

SUNDAY, SEPTEMBER 2ND 2012

## 91. Diffuse parenchymal lung disease: clinical profiles and collagen vascular disease

### P700

#### Corticosteroid (CS) therapy does not influence immune reactivity in patients with non-specific interstitial pneumonia (NSIP)

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**Aim.** To assess the influence of CS therapy on immune reactivity in patients with NSIP.

**Patients and methods.** 27 patients (8 male 19 female, average age  $57.3 \pm 2.3$  yrs) with histologically proved NSIP were included. In 11 patients of group 1 the diagnosis was recently established and treatment was not yet started. 16 patients of group 2 received CS during 2-10 yrs. Blood level of IL-1 $\beta$ , IL-2, IL-8, TNF- $\alpha$  basal and after FGA stimulation was assessed by solid-phase immune-enzyme assay. CD20, CD4, CD8, CD3, CD16 in blood were detected by means of monoclonal antibodies.

**Results.** Basal IL-1, IL-2 and TNF were increased ( $171.0 \pm 55.5$  pg/ml,  $14.5 \pm 3.2$  pg/ml,  $101.3 \pm 43.3$  pg/ml, correspondingly) and basal level of IL-8 was normal ( $777.8 \pm 140.8$  pg/ml) in patients of group 1. In patients of group 2 basal IL-2 ( $16.3 \pm 2.7$  pg/ml) and TNF ( $86.4 \pm 40.6$  pg/ml) were increased and IL-1 ( $62.1 \pm 21.6$  pg/ml), IL-8 ( $590.4 \pm 127.0$  pg/ml) were normal. IL-1, IL-2, IL-8, TNF levels after stimulation were not increased in patients of both groups. There was no difference of CD20, CD4, CD8, CD3, CD16 cells quantity in patients of both groups.

**Conclusions.** Continuous treatment by low doses of corticosteroids does not influence immune reactivity in patients with NSIP.

### P701

#### Does emphysema influence the application of du Bois score in idiopathic pulmonary fibrosis?

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Idiopathic pulmonary fibrosis (IPF) is the most frequent interstitial pulmonary fibrosis. Development in CT scan technology improved accuracy in lung study. Emphysema can be associated to IPF, the most common form is the "Combined pulmonary fibrosis and emphysema" syndrome (CPFE).

The aim of this retrospective cohort study was to assess the impact of emphysema associated to IPF on functional parameters (Forced Vital Capacity FVC and Total Lung Capacity TLC) at baseline (t0) and on the loss of FVC after 6 months (t6) which is used in the du Bois prognostic score.

Data from 73 patients suffering from IPF were collected between 1982 and 2011 in an University Hospital with access to pharmacological studies and lung transplantation. Fifty six patients (M/F: 44/12; age: 65.5±10.8) were considered for analysis. Diagnosis of emphysema was based on CT scan criteria used by Schmidt et al [1].

IPF	With emphysema	Without emphysema	p
N	21	35	
Age t0 (years)	65.9±9.3	65.3±11.8	
Tobacco use	15 (71%)	24 (69%)	
History of respiratory hospitalization	5 (24%)	9 (26%)	
FVC t0 (% pv)	86.75±18.4	72.62±20.6	0.02
TLC t0 (% pv)	86.6±17.2	72.0±15.0	0.004
FVC t6-t0 (%)	-1.24±20.1	-0.04±11.4	NS
Du Bois score	14.6±14.0	18.0±13.9	NS

Emphysema seemed to influence significantly TLC and FVC at t0. Du Bois score was not statistically different between the two groups although they corresponded to different subclasses of 1-year mortality risk. According to the du Bois score, patients with emphysema were at lower risk of mortality than the others.

[1] Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. *Eur Respir J* 2011; 38: 176–183.

### P702

#### Telomerase expression in idiopathic pulmonary fibrosis (IPF) and non small cell lung cancer (NSCLC)

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**Rationale:** Telomeres protect chromosome ends since chromosomes lacking telomeres undergo fusion, rearrangement and translocation. Telomerase dysfunction has been linked with pathologic autoimmune responses and could play a role in both fibrogenesis and carcinogenesis. We aim to evaluate telomerase expression (mRNA levels of both subunits TERT and TERC) in Bronchoalveolar Lavage Fluid (BALF) and lung tissue of patients with NSCLC and IPF, since there are indications of common pathogenetic pathways in both diseases.

**Patients and methods:** We prospectively studied 44 BALF samples from NSCLC patients, 29 BALF samples from IPF patients and 13 BALF samples from control subjects. We also studied lung tissue samples from 32 IPF patients, 10 NSCLC patients and 21 control subjects. mRNA expression for both hTERT and hTERC was measured by Real-Time RT-PCR.

**Results:** (a) *Lung tissue:* IPF mRNA hTERT levels (0.24±0.14) were significantly lower compared to controls (0.46±0.30) (p=0.030). hTERC mRNA levels were higher in the control group (4.3±1.9) compared to NSCLC (2.87±1.51) and IPF (1.21±0.97), with strong grouped statistical significance (p=0.0001). (b) *BALF:* hTERT expression was higher in the control group (0.78±0.06) compared to IPF (0.39±0.14) and NSCLC (0.34±0.29) (p=0.005). hTERC expression was higher in the IPF group (1.09±0.39) compared to controls (0.54±0.40) and NSCLC (0.62±0.19), with no grouped statistical significance.

**Conclusion:** The attenuated expression of both telomerase subunits measured in NSCLC and IPF patients when compared to controls, suggests that telomerase genes may play a significant role in fibrogenesis and carcinogenesis, supporting the hypothesis of a common pathway.

### P703

#### Specific features of pulmonary mechanics and gas exchange in patients with histiocytosis X (HX)

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**Aim:** To assess the changes of pulmonary mechanics and gas exchange parameters, which are typical for histiocytosis X.

**Materials and methods:** 67 patients with HX have been examined, including 48 men (mean age 29.1±1.4 yrs) and 19 women (mean age 27.1±2.6 yrs). Spirometry, bodyplethysmography, compliance measurement, diffusion capacity (DLCO) and blood gases were carried out for all patients.

**Results:** For either men or women the mean values of the lung mechanics parameters didn't overstep the bounds of normal value, except for DLCO. Excluding 39 patients with normal value of indices, two groups of patients were identified. The first group of 20 patients shown signs of airflow limitation: decrease of the forced exhalation FEV1 (59.7±5.5%Pred), MEF25-75 (39.7±8.9%Pred) and reorganization normal TLC (98.8±4.5%Pred) by obstructive type (RV/TLC – 168.0±11.2%Pred). The second group contained 8 patients with restrictive respira-

tory pattern: reduction of TLC (70.4±2.5%Pred) and VC (71.9±4.0%Pred) without airflow limitation. Increase of pulmonary tissue retraction index (0.62±0.10 and 0.92±0.10 kPa/l) in both groups was an interesting find. DLCO has reduced in both groups (51.4±4.2 and 56.8±6.2%Pred), but the DLCO/VA (61.0±8.2 and 70.7±5.0%Pred) has been reduced in a greater degree in patients of the first group.

**Conclusions:** DLCO decrease is characteristic for HX patients. Changes of lung mechanics parameters are observed much rarer. When it is the case, the obstructive pattern dominates restrictive one. In contrast to COPD, the obstructive pattern in HX is combined with increase of pulmonary tissue elasticity.

### P704

#### The EDD (exercise, DLco, dyspnea) index in diffuse systemic sclerosis with pulmonary fibrosis

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**Introduction:** Pulmonary fibrosis secondary to systemic sclerosis (SSc) is the major cause of morbidity and mortality in these patients. The aim of this study was to determine the correlation of important lung function parameters with chest high resolution CT scan (HRCT).

**Methods and materials:** Thirty-two consecutive diffuse SSc patients (according to the criteria of american college of rheumatology) with pulmonary involvement were enrolled in this cross-sectional study. Patients with pulmonary fibrosis secondary to other reasons, previous restrictive lung disease, and history of smoking were excluded. Complete lung function evaluation was performed. Also the severity of dyspnea was evaluated by Modified Medical Research Council (MMRC) scale. EDD index was calculated based on 6MWT, DLco, and MMRC.

The EDD index in scleroderma lung fibrosis

	0	1	2	3
6MWT	≥350	250-349	150-249	<150
DLco	≥80%	60-79%	40-59%	<40%
MMRC	0-1	2	3	4

The chest HRCT was performed and the Warrick score recorded in all patients.

**Results:** The mean age of the patients was 39.18 years ±9.39 (SD). Seventeen (53%) of patients were in EDD stage 1 (score: 0≤score≤3), 9 patients (28%) in stage 2 (3<score≤6), and 6 patients (19%) in stage 3 (6<score≤9). The mean Warrick score was 10.84±6.94 (SD). There was statistically significant correlation between EDD index and Warrick score (p=0.001, r=0.72). Also there was statistically significant relation in EDD stages with Warrick scores (p=0.002).

**Conclusion:** The EDD as a useful lung function index is completely related to chest HRCT findings in SSc pulmonary fibrosis and can be used in clinical practice.

### P705

#### Increased exhaled nitric oxide precedes lung fibrosis in a murine model of systemic sclerosis

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**Background:** Exhaled nitric oxide (eNO) increased in patients with systemic sclerosis (SSc) and interstitial lung disease. Reactive oxygen species (ROS) and bleomycin induced skin and lung fibrosis in mice, mimicking the SSc in humans.

**Objectives:** This study aimed to validate eNO measurement method in mice and to study the evolution of lung inflammatory and fibrotic processes in mice injected with HOCl or bleomycin.

**Methods:** C57BL/6 mice were randomized into 3 groups receiving subcutaneous injections of HOCl, bleomycin, or PBS for 2, 4, or 6 weeks. Exhaled NO was measured at the end of each injection period and after 2 resting weeks without injection (8 weeks). Mice were then sacrificed to obtain skin and lung tissues for NO synthases (NOS) expression analysis.

**Results:** Increased exhaled NO, inducible NOS and 3-nitrotyrosine expression in bronchial epithelium, lung neutrophils and macrophages were observed at early phases (2 and 4 weeks) in HOCl- and bleomycin-treated mice. Inversely, lung vascular endothelial NOS expression decreased significantly at 6th and 8th week. Skin fibrosis was significantly increased from the 4th week and lung fibrosis from 6th week.

**Conclusions:** Exhaled NO can be used as a sensitive biomarker of lung inflammation in these murine models in which inflammation precedes fibrotic processes in skin and lungs. Mechanisms linking inflammation and fibrosis remain to be clarified.

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**P706**

**Elevated serum B cell activating factor belonging to the TNF family (BAFF) in interstitial lung diseases associated with collagen vascular disease**  
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**Background:** BAFF is a vital homeostatic cytokine for B cells. Increased serum levels of BAFF were found in a number of different autoimmune diseases and patients with polymyositis with interstitial lung disease (ILD) had higher BAFF levels than those without ILD. However, serum BAFF levels have not been reported in patients with ILD associated with collagen vascular disease (CVD-IP) and idiopathic interstitial pneumonia (IIP).

**Aim:** We investigated serum levels of BAFF in patients with CVD-IP and with IIP to determine whether they correlate with pulmonary function.

**Methods:** Twenty-seven patients with IIP (n=15) and CVD-IP (n=12), who visited our institution from 2008 to 2010 and underwent pulmonary function test, were enrolled. Underlying CVDs consisted of rheumatoid arthritis (n=4), dermatomyositis (n=2), systemic sclerosis (n=2), ANCA-associated systemic vasculitis (n=1), and mixed connective tissue disease (n=1). Twenty-three healthy volunteers were included as a control group. Serum BAFF levels were measured by ELISA.

**Results:** Serum BAFF levels were  $4.4 \pm 1.2$  ng/ml for CVD-IP,  $3.1 \pm 0.6$  ng/ml for IIP, and  $2.0 \pm 0.1$  ng/ml for the control. BAFF was significantly elevated in CVD-IP compared with control subjects. An inverse relationship between serum BAFF levels and DLco was noted in patients with CVD-IP.

**Conclusion:** We found elevated serum BAFF levels in CVD-IP patients and correlation with severity for ILD.

**P707**

**Grape seed proanthocyanidin extract (GSPE) attenuates bleomycin-induced pulmonary fibrosis in the mice**

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**Background:** Grape seed proanthocyanidin extract (GSPE) has more powerful antioxidative activity than other well-known antioxidants, including vitamin C and E. Idiopathic pulmonary fibrosis is a chronic progressive disorder with a poor prognosis. An oxidant-antioxidant imbalance may contribute to the disease process in idiopathic pulmonary fibrosis.

**Objectives:** To examine whether GSPE which is known to act as an antioxidant has therapeutic effect on bleomycin-induced pulmonary fibrosis in mice, an animal model of idiopathic pulmonary fibrosis.

**Methods:** Mice were treated by intratracheal instillation of bleomycin. GSPE was administered by intraperitoneal (IP) injections (30, 60, or 90 mg/kg). Mice were sacrificed on days 21 after bleomycin instillation.

**Results:** Compared with the BLM/Veh group, histologic findings in mice treated with BLM and IP injection of GSPE (BLM/GSPE) showed less fibrotic lesions in a dose-dependent manner. The mean Ashcroft's fibrosis score in the BLM/Veh group was significantly higher than in the BLM/GSPE group.

The lung hydroxyproline concentration on Day 21 was significantly higher in the BLM/Veh group than in the BLM/GSPE group ( $62.9$  vs  $55.3$ ,  $51.9$ ,  $50.4$  ug/ml).

**Conclusions:** GSPE attenuated bleomycin-induced pulmonary fibrosis in mice, suggesting that GSPE may be useful in the treatment of idiopathic pulmonary fibrosis.

**P708**

**Clinical impact of irradiated lung volumetric modeling in adjuvant breast radiotherapy (RT)**

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**Objectives:** To prospectively evaluate the lung dose-volume histogram (DVH) data in adjuvant breast RT; deduce the % irradiated volume (PIV) from 2-D parameters and analyze clinical impact with PFT & HRCT.

**Methods:** Patients (Pt) beginning breast RT between June '07 & March '10 were prospectively reviewed. Pts included were women with DCIS or Stage I-III carcinoma, who received RT using a 3D-CRT technique to the breast or chest wall (2-field RT [2FRT])  $\pm$  supraclavicular/postaxillary boost (4-field RT [4FRT]), to 50.4 Gy in 28 fr. Lung DVH parameters, 2D parameters are reported. Post RT all Pt underwent 3 monthly (mo) clinical/PFT & 6 monthly HRCT scan. Modelling equations to predict the PIV from 2D parameters was developed using linear regression analysis. Mann-Whitney U test was used to analyse PFT & HTCT

changes over time. Binary logistic regression used to evaluate relation between PIV and Radiation pneumonitis (RP).

**Results:** 44 Pt met the inclusion criteria: 6 had 2FRT & 38 had 4FRT. With a median follow-up of 14 months, 3 Pts reported mild respiratory symptoms at 1mo, which resolved completely at 3mo post-RT. A significant decrease of FVC, FEV1, MMEF<sub>25-75</sub> & DLCO was observed at 3mo, with partial recovery at 9 mo in the Pt treated with 4FRT, but there was no decrease of PFT in Pt treated with 2FRT. In HRCT at 6mo grade I opacity was present in 4 & 1 Pt(s) (PIV 15-19.9 and Mean lung dose 10.1-15) undergoing 4FRT & 2FRT.

**Conclusions:** Within the range evaluated in this study, the 3D parameters (PIV) better predicted an early decrease in pulmonary function, although HRCT detected RP was observed only when > 11% of the lung was irradiated in 4FRT. 4FRT is associated with significant reduction in PFT but not 2FRT.

**P709**

**Impact of diagnostic pitfalls on the management of pulmonary sarcoidosis**

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**Background:** Work-up in patients with sarcoidosis includes differentiation mainly with pulmonary TB, hypersensitivity pneumonitis and community-acquired pneumonia. Usually bronchoscopy is performed with lung biopsy and BAL, but often this option is not available, and thus diagnostic mistakes arise.

**Aim:** To evaluate frequency and possible impact of diagnostic pitfalls on management of sarcoidosis patients.

**Materials:** 127 patients with newly diagnosed sarcoidosis based on results of lung biopsy and BAL during bronchoscopy were enrolled into study. We analyzed primary diagnosis and treatment, duration of treatment, age, sex, usage of systemic steroids after the final diagnosis and mean dose of them in patients with correct (controls) and incorrect primary diagnose (study group).

**Results:** 23 patients (18,11%) had diagnostic pitfalls, from them 12 were treated from pulmonary TB in HRZE regimen around a year ( $46,57 \pm 3,32$  wks), 7 treated from pneumonia for  $3,11 \pm 1,13$  wks with further observation for  $20,33 \pm 5,52$  wks, and 4 pts were diagnosed as having an hypersensitivity pneumonitis with mean treatment with steroids for  $12,75 \pm 2,49$  wks. Groups were comparable for sex and age. In study group, 10/23 (43,5%) pts had relapse of disease versus 30/104 (28,8%) in controls ( $p < 0,05$ ), frequency of systemic steroids use was also higher (15/23 (65,2%) versus 59/104 (56,7%) in controls). The mean dose of prednisone in study group was significantly higher than in controls:  $21,7 \pm 0,9$  mg vs  $17,2 \pm 0,7$  mg ( $p < 0,05$ ).

**Conclusions:** Diagnostic pitfalls in work-up process among sarcoidosis patients are quite frequent, and lead to a more severe disease flow with higher frequency of systemic steroids usage and higher dose of them.

**P710**

**Pulmonary hypertension in different interstitial lung diseases**

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**Background:** Pulmonary Hypertension (PH) has been proposed a higher incidence in Interstitial Lung Diseases (ILDs). PH in different ILDs has different pathogenesis. PH in patients with ILDs is not well recognized and can occur in the absence of advanced pulmonary dysfunction or hypoxemia.

**Objective:** To investigate the incidence of pulmonary hypertension in different types of interstitial lung diseases.

**Methods:** Two hundred and five patients with ILD between 24 and 89 years old (mean age one hundred and four male, one hundred and one female) were evaluated, to discuss the incidence with different primary diseases, age and gender. ILD was diagnosed according to ATS/ERS classification standards in 2002, and according to ESC/ERS Guidelines in 2009, PH was diagnosed when SPAP of > 50mmHg was measured by UCG.

**Results:** Two hundred and five ILDs in Beijing Chao-Yang Hospital, ranging from January 1st 2010 to June 8th 2011, 27 were diagnosed as PH, so the incidence of PH in ILD is 13.2%. There was no significant difference of the incidence of PH in ILD between males and females ( $p = 0.901$ ).

There was a significant difference of the incidence of PH in ILD between age > 60ys and < 60ys ( $p = 0.017$ ). The incidence of PH has no statistically significant difference among different types of ILD ( $p = 0.455$ ).

**Conclusion:** The total incidence of PH in ILDs is 13.2%, the patients with age  $\geq 60$ ys have higher incidence of PH. Whether PH develops in ILD seems to have no relation with the ILD types.

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**P711****Profile of interstitial lung diseases in Pakistan, Karachi pulmonology clinics registry data, 2008 – 11**Mosavir Ansarie<sup>1,2</sup>, Asif Naseem<sup>3</sup>, Rashid Ahmed<sup>4</sup>, Azeemuddin Muhammad<sup>5</sup>.<sup>1</sup>Pulmonology, Liaquat National Postgraduate Medical Centre, Karachi,Pakistan; <sup>2</sup>Pulmonology, Health Care Hospital, Karachi, Pakistan;<sup>3</sup>Pulmonology, Kharadar General Hospital, Karachi, Pakistan; <sup>4</sup>Radiology, Advance Radiology Clinics, Karachi, Pakistan; <sup>5</sup>Radiology, Aga Khan University Hospital, Karachi, Pakistan

**Background & Objective:** No published data is available about the status of Interstitial Lung Diseases (ILD) in Pakistan. This study pioneers to determine the incidence and relative frequency of various ILDs in Karachi, its most populous multi-ethnic city.

**Methods:** We reviewed data from a registry catering to 3 pulmonology clinics in different areas of the city. Based on a detailed questionnaire it records age, gender, exposure history, clinical presentation, HRCT and PFT findings mandatorily and BAL/VATS data if available. It prospectively recorded diagnosed ILD cases between Jan 2008 and Dec 2011 and deaths occurring during follow-up.

**Results:** In a total of 5680 pulmonology referrals, the incidence of ILD was 2.3% (n=133) with a mean age of 55.1 years (+12.9 SD), mortality of 22.6% and median survival of 3 years. Idiopathic Pulmonary Fibrosis (IPF) (49.6%), Non Specific Interstitial Pneumonitis (NSIP) (19.5%) and Sarcoidosis (17.3%) were the most frequent ILDs followed by Collagen Vascular Disease Related (5.3%), Drug Induced ILD (4.5%) and Hypersensitivity Pneumonitis (3.8%). Reporting females (n=91) outnumbered males (n=42). The incidence of IPF/NSIP was greater in males (76%) while sarcoidosis and other ILDs occurred more in females (34%). Interestingly, out of 45 IPF diagnosed housewives living in congested areas, 42% had chronic avian exposure due to home breeding/pets.

**Conclusion:** The study establishes for the first time considerable presence of ILD in Pakistani population and describes its salient features. Hopefully this will improve disease awareness and help us expand this registry to other major cities for greater input towards research.

**P712****BAL protein profiles specific of different interstitial lung diseases**Elena Bargagli<sup>1</sup>, Claudia Landi<sup>2</sup>, David Bennett<sup>1</sup>, Pasquale Di Sipio<sup>1</sup>, Luca Bini<sup>2</sup>, Paola Rottoli<sup>1</sup>. <sup>1</sup>Respiratory Disease Sect., Dept. of Clinical Medicine and Immunological Science, University of Siena, Italy; <sup>2</sup>Functional Proteomic Lab., Dept. of Biotechnology, University of Siena, Italy

Interstitial lung diseases (ILD) are a heterogeneous group of lung disorders with different etiopathogenesis, clinical courses and prognosis. In the last ten years our group of research is focusing on the proteomic analysis of BAL in different interstitial lung diseases.

Aims of this proteomic study were to compare protein profiles of Sarcoidosis (S), Idiopathic Pulmonary Fibrosis (IPF), Langerhans cell Histiocytosis (PLCH), pulmonary fibrosis associated with Systemic sclerosis (SSc) patients in order to identify proteins of interest involved in specific pathogenetic networks or potential biomarkers with clinical value.

**Methods:** Population of patients was composed by 9 S, 7 IPF, 9 PLCH, 7 SSc. Proteomic analysis was performed by 2D-electrophoresis. Image analysis was done by Image Master Platinum 7.0 software. Protein identification was performed by mass spectrometry.

**Results:** Image analysis revealed distinct expression profiles for each ILD. Among the proteins differently expressed in our ILD samples there were Complement C3, complement factor B, complement factor I, antithrombin III, angiotensinogen, vitamin D binding protein, Leucin-rich alpha-2-glycoprotein, 14-3-3 protein epsilon, calyphosin, kininogen N-term, alpha-2-HS-glycoprotein.

**Conclusion:** The proteomic analysis of BAL confirmed the possibility to use 2D-electrophoresis to highlight different protein profiles among specific ILDs.

**P713****Idiopathic pulmonary fibrosis: Clinical, radiological and functional significance of biomarkers of proliferation**Edwin Roger Parra, Marcel Lekevicus Costardi, Vera Capelozzi. *Pathology, Faculdade de Medicina da Universidade de São Paulo, Brazil*

**Background:** Natural course of idiopathic pulmonary fibrosis (IPF) could be predicted by proliferative markers of the fibrotic process, such as myofibroblasts and interleukins (IL)-13 and IL14. Our primary aim was to determine whether these proliferative markers influence the course of IPF course measured by a radiological/functional score.

**Methods:** Twenty-eight patients with biopsy-proven IPF disease, who underwent pulmonary evaluation by high-resolution computed tomography (HRCT) fibrosis score and pulmonary function tests were studied. Five normal lung tissues (NLT) were included. Biomarkers in lung tissues were detected by immunohistochemistry and quantified by histomorphometry for myofibroblasts alpha-smooth muscle actin ( $\alpha$ -SMA), anti-interleukin (IL)-4 and IL-13.

**Results:** Myofibroblast amount, IL-4 and IL-13 expression were higher in IPF than in NLT ( $p<0.01$ ). Myofibroblast expression of  $\alpha$ -SMA was positively correlated to IL-14 and IL-13 expression. Lung tissue from patients with high HRCT fibrosis scores expressed significantly greater  $\alpha$ -SMA+, IL-4 and IL-13 when compared

with patients with low HRCT fibrosis scores ( $p<0.05$ ). Negative correlations were found between myofibroblasts  $\alpha$ -SMA+ and VC and DLCO.

**Conclusions:** Proliferative markers, detected by immunohistochemistry, in lung tissue allowed recognizing a dichotomous distribution of HRCT fibrosis course and influenced pulmonary function tests, suggesting that they may be promising markers of prognosis in these patients.

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**P714****Significance of protein S in patients with interstitial lung disease**Masahiro Naito<sup>1</sup>, Osamu Taguchi<sup>1</sup>, Kentaro Fujiwara<sup>1</sup>, Masahiro Onishi<sup>1</sup>, Takehiro Takagi<sup>1</sup>, Tetsu Kobayashi<sup>1</sup>, Hiroyasu Kobayashi<sup>1</sup>, Corina D'Alessandro-Gabazza<sup>2</sup>, Esteban Gabazza<sup>2</sup>. <sup>1</sup>Department of Respiratory Division, Mie University School of Medicine, Tsu, Japan; <sup>2</sup>Department of Immunology, Mie University Graduate School of Medicine, Tsu, Japan

**Background:** Protein S exerts anticoagulant activity by acting as a cofactor of activated protein C for the inactivation of coagulation factors Va and VIIIa. We have previously reported that protein S protects against lipopolysaccharide-induced acute lung injury by directly inhibiting the local expression of inflammatory cytokines without affecting coagulation (Takagi T, et al. 2009). However, the role of protein S in interstitial lung disease remains unclear.

**Objective:** The aim of this study is to evaluate the clinical significance of protein S in patients with interstitial lung disease.

**Methods:** This study comprised 106 patients with interstitial lung disease admitted in our institution between August 2008 and December 2011. There were 39 patients with interstitial pneumonia, 25 with sarcoidosis, 9 with collagen vascular disease-associated interstitial lung disease, 8 with organizing pneumonia, 7 with eosinophilic pneumonia, 5 with tumor-associated lung disease, 5 with inflammatory disease, 4 with hypersensitivity pneumonitis, 2 with IgG4 related multi-organ lymphoproliferative syndrome, 1 with alveolar proteinosis, and 1 patient with alveolar hemorrhage. Levels of protein S in BALF were measured using an enzyme-linked immunosorbent assay.

**Results:** Significant changes in the BALF levels of protein S were observed among the different types of interstitial lung diseases. The BALF level of protein S was significantly correlated with the number of macrophages, lymphocytes and with the BALF concentration of total protein and albumin.

**Conclusion:** These results suggest that protein S plays role in the pathogenesis of interstitial lung disease.

**P715****Combined pulmonary fibrosis and emphysema syndrome (CPFE)**Francisco Muñoz<sup>1</sup>, Inmaculada Herráez<sup>2</sup>, Elena Bollo<sup>1</sup>, Silvia Fernández<sup>1</sup>, Beatriz Cartón<sup>1</sup>, Emilio Santalla<sup>1</sup>, Florentino Díez<sup>1</sup>. <sup>1</sup>Respiratory Department, Complejo Asistencial Universitario de León, León, Spain; <sup>2</sup>Radiology Department, Complejo Asistencial Universitario de León, León, Spain

**Introduction:** CPFE is a clinic entity which consists in the coexistence of emphysema of the upper lobes and pulmonary fibrosis of the lower lobes.

**Method:** Retrospective descriptive study of cases diagnosed of CPFE between 2007 and 2012.

**Results:** 44 patients, all of them men, with an average age of 69 years. All were current or ex smokers. 50% had a UIP (usual interstitial pneumonia) pattern at the HRCT, 11.4% possible UIP pattern, and 38.6% inconsistent UIP pattern. All the patients had emphysema, above all paraseptal and centrilobular. PAH was present in 10 patients. The final diagnosis was: 18 IPF, 1 possible IPF, 1 NSIP, 3 possible NSIP, 6 fibrosis associated connective tissue diseases, 1 asbestosis, 1 hypersensitivity pneumonitis, 1 drug associated fibrosis, and 12 non classifiable interstitial pneumonias. During follow-up 8 patients died, 6 were diagnosed of lung cancer

Table 1. Results

	n	
Age	44	69±12 (43–88)
Men	44	100%
Current smokers	15	34.1%
Ex-smokers	29	65.9%
PAH	10	22.7%
PAPs	10	56.3±17.1 (36–90)
FVC (ml)	38	3514.2±940.9 (1600–5820)
FVC (%)	38	101.7±21.3 (47.3–152.5)
FEV1 (ml)	38	2517.6±733 (1340–4070)
FEV1 (%)	38	93.9±21.2 (50.3–127.5)
FEV1/FVC (%)	38	72.4±12.5 (45–97.8)
TLC (%)	20	89.2±23.1 (45.1–139.7)
RV (%)	20	84.3±38.2 (27.4–185)
DLCO (%)	34	50.8±22.8 (19.2–104.1)
DLCO/VA (%)	34	60.7±24.8 (25.4–123.7)

**Conclusions:** All of the patients from this study are men with smoking history. These patients have, lung volumes preserved with a severe impairment of gas exchange. The high prevalence of PAH and its important role in the prognosis justify echocardiography. As these patients might have a high prevalence of lung cancer, a close follow-up would be advisable.



## P716

**Nine cases of interstitial lung disease associated with anti-CADM140 antibody positive dermatomyositis**

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**Background:** Anti-CADM140 antibody (CADM) was found in some amyopathic dermatomyositis (DM) patients (pts) in 2005. It was reported that about 50% of CADM positive pts died from acute exacerbation (AE) of DM-related interstitial lung disease (DM-ILD) despite treatment. As compared with CADM negative pts (about 6%), the rate of AE of ILD is clearly high in CADM positive pts. [Objective] To elucidate the clinical characteristics of ILD associated with CADM positive DM.

**Methods:** Blood examination, arterial blood gas analysis, pulmonary function testing, bronchoalveolar lavage (BAL) analysis and pattern of chest CT were examined in 9 pts who were diagnosed with CADM positive DM in our hospital.

**Results:** Since the average value of WBC and CRP at the time of the first medical examination was 6629/ $\mu$ l and 0.56 mg/dl, we thought that inflammation was slight. The value of CK was in the normal range in 7 pts, slightly high (217 IU/l) in 1, and significantly high (26300 IU/l) in 1. The value of KL-6 was in the nearly cut-off range in 8 pts, and significantly high in 1 (3764). Alveolar-arterial oxygen difference was increased in 3 pts. In 4 pts in which BAL was performed, the lymphocyte differentiation was all high. Concerning chest CT image, patchy shadow or patchy shadow and trabecular shadow in outside layer of the lung field were seen in 7 pts, GGO around broncho-vascular bundle in 1, and no abnormal shadow in 1. All of the shade were slight. Although one pt died of AE, 8 pts survive as of February, 2012.

**Conclusion:** In DM-ILD, even if the CT image and data are slight, whenever the CT image is not typical NSIP pattern, we have to take the possibility of CADM into consideration.

## P717

**Chitotriosidase activity and CHIT1 gene polymorphism in sarcoidosis**

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**Introduction:** Among several biomarkers of sarcoidosis activity chitotriosidase (CTO) has been found to be useful. Some subjects have a 24-base pair duplication in the CTO gene (CHIT1) that results in the production of inactive enzyme which might interfere with the validity of the marker.

**Aims:** The study was conducted 1) to confirm previous observations of increased CTO activity in patients with sarcoidosis and 2) to evaluate influence of CHIT1 polymorphism on CTO activity.

**Methods:** The study comprises 47 patients with newly diagnosed active sarcoidosis (27 females, 20 males, average age 42.3 years). CTO activity was determined in serum and BAL using a standard fluorimetric method. CHIT1 genotyping was done by polymerase chain reaction (PCR).

**Results:** A normal CHIT1 genotype (NN) was present in 61.7% of the subjects, 34.0% were heterozygotes for detected allele (ND) and 4.3% were homozygotes (DD). The mean serum CTO value was 736 nmol/mL/h ( $\pm$  583) and was increased in 93.6% of patients. The mean BAL CTO value was 9.01 nmol/mL/h ( $\pm$  12.8). There was a correlation between serum and BAL CTO activities ( $r$  0.710,  $p$  < 0.001).

There was no significant difference between NN and ND subjects in serum CTO activity (855 $\pm$ 657 nmol/mL/h, 612 $\pm$ 348 nmol/mL/h,  $p$  0.331), but a significant difference in BAL CTO activity (12.24 $\pm$ 15.02 nmol/mL/h, 4.31 $\pm$ 5.07 nmol/mL/h,  $p$ =0.001). There was no CTO activity in mutation homozygotes.

**Conclusions:** The results confirm previous observations that the CTO activity is increased in patients with sarcoidosis. Unexpectedly, there was no significant difference in serum CTO activity between CHIT1 normal homozygotes and heterozygotes which warrants further study.

## P718

**Safety and tolerability of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF) receiving commonly used concomitant medications**

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**Introduction:** The CAPACITY Program (CAP) included two Phase 3 trials of

PFD in 779 patients with IPF. Analyses were conducted to assess the safety of PFD in patients receiving commonly used concomitant medications.

**Objective:** Examine the safety/tolerability of PFD in IPF patients receiving commonly used concomitant medications.

**Methods:** Pooled data from the CAP trials were analyzed. Commonly used concomitant medications were defined as those used by  $\geq$ 25% of patients in any treatment group between the first and last dose of study drug. The percentage of patients with selected treatment emergent adverse events (TEAEs) while on or within 28 d of cessation of commonly used concomitant medications was assessed. Patients in the PFD 2403 mg/d group were evaluated using a composite safety endpoint that included any Grade 3 or 4 TEAE, discontinuation of PFD, interruption/dose reduction of PFD, or any TE serious AE.

**Results:** Commonly used concomitant medications and vaccines included: acetylsalicylic acid, azithromycin, influenza vaccine, multivitamins, omeprazole, paracetamol, salbutamol, and simvastatin. No evidence of a clinical pattern of TEAEs was observed with the use of PFD and these commonly used medications or vaccines. Patients receiving these agents were no more likely to meet the composite safety endpoint than those not receiving a commonly used concomitant agent.

**Conclusions:** These data suggest that PFD is safe and generally well tolerated in patients with IPF when used with a spectrum of common medications. More long-term data will be collected in RECAP, an open-label extension trial evaluating PFD in patients with IPF.

## P719

**Systemic lupus erythematosus (SLE): Cyto- and chemokines as possible serum markers for pulmonary involvement?**

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SLE is a systemic autoimmune disease associated with high prevalence of lung involvement. Pulmonary manifestations (PM) in SLE are difficult to diagnose and the ability of its detection with serum markers could be useful for early detection and specific treatment.

Twenty three patients with SLE (age: 45.4 $\pm$ 14.6 years; 22 female, 10 smokers) were enrolled in pulmonary examination including physical examination, chest X-ray, lung function test, CO diffusion capacity (DLCO) measurement and blood gas analysis. Plasma of 17 patients was analyzed by protein array system with chemiluminescence imaging, including the cytokines and chemokines: 4-1BB, IP-10, IL-12 p70, IL-17, CCL14a, CCL21, CCL28, MCP-1, MCP-4, I-TAC.

PM was diagnosed in 12 patients (52.2%; age:41.3 $\pm$ 14.2 years), including pulmonary fibrosis (3), shrinking lung syndrome (1) and ventilatory disorder (8). Eleven patients had no PM (47.8%; age:50.0 $\pm$ 12.1 years). In patients with PM significant decrease of static lung volumes and DLCO were noted (TLC % pred: 81.1 $\pm$ 3.4 vs. 93.7 $\pm$ 3.9  $p$ <0.05; FEV1 % pred: 77.8 $\pm$ 5.7 vs. 94.2 $\pm$ 5.5  $p$ =0.05; DLCO (%): 62.4 $\pm$ 4.4 vs. 97.3 $\pm$ 7.3  $p$ <0.001). Microarray measurements confirmed significantly higher CCL21 level in SLE patients with PM, negatively correlating with FEV1 ( $r$ =0.65,  $p$ =0.04) and positively with resistance of the airways ( $r$ =0.73,  $p$ =0.02). The biomarkers MCP-1 and IP-10 were above the detection limit in all patients and higher levels were detected in SLE patients with PM.

In lupus patients PMs are prevalent and are associated with decreased lung volumes and DLCO. Microarray results identified CCL21 and MCP1, IP10 as potential candidates for further analysis of PM in SLE patients.