292–8.
[9] Iwama N, Maehira N, Takahashi S, et al. A case of idiopathic pulmonary upper lobe fibrosis. Shindan Byori 2000;17:249–51.
[10] Nei T, Kawamoto M, Satoh E, et al. A case of suspected idiopathic pulmonary upper lobe fibrosis (Amitani disease) with acute exacerbation. Nihon Kokyuki Gakkai Zasshi 2009;47:116–21.
[11] Morimoto A, Mochizuki Y, Nakahara Y, et al. A case of idiopathic pulmonary upper lobe fibrosis. Nihon Kokyuki Gakkai Zasshi 2010;48:944–8.
[12] Shiota S, Shimizu K, Suzuki M, et al. Seven cases of marked pulmonary fibrosis in the upper lobe. Nihon Kokyuki Gakkai Zasshi 1999;37:87–96.

[13] Jingu K, Kawana A, Furihata K, et al. Two cases of marked pulmonary fibrosis in the upper lung field. Kokyu 1999;18: 318–23.
[14] Frankel SK, Cool CD, Lynch DA, et al. Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. Chest 2004;126:2007–13.
[15] Becker CD, Gil J, Padilla ML. Idiopathic pleuroparenchymal fibroelastosis: an unrecognized or misdiagnosed entity?. Mod Pathol 2008;21:784–7.
[16] Piciucchi S, Tomassetti S, Casoni G, et al. High resolution CT and histological findings in idiopathic pleuroparenchymal fibroelastosis: features and differential diagnosis. Respir Res 2011;23:111–15.
[17] Reddy TL, Tominaga M, Hansell DM, et al. Pleuroparenchymal fibroelastosis: a spectrum of histological and imaging phenotypes. Eur Respir J 2012;40:377–85.
[18] Kaneko Y, Kikuchi N, Ishii Y, et al. Upper lobe-dominant pulmonary fibrosis showing deposits of hard metal component in the fibrotic lesions. Intern Med 2010;49:2143–5.
[19] Japanese Respiratory Society guidelines for respiratory function tests. Medical Review Publishers: Tokyo; 2004. p. 20.
[20] Foster RE, Fowler WS, Bates DV, et al. The absorption of carbon monoxide by the lungs during breath holding. J Clin Invest 1954;33:1135–45.
[21] Comroe JH, Foster RE, Dubois AB, et al. The lung: clinical physiology and pulmonary function tests. 2nd ed. Chicago: Year Book Medical Publishers; 1973. p. 7–26.
[22] Burrows B, Kasik JE, Niden AH, et al. Clinical usefulness of the single-breath pulmonary diffusing capacity test. Am Rev Respir Dis 1961;84:789–806.
[23] Akagi T, Matsumoto T, Harada T, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. Respir Med 2009;103:1209–15.
[24] Buchanan DR, Johnston IDA, Kerr IH, et al. Cryptogenic bilateral fibrosing pleuritis. Br J Dis Chest 1988;82:186–93.
[25] Hayes JP, Wiggins J, Ward K, et al. Familial cryptogenic fibrosing pleuritis with Fanconi's syndrome (renal tubular acidosis): a new syndrome. Chest 1995;107:576–8.
[26] Konen E, Weisbrod GL, Pakhale S, et al. Fibrosis of the upper lobes: a newly identified late-onset complication after lung transplantation?. Am J Roentgenol 2003;181:1539–43.
[27] von der Thusen JH, Hansell DM, Tominaga M, et al. Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation. Mod Pathol 2011;24:1633–9.
[28] Kohno N, Kyoizumi S, Awaya Y, et al. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Chest 1989;96:68–73.
[29] Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:830–5.
[30] Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in idiopathic pulmonary fibrosis versus combined pulmonary fibrosis and emphysema. Eur Respir J 2011;38:176–83.

Oral Science International 9 (2012) 49–54

Contents lists available at SciVerse ScienceDirect

Oral Science International

journal homepage: www.elsevier.com/locate/osi

Original Article

Treatment outcome of the two-part semi-rigid oral appliance in obstructive sleep apnea

George Umemoto[a,*], Chikara Yoshimura[b,c], Naoko Aoyagi[a], Hideo Toyoshima[b,d], Takemasa Matsumoto[b], Kentaro Watanabe[b], Hideaki Maki[a], Toshihiro Kikuta[a]

[a] Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[b] Department of Respiratory Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[c] Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
[d] Center for Sleep Disorders at Fukuoka, Fukuoka Urasoe Clinic, 9F, BCC Bldg., 2-12-19 Ropponmatsu, Chuo-ku, Fukuoka 810-0044, Japan

ARTICLE INFO

Article history:
Received 8 November 2010
Received in revised form 1 March 2011
Accepted 7 March 2011

Keywords:
Obstructive sleep apnea
Cephalometry
Two-part semi-rigid oral appliance

ABSTRACT

Aim: The aim of this study was to assess the effectiveness of the two-part semi-rigid oral appliance, Silensor® (Erkodent, Tuttlingen, Germany) which prevents the mandible from retracting during mouth opening.

Materials and methods: Ten patients with mild or moderate obstructive sleep apnea (2 males and 8 females; mean age = 62.5 ± 10.0 years) were recruited and lateral cephalometric radiographs were taken. The patients underwent polysomnography before and after 3 months of receiving treatment with the Silensor®. The relationship between the improvement in the polysomnographic variables after the therapy and the cephalometric features was analyzed.

Results: A significant difference was observed in the apnea–hypopnea index after 3 months of Silensor® therapy (1st (baseline), 17.1 ± 5.5; 2nd (therapy of Silensor®), 11.0 ± 7.2, $p = 0.011$). Furthermore there was a significant positive correlation between the improvement in the degree of slow wave sleep (%) and the mandibular plane angle ($R = 0.662$, $p = 0.037$), as well as between the improvement in degree of slow wave sleep (%) and the lower face height ($R = 0.845$, $p = 0.002$). A significant negative correlation was observed between the improvement in degree of sleep efficiency (%) and the soft palate area ($R = -0.809$, $p = 0.005$).

Conclusion: These results suggested that keeping the nasopharyngeal airway space during mouth opening improves apnea–hypopnea index of some patients with mild or moderate obstructive sleep apnea and quality of sleep in obstructive sleep apnea patients with a long lower face height and a small soft palate.

1. Introduction

Obstructive sleep apnea (OSA) is caused by narrowing of the pharyngeal space and a sleep-induced loss of muscle tone. Nasal continuous positive airway pressure (nCPAP) has become a standard treatment of OSA, while mandibular advancement splints (MASs) have been used for patients with mild to moderate OSA or those who were unable to tolerate nCPAP. By advancing the mandible and stretching the tongue, MASs enlarge the pharyngeal airway space. Most of the MASs take a monobloc form, but a rigid MAS puts a strain on the temporomandibular joints [1]. On the other hand, a two-part and semi-rigid oral appliance (OA) produced less discomfort and obtained an adequate result in compliance [2] in spite of an inferior effectiveness compared to a rigid MAS [3]. The characteristic of the two-part semi-rigid OA, Silensor® (Erkodent, Tuttlingen, Germany) is to advance the mandible during mouth opening and return the mandible near the occlusal position during mouth closing. Therefore, avoiding the mandible retracting during opening is thought to be the main treatment mechanism of Silensor®.

However, there were not precise criteria for the selection of an appliance design and information as to which patients may be expected to benefit from Silensor® was not available. Cephalometric features associated with a good airway response to protrusion are a reduced lower facial height, a low mandibular plane angle, and a high hyoid position [4–6], and the perpendicular distance from the hyoid bone to the mandibular plane is an important predictor of improvement in the apnea–hypopnea index (AHI) by MAS therapy [6,7]. The aims of the present study were to assess the effectiveness of Silensor®, analyzing the change in sleep quality before and after the therapy and the relationship between the improvement in the degree of the polysomnographic variables after the therapy and the

* Corresponding author. Tel.: +81 92 801 1011; fax: +81 92 801 1044.
E-mail address: george@minf.med.fukuoka-u.ac.jp (G. Umemoto).

1348-8643/$ – see front matter © 2012 Japanese Stomatological Society. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/S1348-8643(12)00028-6

cephalometric features, and to demonstrate which patients may be suitable for Silensor® therapy.

2. Patients and methods

2.1. Participants

Thirty-four patients were diagnosed as having mild or moderate OSA (AHI, 5–30/h) which was not susceptible to nCPAP treatment by pulmonologists after polysomnography (PSG) at the Department of Respiratory Medicine, Faculty of Medicine, Fukuoka University, between July 2007 and March 2010. They were referred to our department for the purpose of receiving treatment with OA and edentulous patients or those with severe periodontic or temporomandibular joint disease were excluded. Ten participants (2 males and 8 females; mean age = 62.9 ± 10.0 years; age range, 38–76 years) of the thirty-four patients wore Silensor® for 3 months and underwent second follow-up PSG (Table 1). The participants had a mean body mass index (BMI) of 23.8 ± 3.9 kg/m^2 and a mean body weight of 58.0 ± 6.9 kg. Two patients had type 2 diabetes mellitus and five patients showed cardiovascular diseases. All of the participants started the Silensor® therapy with no nCPAP therapy. Informed consent was obtained from all participants.

2.2. Facial morphology by cephalogram analysis

Lateral cephalometric radiographs were taken with the teeth in occlusion and following a standardized procedure. The maxillary plane horizontal (S, center of Sella turcica to N, most anterior point of frontonasal suture), mandibular plane (Go, the left end of lower jaw border line to Me, the right end), point 'A' which is the anterior point of the maxillary apical base, and point 'B' which is the mandibular apical base and anterior nasal spine (ANS) were identified. The mandibular plane angle, which is formed from the intersection of the mandibular plane and the Frankfurt plane (Po, the highest point of the external acoustic meatus to Or, the most inferior point of the infraorbital rim), position of the maxilla (SNA angle), position of the mandible (SNB angle), lower face height (ANS-Me/N-Me ratio), hyoid to mandible plane (hyoid bone vertical position relative to mandible plane), tongue area (bounded by dorsum configuration of tongue surface and lines that connect tongue tip, retrognathion, hyoidale, and base of epiglottis) and soft palate area (starts and ends at posterior nasal spine through most inferior tip of soft palate) [8] were measured by cephalogram analysis (Fig. 1). A high mandibular plane angle, a low SNA angle, and a high lower face height were regarded as a steep mandibular plane and a posteriorly positioned maxilla, or a "long face" as it is commonly called. In addition to the variables, a low SNB angle which indicates a retractive mandible, a low hyoid position, a large tongue proportion, and a long thick palate were thought to be high risk factors for a decrease in oropharyngeal airway space or OSA [4].

2.3. The two-part semi-rigid OA, Silensor®

The two-part, semi-rigid OA, Silensor®, made of transparent hard polyethylene materials 2 mm thick, was used for the study (Fig. 2). Upper and lower elements were joined by plastic straps 23 mm or 24 mm long running from the upper canine to the lower molar regions. During mandibular closing, Silensor® was so adjusted that the mandible could return to the position, in which vertical dimension was increased by approximately 4 mm by the splint material from the occlusal position. This orientation of the connectors permitted only forward movement of the mandible during approximately 4–8 mm mouth opening, and avoided the reduction of the airway normally associated with mandibular opening. Participants were instructed on how to fit the Silensor® and

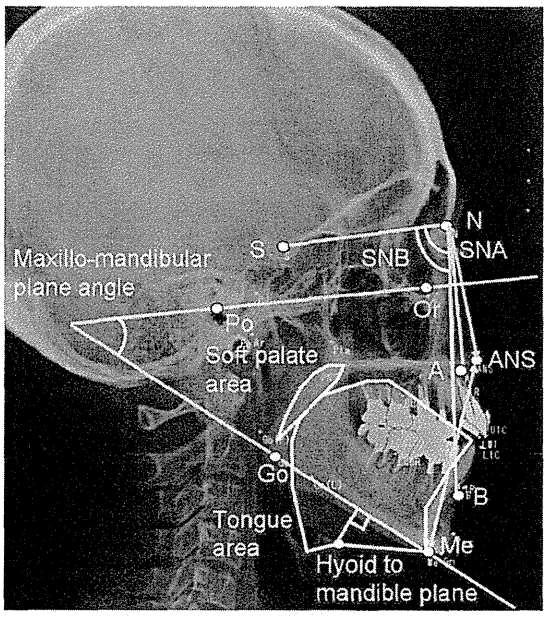

Fig. 1. Variables used for cephalometric analysis. The maxillary plane horizontal (S, center of Sella turcica to N, most anterior point of frontonasal suture), mandibular plane (Go, the left end of lower jaw border line to Me, the right end), point 'A' is the anterior point of the maxillary apical base, and point 'B' is the mandibular apical base and anterior nasal spine (ANS). The mandibular plane angle, is formed from the intersection of the mandibular plane and the Frankfurt plane (Po, the highest point of the external acoustic meatus to Or, the most inferior point of the infraorbital rim), position of the maxilla (SNA angle), position of the mandible (SNB angle).

it was worn nightly for 3 months. After 3 months of receiving treatment, they were asked about the existence of side effects and improvement of daytime sleepiness using the Epworth Sleepiness Scale (ESS) [9], sound sleep, and feelings on waking up.

2.4. Polysomnography

Standard overnight PSG included continuous monitoring using central electroencephalograms, electrooculograms, submental and anterior tibial electromyograms, and electrocardiograms with conventional leads. Airflow was monitored using oral and nasal thermistors, and respiratory effort was measured by respiratory inductance plethysmography with transducers placed around the chest and abdomen. Oxyhemoglobin saturation was recorded continuously using a pulse oximeter. All variables were recorded continuously using Rembrandt (Medcare, Amsterdam, The Netherlands). Apnea was defined as the cessation of airflow for at least 10 s, and hypopnea was defined as a 50% or greater reduction in airflow for at least 10 s with oxygen desaturation of more than 3%. All recordings were scored directly on the screen by a RPSGT (Registered Polysomnographic Technologist) and a certified physician of sleep medicine, Japanese Society of Sleep Research using the standard criteria of Rechtshaffen and Kales [10,11].

2.5. Change in sleep quality between before and after the Silensor® therapy

To assess the change in sleep quality by Silensor® therapy, two sets of polysomnographic variables were obtained before and after 3 months of receiving treatment with Silensor® and the results obtained from each time point were compared. Polysomnographic variables included the AHI, lowest SpO2, arousal index, snoring index, periodic leg movement (PLM) index, sleep efficiency (SE), sleep ratio (stages 1–4 and REM), and slow wave sleep percent

Table 1
Clinical features of the 10 obstructive sleep apnea participants.

	Sex	Age (years)	Body mass index (kg m^{-2})	Mandibular plane angle (deg.)	SNA (deg.)	SNB (deg.)	ANB (deg.)	Lower face height (%)	Hyoid to mandible plane (mm)	Tongue area (mm^2)	Soft palate area (mm^2)
Case 1	F	38	23.6	33.7	85.8	83.6	2.2	58.5	13.3	1754	168
Case 2	M	63	19.1	27.3	79.5	79.6	−0.1	56.9	7.0	2120	202
Case 3	F	60	22.1	45.6	80.1	77.8	2.3	58.6	10.5	1860	164
Case 4	M	62	22.4	34.2	78.9	80.2	−1.3	57.1	17.9	2180	216
Case 5	F	66	30.1	32.3	79.7	75.5	4.2	57.2	9.5	1974	173
Case 6	F	66	23.5	24.5	79.7	77.7	2.0	58.0	0	2109	153
Case 7	F	67	29.1	29.1	78.4	79.4	−1.0	53.6	15.5	1905	262
Case 8	F	76	26.5	28.3	78.7	77.5	1.2	56.0	17.4	1791	162
Case 9	F	58	23.9	24.4	83.1	81.5	1.6	57.4	5.7	2100	155
Case10	F	69	18.1	30.9	72.5	70.4	2.1	58.7	0	2137	172
Mean		62.5	23.8	31.0	79.6	78.3	1.3	57.2	9.7	1993	182.7
(SD)		(10.0)	(3.9)	(6.2)	(3.4)	(3.6)	(1.7)	(1.5)	(6.5)	(156.5)	(34.4)

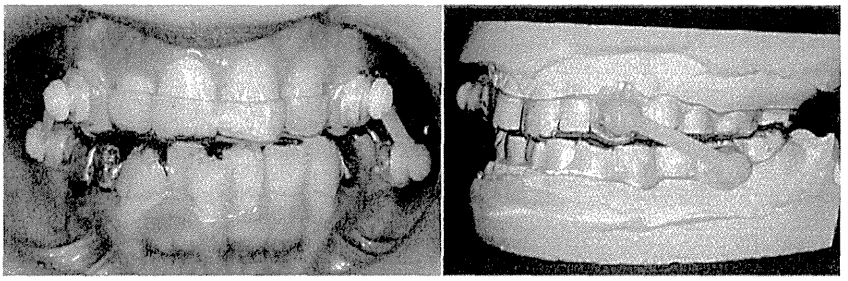

Fig. 2. The two-part, semi-rigid OA, Silensor®.

of total sleep time. The improvements in degree of AHI, arousal index, and snoring index were calculated by subtracting the second value obtained after Silensor® therapy from the first value and the improvements in degree of lowest SpO2, SE, and slow wave sleep (%) were calculated by subtracting the first value from the second value.

2.6. Data analysis

Paired *t*-tests were used to compare the two sets of polysomnographic variables.

Pearson correlation coefficient was used to measure linear relationships between the improvement in degree of polysomnographic variables and cephalometric variables.

Statistical data were analyzed using the Statistic Package for Social Science (IBM SPSS, Armonk, NY, USA) for Windows and $p < 0.05$ was considered significant.

3. Results

There was no significant difference between the body weight obtained before and after 3 months of receiving treatment with Silensor® [1st (baseline), 58.0 ± 6.9 kg; 2nd (therapy with Silensor®), 58.0 ± 7.0 kg, $p = 0.967$]. The body weight of the participants did not change more than 2 kg during the 3 months.

A significant difference was observed in the AHI obtained before and after the Silensor® therapy (17.1 ± 5.5 and 11.0 ± 7.2, respectively, $p = 0.011$) (Table 2). There were three (30%) complete responders (AHI with Silensor® < 5), six (60%) responders (AHI with Silensor® ≧ 5), and four (40%) non-responders (defined as improvement in AHI of <25%) (Fig. 3). However, there was no significant difference in the other polysomnographic variables obtained before and after the treatment.

A significant positive correlation was observed between the improvement in degree of slow wave sleep (%) and the mandibular plane angle ($R = 0.719$, $p = 0.019$), as well as between the improvement in degree of slow wave sleep (%), and the lower face height ($R = 0.845$, $p = 0.002$) (Fig. 4). Furthermore, a significant correlation was observed between the improvement in degree of sleep efficiency (%) and the lower face height ($R = 0.742$, $p = 0.014$), as well as between the improvement in degree of sleep efficiency (%) and the soft palate area ($R = -0.809$, $p = 0.005$) (Fig. 5). No significant correlation was observed between the other improvements in degree of other polysomnographic variables, including AHI, and the cephalometric variables (Table 3).

After 3 months of the Silensor® therapy, no participants reported discomfort with Silensor® or side effects with the Silensor® therapy, including temporomandibular pain or occlusion change in the morning. Five of the ten participants (50%) reported improvement in daytime sleepiness after the treatment and there was a significant difference in the ESS before and after the Silensor® therapy (6.3 ± 2.4 and 4.1 ± 1.7, respectively, $p = 0.013$). During the Silensor® therapy, seven participants (70%) felt as though they were

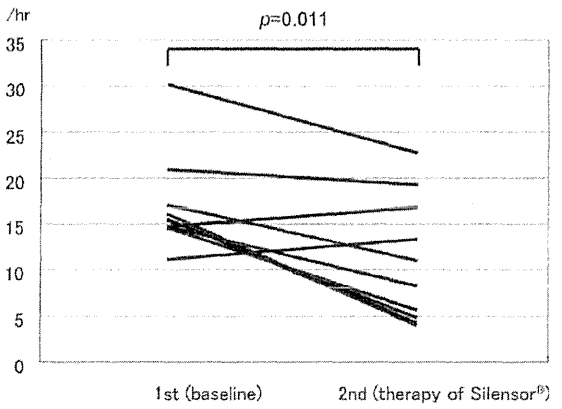

Fig. 3. Change in apnea–hypopnea index between the two points.