FIBROSING INTERSTITIAL LUNG DISEASES OF IDIOPATHIC AND EXOGENOUS ORIGIN. PHENOTYPE APPROACH.

Conference, Postgradual and Scientific Course

PRAGUE

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HOTEL ARTEMIS

U SLUNCOVÉ 14, PRAGUE 8

Pathogenesis of nonspecific idiopathic interstitial pneumonias.

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The initial description of NSIP referred to a *nonspecific* histological lesion in HIV-infected patients.

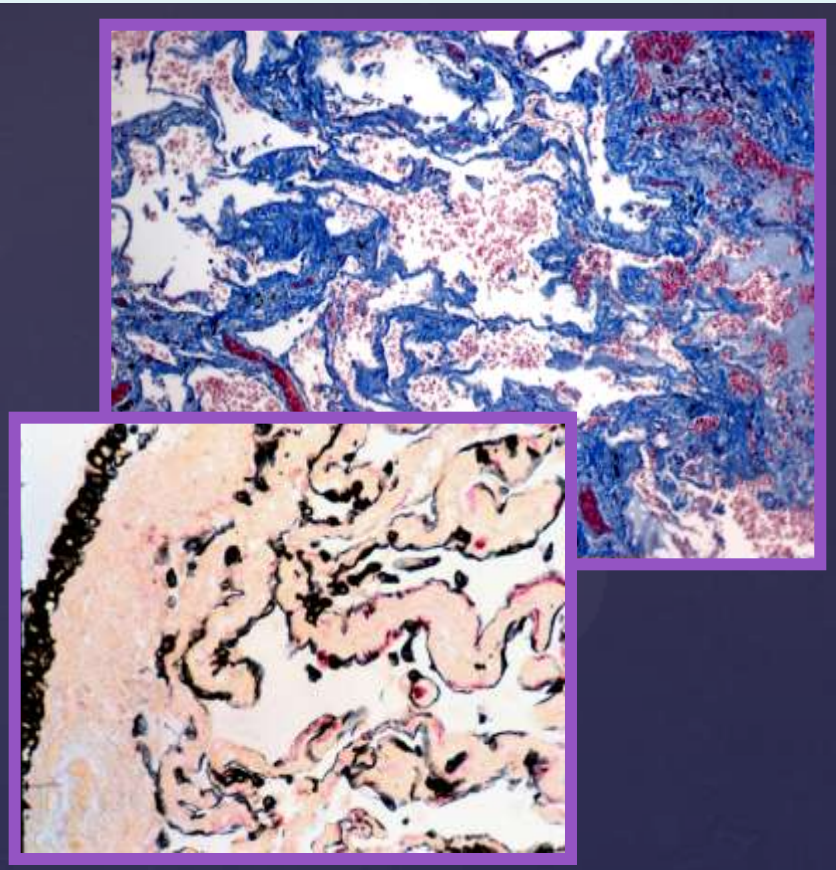
Suffredini AF, Annal Int Med 1987
Griffiths MH, Thorax 1995

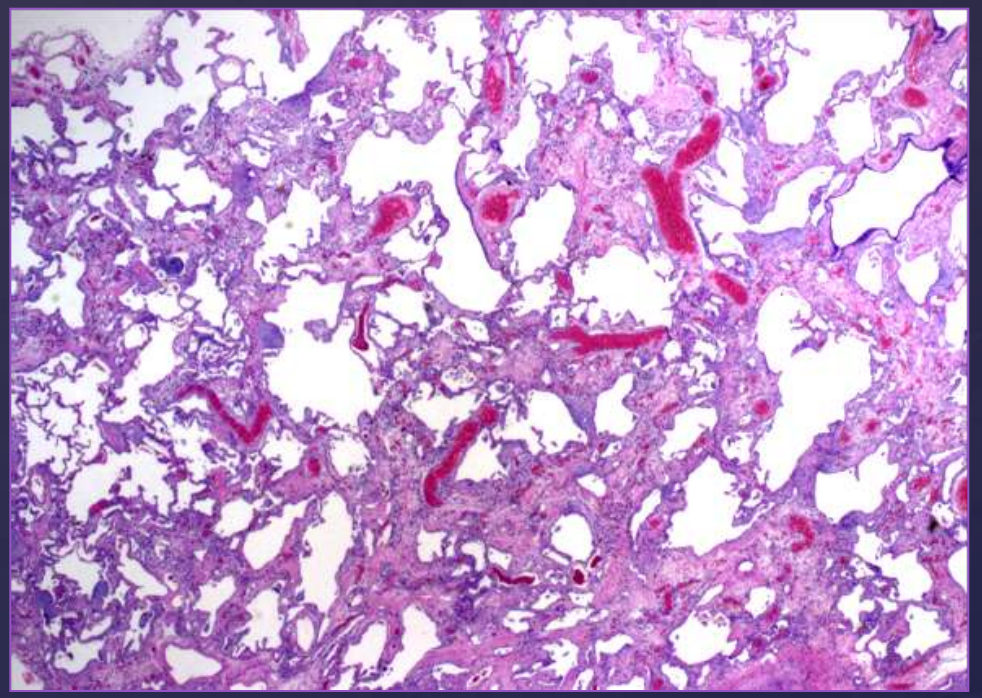
Subsequently Katzestein and Fiorelli described 95 cases of surgical lung biopsy previously diagnosed as *nonspecific interstitial pneumonia*.

A key feature being change of apparent similar age: *temporal homogeneity*.

Katzestein, Am J Sutg Pathol 1994

Nonspecific Interstitial Pneumonia NSIP

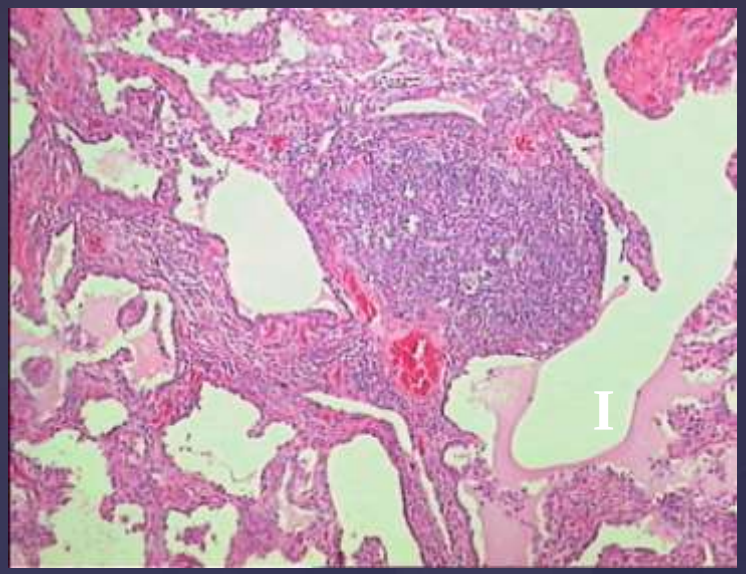




Temporal uniformity, diffuse inflammatory infiltration, thickening of interstiatial spaces, variable fibrosing process

Katzenstein and Fiorelli: Nonspecific interstitial pneumonia/fibrosis: histologic patterns and clinical significance. Am J Surg Pathol 1994; 18:136-147

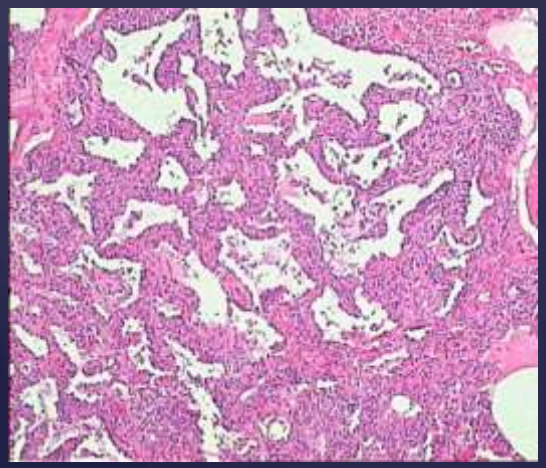
Key Histologic Features

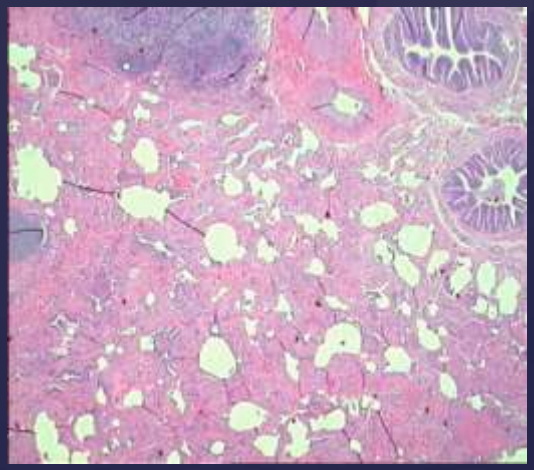


Cellular NSIP

Mild to moderate interstitial chronic inflammation

Type II pneumocyte hyperplasia in areas of inflammation





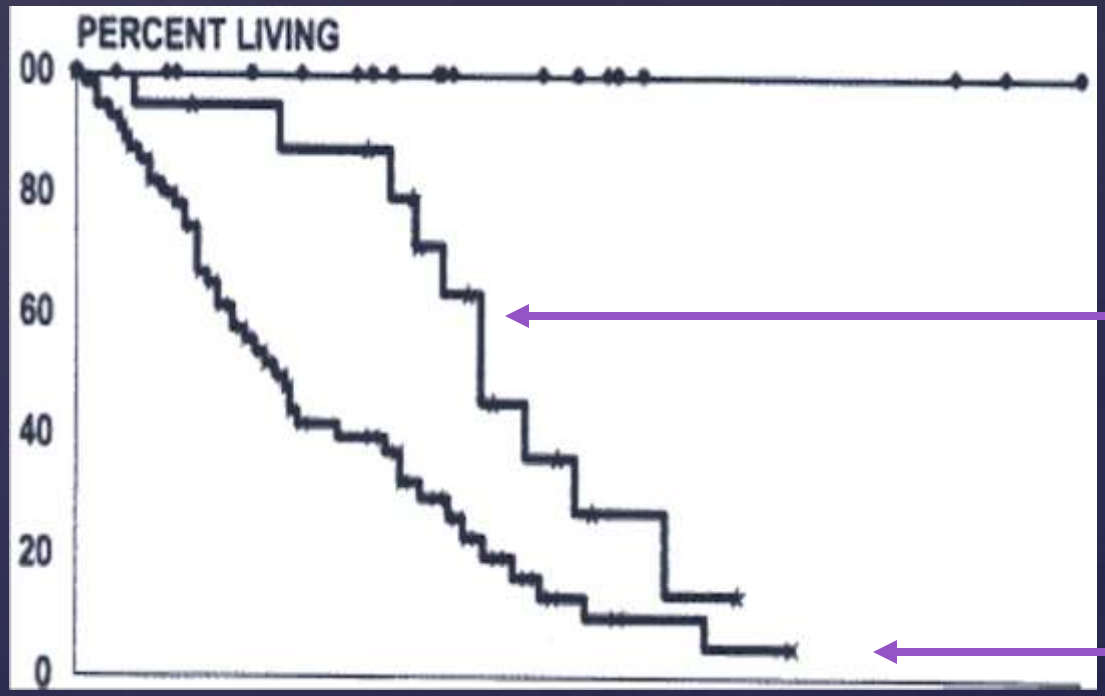
Fibrosing NSIP

Dense or loose interstitial fibrosis, temporal homogeneity

Lung architecture relatively preserved with elastic stains

Interstitial chronic inflammation—mild or moderate

NSIP



DIP + NSIP cellular pattern

NSIP fibrosing pattern

UIP

Travis WD et al. : Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns. Survival comparison with UIP and DIP. Am J Surg Pathol 2000; 24:19-33

Non-Specific Interstitial Pneumonia

Idiopathic NSIP
=
Distinct clinical entity

NSIP histopathological pattern
=
found in a wide variety of clinical contexts

The term NSIP has been referred to a *nonspecific histopathologic lesion* in immunocompromised patients, and most recently to a type of IP associated with:

CVD
HP
Drugs
Infections
Other *slowly healing diffuse alveolar damage
*occupational exposure
*graft versus host disease (GVHD)
*familial pulmonary fibrosis
*multicentric Castleman disease
*IgG4 related disease
*myelodisplastic syndrome

If no etiology is identified a diagnosis of *iNSIP* can be made.

TABLE 3. RADIOLOGIC FEATURES AND DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

Clinical Diagnosis	Histologic Pattern	Usual Radiographic Features	Typical Distribution on CT	Typical CT Findings	CT Differential Diagnosis
NSIP, provisional	NSIP	Ground glass and reticular opacity	Peripheral, subpleural, basal, symmetric	Ground glass attenuation Irregular lines Consolidation	UIP, DIP, COP Hypersensitivity pneumonitis

ATS/ERS international consensus classification, 2002

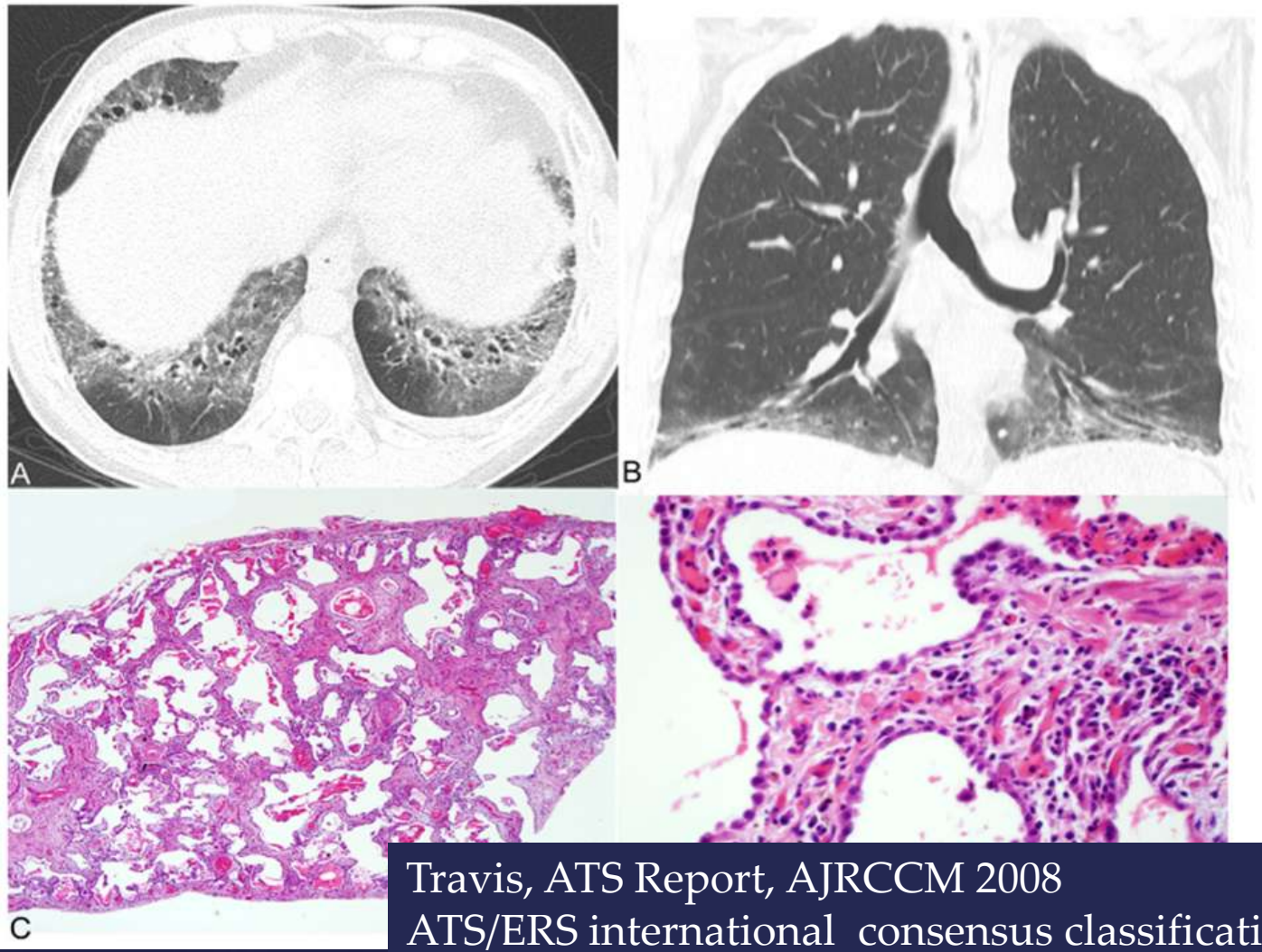


Figure 2. Nonspecific interstitial pneumonia. Computed tomography (CT) features: (*A*) Axial and (*B*) coronal CT reconstructions show confluent bilateral lower lobe ground-glass opacities with marked traction bronchiectasis and lower lobe volume loss. The peribronchovascular predominance with subpleural sparing is well shown on the axial image. (*C* and *D*) Histologic features: Lung biopsy shows diffuse alveolar wall thickening by uniform fibrosis. The alveolar architecture is preserved and no honeycombing or fibroblastic foci are seen. Interstitial inflammation is mild.

Travis, ATS Report, AJRCCM 2008
ATS/ERS international consensus classification, AJRCCM 2013

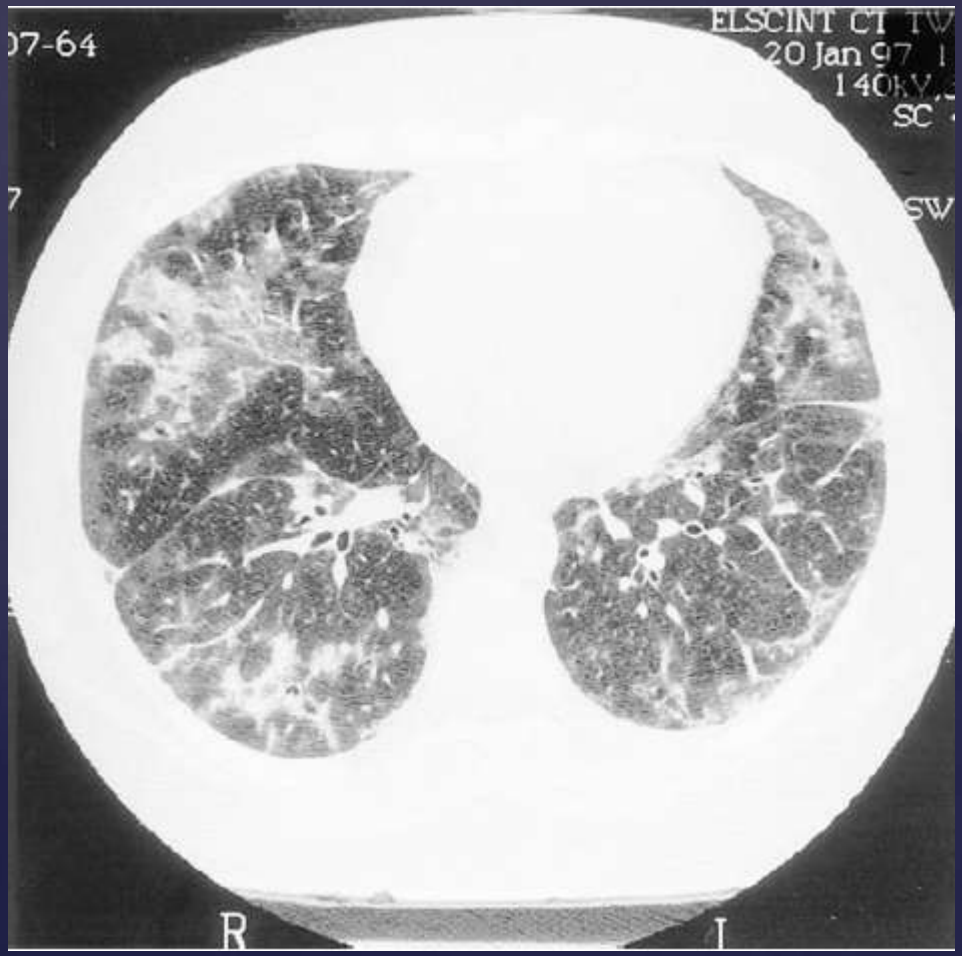
The eterogeneity of iNSIP: HRCT profile

Nonspecific Interstitial Pneumonia

Individualization of a Clinicopathologic Entity in a Series of 12 Patients

VINCENT COTTIN, ANNE-VALÉRIE DONSBECK, DIDIER REVEL, ROBERT LOIRE, and JEAN-FRANÇOIS CORDIER

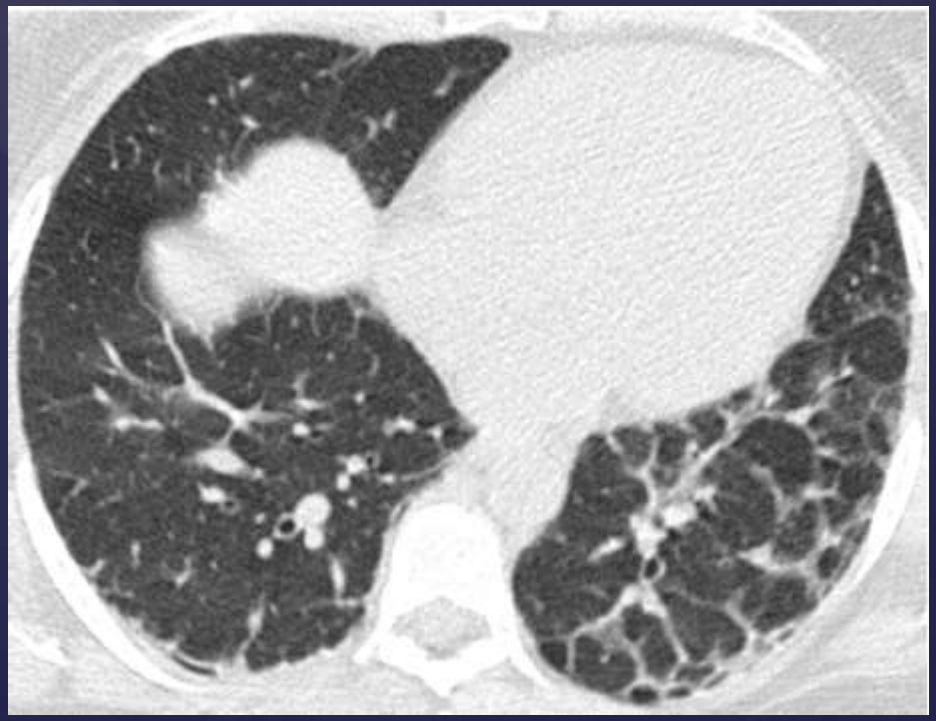
AJRCCM 1998



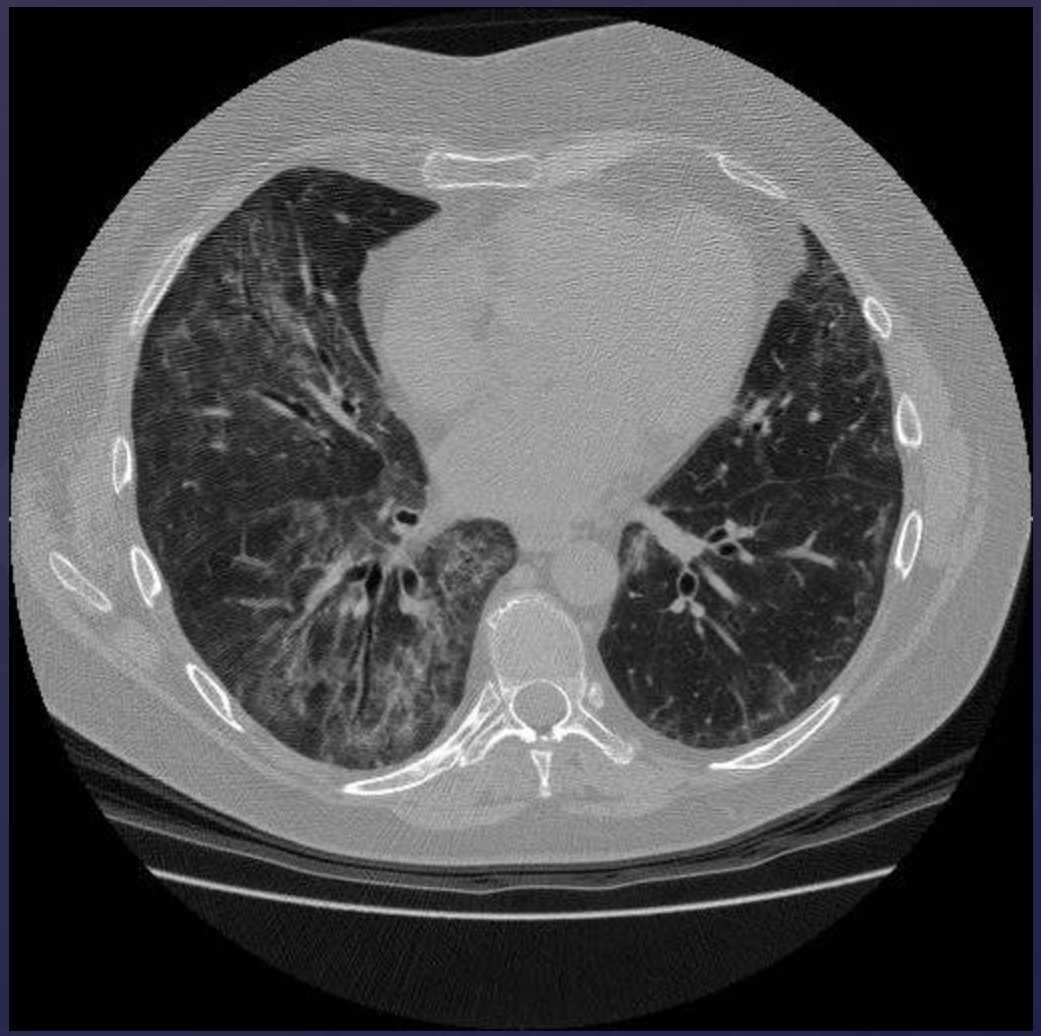
Main CT Findings			
Ground-glass	Alveolar Opacities	Abnormalities of Septa	Linear Opacities
−	+	+	+
+	−	−	−
+	+	+	+
−	+	+	+
+	+	+	−
+	−	−	−

Organizing Pneumonia: Perilobular Pattern at Thin-Section CT[1]

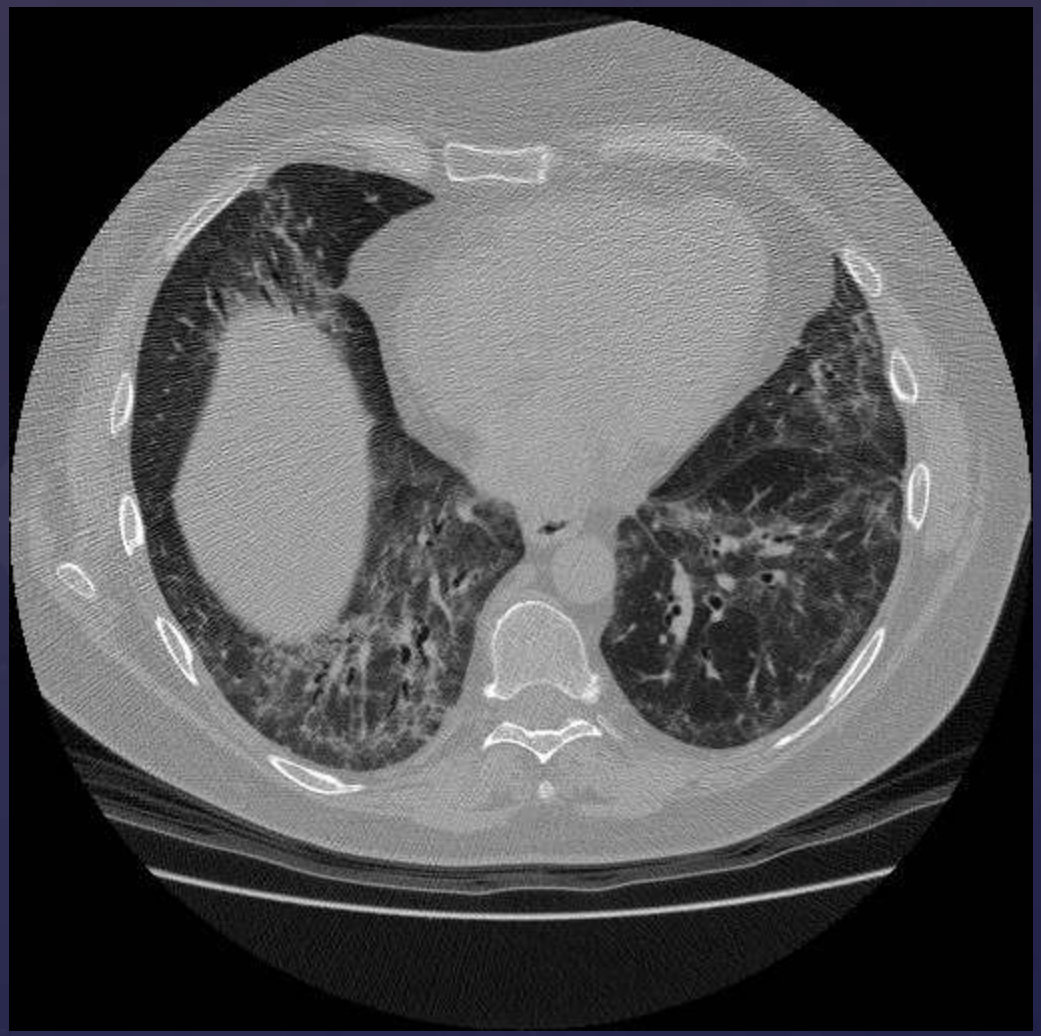
Uijta M, et al. Radiology 2004

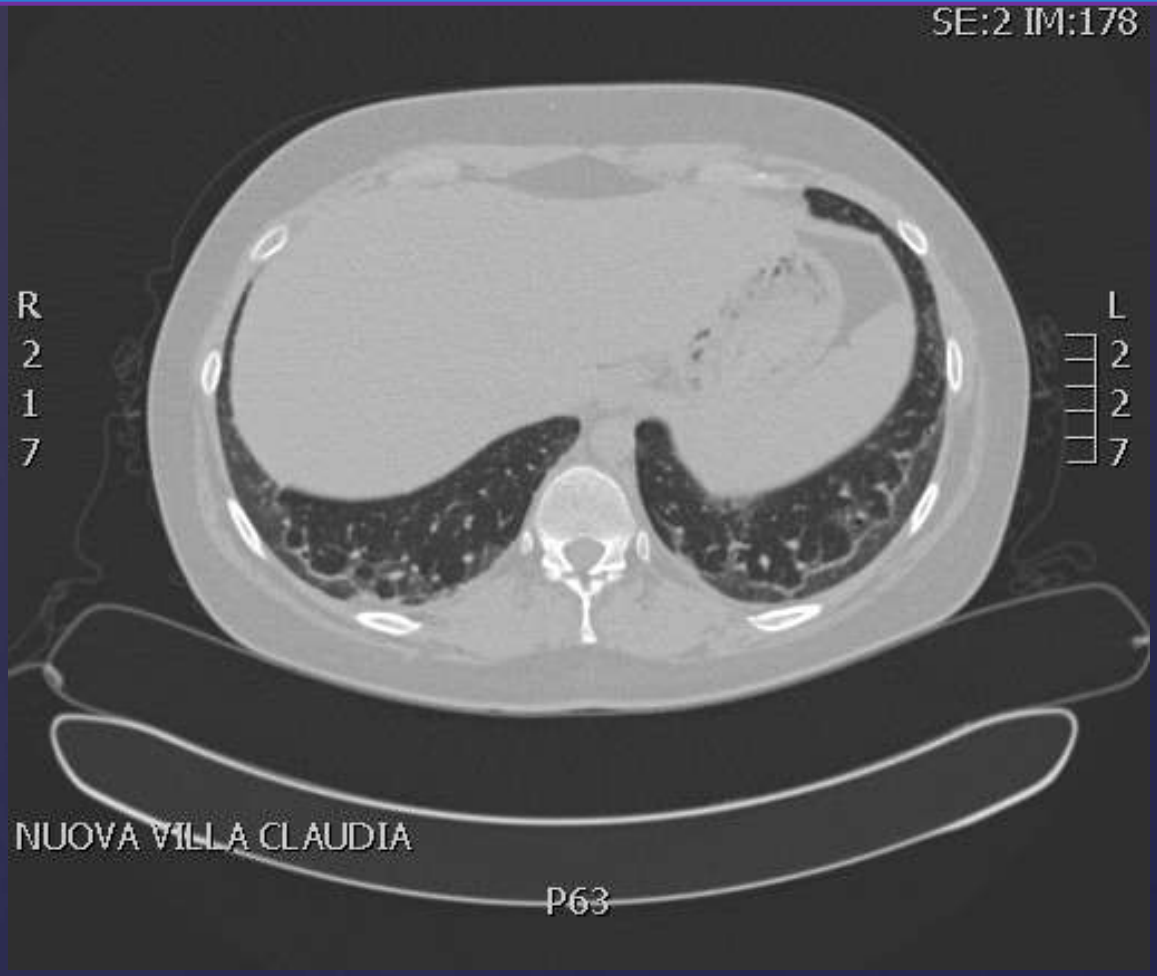


Idiopathic NSIP: HRCT scan: mixed pattern (reticular+GG+alveolar opacification)



Idiopathic NSIP: subpleural sparing





Subplerual sparing remembering reversed halo sign
Hong SH, et al. Br J Radiol 2011, 84: e103-105

The eterogeneity of iNSIP: Histopathologic features and BAL profile

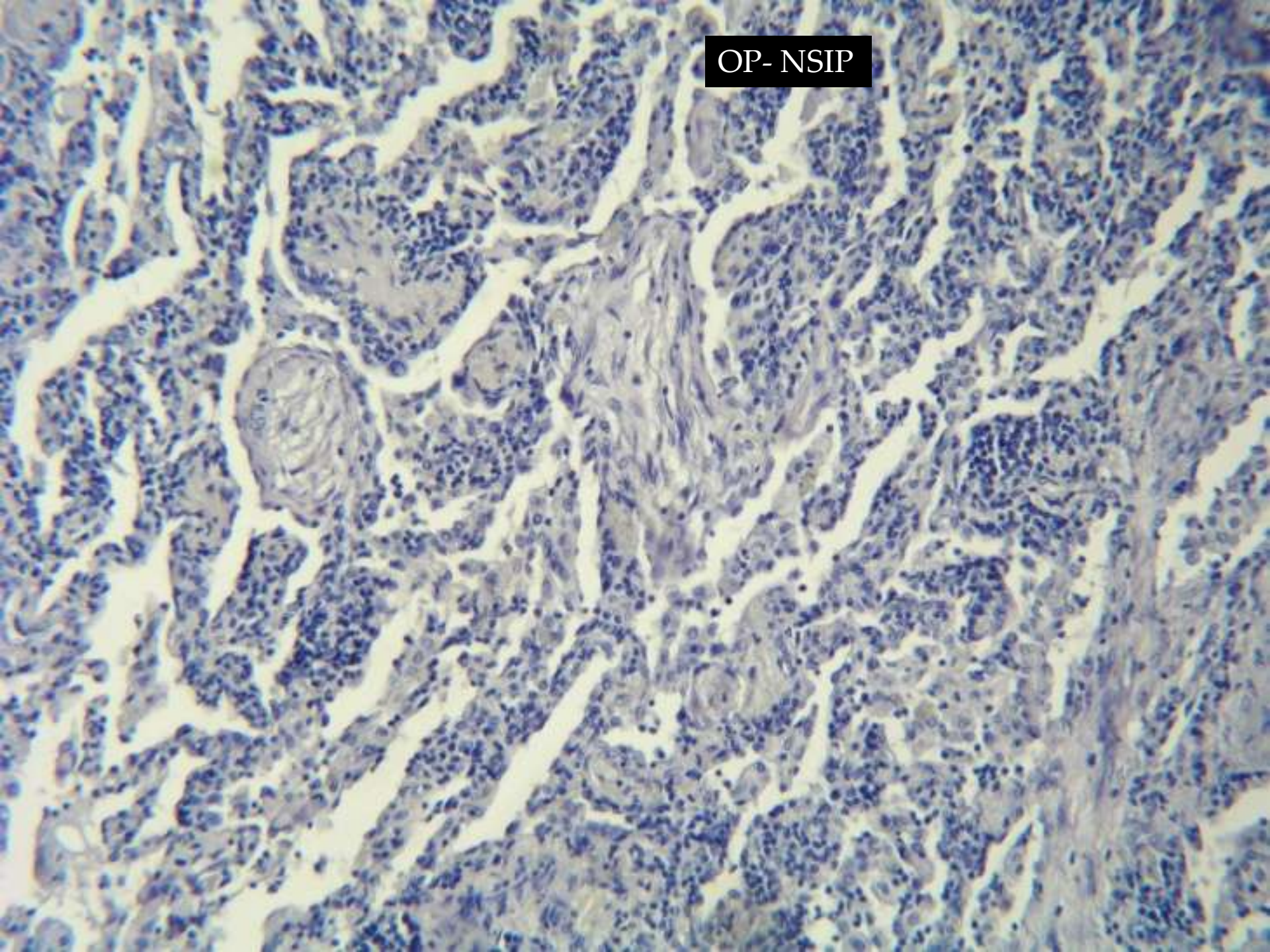
Idiopathic Nonspecific Interstitial Pneumonia: Prognostic Significance of Cellular and Fibrosing Patterns

Survival Comparison With Usual Interstitial Pneumonia and Desquamative Interstitial Pneumonia

William D. Travis, M.D., Kazuhiro Matsui, M.D., Joel Moss, M.D., Ph.D., and Victor J. Ferrans, M.D., Ph.D.

AJSP 2000

Cellular NSIP		Fibrotic NSIP	
Organizing pneumonia	58%	Organizing pneumonia	32%
Lymphoid aggregates	71%	Lymphoid aggeragtes	86%
Chronic pleuritis	71%	Pleural fibrosis/pleuritis	84/64%
Bronchiolar inflammation	86%	Bronchiolar inflammation	86%
Bronchiolar fibrosis	14%	Bronchiolar fibrosis	77%


OP- NSIP

Nagai S, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with Idiopathic pulmonary fibrosis and BOOP.
ERJ 1998, 12: 1010-1019.

Table 6. – Bronchoalveolar lavage fluid cell findings

	Idiopathic NSIP				
	Cellular	Fibrotic	Overall	Idiopathic BOOP	Idiopathic UIP
Cell recovery $\times 10^5 \cdot mL^{-1}$	3.17±2.65	5.89±9.84	4.41±6.86	3.52±2.54	1.87±0.87
Cell differentials %					
Macrophages	51.8±20.6	42.3±27.3	47.4±5.2	45.5±7.1	83.0±14.7
Lymphocytes	40.0±19.2	34.4±27.3	37.3±5.2	44.4±7.3	7.2±7.4
Neutrophils	2.5±3.9	13.9±18.4	8.0±2.8	6.4±3.7	5.9±9.8
Eosinophils	5.7±12.7	5.4±7.4	5.5±7.1	2.2±3.1	3.3±5.1
CD4/CD8 ratio	0.30±0.17	1.20±1.63	0.63±1.08	0.97±1.35	1.65±1.71

BAL: lymphocytosis
Total cell number < BOOP < subacute HP

54 surgically proven UIP patients
19 surgically proven f-NSIP patients

F-NSIP	M	71 (25-92)%
	N	9 (2-57)
	L	5 (0-18)
	E	7 (1-28)
UIP	M	73 (24-89)
	N	9 (1-58)
	L	4 (0-42)
	E	7 (0-32)

BAL do not discriminate between UIP and NSIP and have no prognostic value, once the distinction between the two has been made histologically.

Veeraghavan S, et al
Eur Respir J 2003, 22: 239-244.

The eterogeneity of iNSIP: Clinical profile

Nagai S, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis:comparison with Idiopathic pulmonary fibrosis and BOOP. ERJ 1998, 12: 1010-1019.

Table 3. – Clinical profiles at the time of detection

	Idiopathic NSIP				
	Cellular	Fibrotic	Overall	Idiopathic BOOP	Idiopathic UIP
Cases n	16	15	31	16	64
Sex M/F	6/10	8/7	15/16	6/10	55/9
Age detection yrs*	57.7±8.0	57.8±8.7	57.7±8.2	56.9±8.6	59.5±10.0
Smoking NS/Ex/S	8/2/6	5/3/7	13/5/13	11/2/3	11/29/24
Duration days+	30 (6–960)	60 (7–720)	60 (6–960)	30 (5–120)	1–2 yrs
Symptoms %					
None	0.0	0.0	0.0	6.3	0.0
Chest‡	100.0	100.0	100.0	93.8	100.0
Fever	6.3	53.3	32.3	43.8	0.01
Clubbing %	6.3	13.3	9.7	0.0	65.6
Crackles %	75.0	92.9	80.6	93.7	93.8
Results of rank tests# p-values§					
Sex	<0.0001	<0.0001	<0.001	<0.0001	
Smoking habits	<0.01	<0.0001	<0.0001	<0.0001	
Symptoms	<0.001	<0.0001	<0.0001	<0.0001	
Clubbing	<0.0001	<0.0001	<0.0001	<0.0001	

Idiopathic Nonspecific Interstitial Pneumonia

Report of an American Thoracic Society Project

TABLE 3. CLINICAL FEATURES AT DIAGNOSIS OF 67 PATIENTS WITH IDIOPATHIC NONSPECIFIC INTERSTITIAL PNEUMONIA

Feature	Number (%
Age, yr	
Mean	52
Range	26–73
Sex	
Female	45 (67)
Male	22 (33)
Contributing institution	
Asian	31 (46)
Non-Asian	36 (54)
Symptoms	
Dyspnea (n = 67)	64 (96)
Duration dyspnea	
Median	7 mo
Range	1–120 mo
Cough (n = 67)	58 (87)
Duration cough	
Median	6 mo
Range	1–147 mo
Weight loss (n = 64)†	16 (25)
Fever (n = 64)†	14 (22)
Arthralgias (n = 64)†	9 (14)
Clubbing (N = 62)†	5 (8)
Raynauds (n = 63)†	5 (8)
Myalgias (n = 58)†	4 (7)
Skin rash (n = 64)†	3 (5)
Arthritis (n = 64)†	2 (3)

AJRCCM 2008

NSIP-lesson from the CVDs

Variations in histology/CT features

Antisynthetase S	OP/NSIP/DAD/UIP
Sjogren	NSIP/follicular bronchiolitis
SS	NSIP/UIP

Clinical onset

Antisynthetase S	Acute/subacute
SS	Chronic

Tansey D, et al. Histopathology 2004

Dail and Hammar's Pulmonary Pathology 2008

OP-NSIP (fibrosing OP)

*Subacute onset

*HRCT:mixed pattern (NSIP-OP-DAD)

*BAL: Lymphocytosis

*Biopsy :NSIP-OP-DAD (OP in TBB specimens)

Prototype: Antisynthetase S.

f-NSIP

*Chronic onset

*HRCT: ground glass

*BAL: no lymphocytosus

*Biopsy: fibrosing NSIP

Prototype: Systemic Sclerosis

PolettiV et al, Semin Respir Crit Care Med , 2012

In conclusion:

NSIP is an eterogenous entity with:

- Acute -> chronic onset
- Different HRCT, histology and BAL profile

Antisynthetase and SS might represent two disease models helpful to further subdivide iNSIP in clinical subgroups

The NSIP / UIP debate

The potential relationship between NSIP and UIP remains undefined:

Similar factors (CTD, HP, genetic mutations) can lead to histopathologic pattern of NSIP or UIP

Individual patient can harbor both patterns*

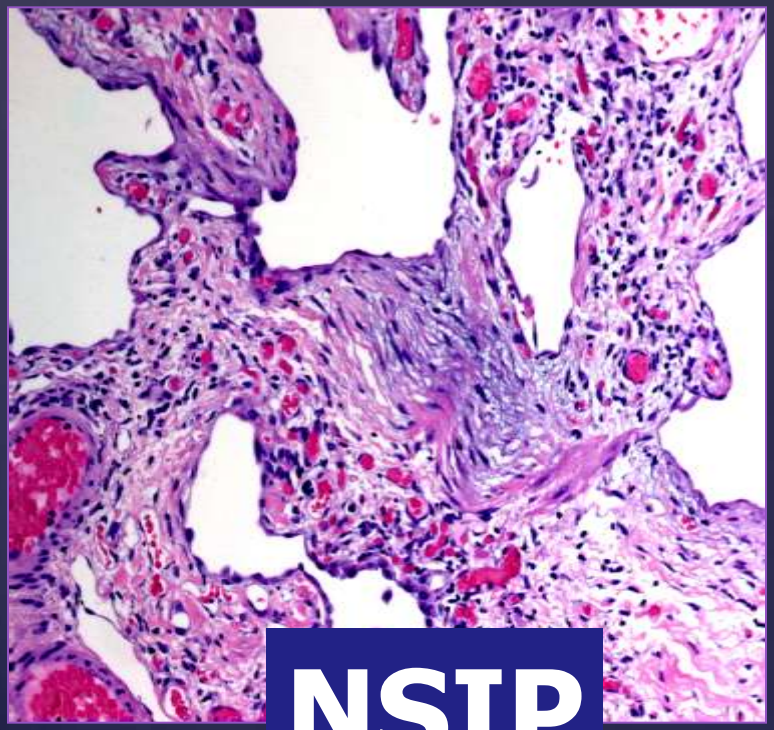
UIP may represent the end stage disease of NSIP^

*Flaherty, AJRCCM 2001
*Monaghan, Chest 2004
^Maher, ERJ 2007

DESPITE THE CONFUSION ABOUT THE POTENTIAL RELATIONSHIP BETWEEN iNSIP and IPF,

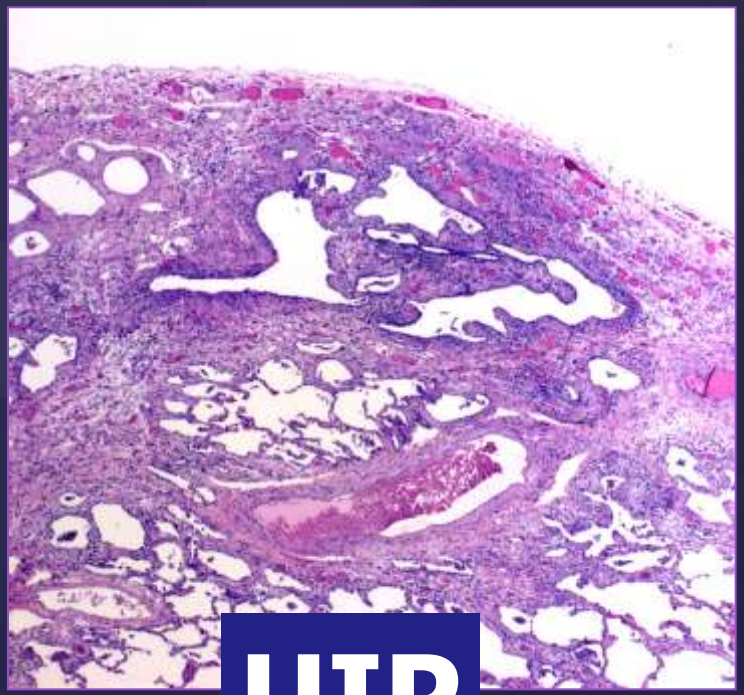
THE TWO DISEASES PRESENT A STRIKINGLY DIFFERENCES

Inflammatory Pathway

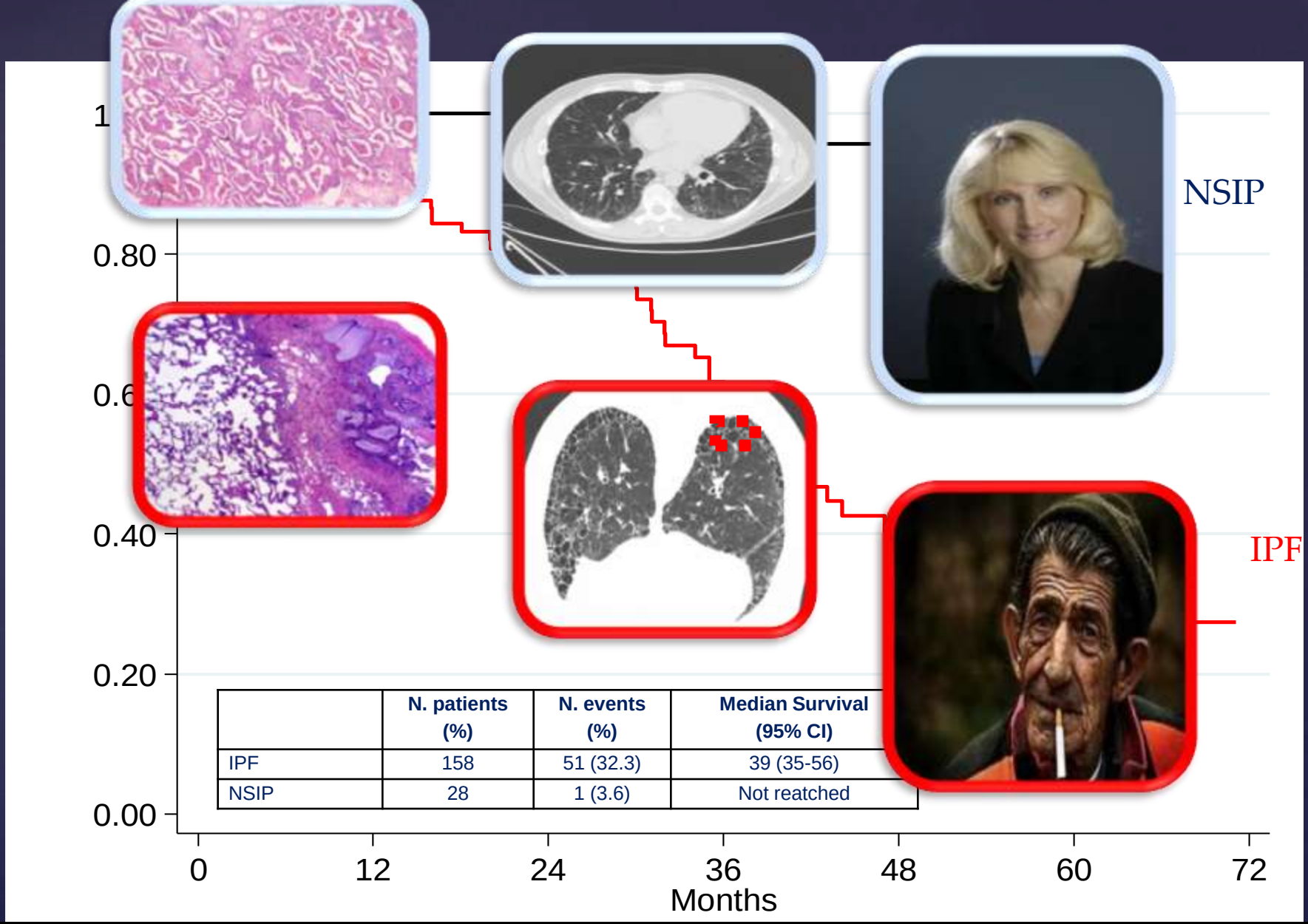


NSIP

Epithelial StemCell Exhaustion



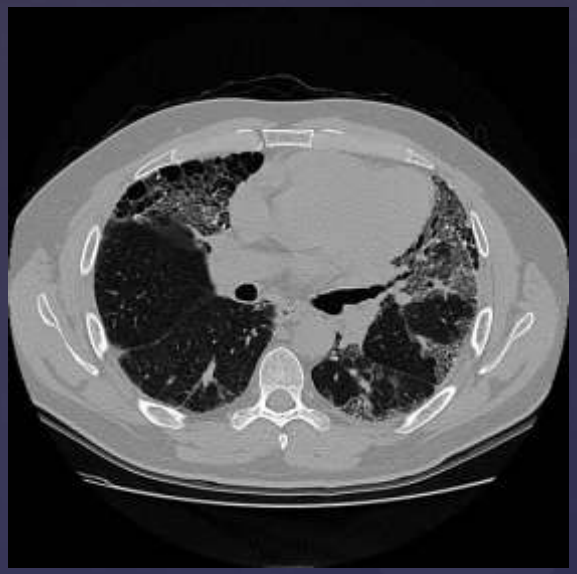
UIP

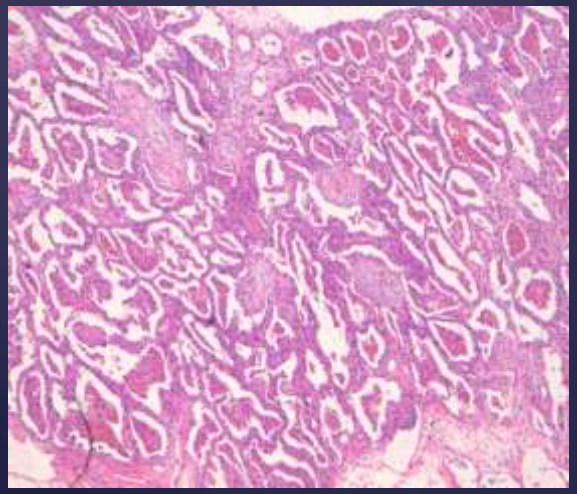


	N. patients (%)	N. events (%)	Median Survival (95% CI)
IPF	158	51 (32.3)	39 (35-56)
NSIP	28	1 (3.6)	Not reatched

N. Pts at risk							
IPF	158	89	59	35	18	12	7
NSIP	28	28	27	24	19	15	13

iNSIP: clinical features





Total Patients N = 27

Age *yr, mean + SD (range)*	**54.2** + 8 (40-68)
Sex, *n (%)*	
Women	19 (**70%**)
Men	8 (30%)
Smoking history, *n (%)*	
Never smokers	16 (**59%**)
Ex smokers	11 (41%)
mean p/y + SD, (range)	21 + 21, 5-80

NSIP histopathology pattern, *n (%)*	
Fibrosing	15 (56%)
Cellular	9 (33%)
Unclassified IP	3 (11%)

FOLLOW-UP 2 years

•6 UCTD	**(22%)**
•3 specific CVD (SS)	**(11%)**

Romagnoli M Eur Respir J. 2011

iNSIP: clinical course

- 12 patients (6 with iNSIP, 6 with CTD-NSIP): on follow up 10 patients (83%) improved clinically and functionally. 5-yr survival=100%.

Cottin V et al, AJRCCM 1998

- 83 patients with iNSIP (72 fibrosing, 11 cellular; 56 females and 27 males): On follow-up, lung function was improved or stable in 80% of the patients. 10% developed CTD. 5-yr survival = 74%.

Park IN et al, Eur Respir J 2009

- 27 patients with iNSIP (21 fibrosing, 6 cellular; 8 males and 19 females): On follow-up, pulmonary symptoms, lung function and HRCT were stable. >50% developed an autoimmune disorder. 5-yr survival = 85%.

Romagnoli M et al, Eur Respir J 2011

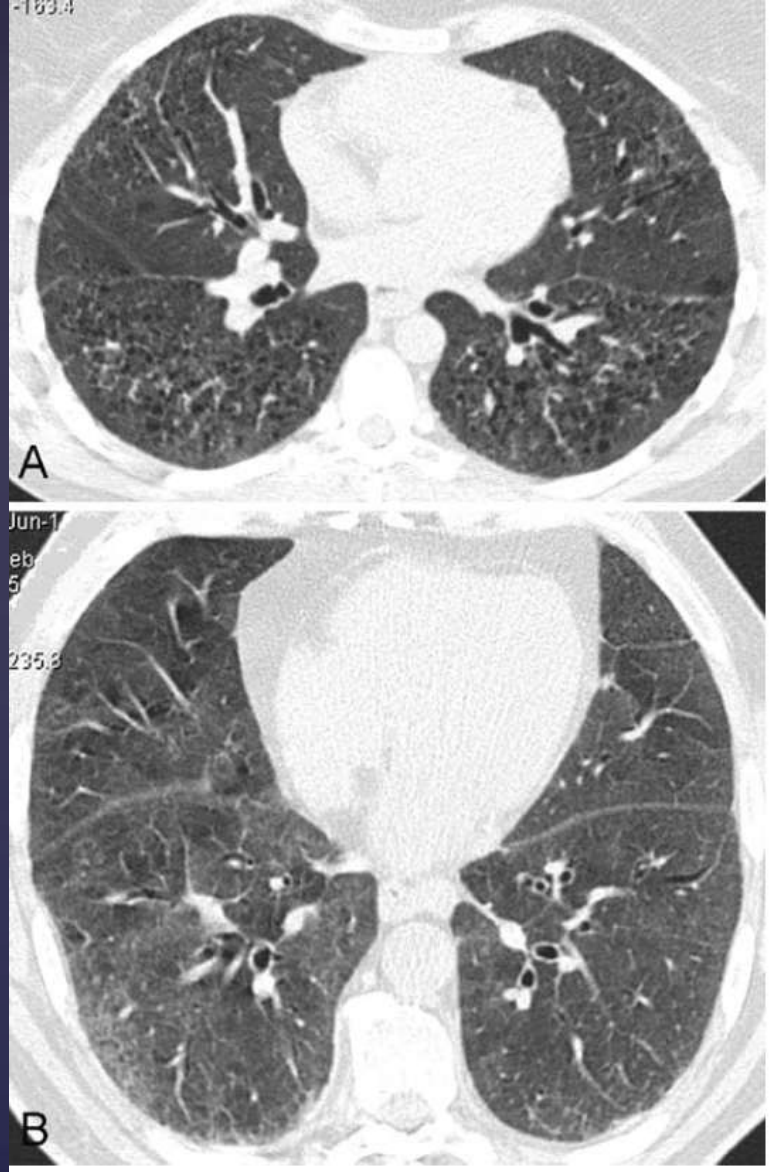


Fig. 2a, b Thin-section CT of two current smokers with NSIP. **a** A 43-year-old woman with a 15-pack-year smoking history displaying diffuse ground-glass opacification with superimposed centrilobular emphysema. Total extent of interstitial disease was scored as 95% (20% attributed to emphysema, and 80% to ground-glass opacification without traction bronchiectasis). **b** A 60-year-old man with a 45-pack-year smoking history with diffuse ground-glass opacification with traction bronchiectasis (extent scored as 100%)

Emphysema is as prevalent in smokers with NSIP as in smokers with
COPD, and is strikinglymore prevalent
in these two groups than in healthy
smoking controls. The association between
NSIP and emphysema provides indirect support for a smoking pathogenesis
hypothesis in some NSIP patients.

Marten, Eur Radiol (2009)

THORAX

Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia

Masanori Akira, Yoshikazu Inoue, Toru Arai, et al.

Thorax published online November 11, 2010
doi: 10.1136/thx.2010.140574

50 patients with biopsy-proven idiopathic NSIP

Interval between initial and last HRCT scans: 3 to 216 months (median, 72 months)

The HRCT patterns progress in a variable manner.

Overall disease extent may decrease over time in some, while fibrosis may progress in others.

In conclusion IPF and NSIP diverge for:

1. Pathogenetic pathways
2. Clinical profiles
3. Disease course

Pathways implicated in the pathobiology of NSIP

Numerous pathways have been implicated in the pathobiology of NSIP:

1. Matrix metalloproteinases [Suga, AJRCCM 2000]
2. Heat shock protein 47 [Kakugawa, Res Res 2005; Anenomori, Res Res 2010; Kakugawas, Res Res 2014]
3. Surfactant protein C [Brasch, ERJ 2004; Chibbar Mod Pathol 2004; Nogee, NEJM 2001; stevens, Pediatr Res 2005; Thomas AJRCCM 2002]
4. Coagulation system [Eitzman, JClinInvest2002; Kim, Mol Med 2003]
5. Adhesion molecules, ICAM-1 [Takehara, Acta Med Okayama 2001]
6. IL-4,IL-13, IL-18, IFN-γ, profibrotic chemokines (CCL7,CCL5) [Choi, AJRCCM 2004]

The role of matrix-degrading proteins in the pathogenesis of UIP-IPF and NSIP.

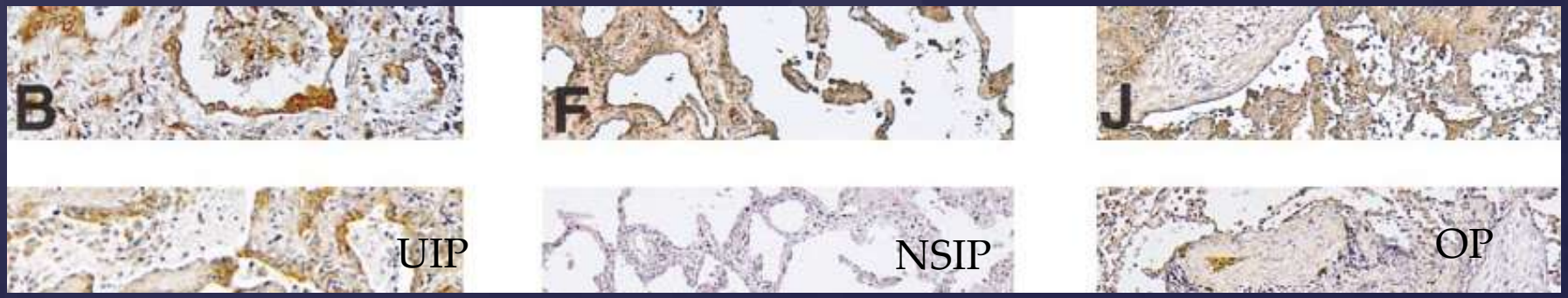
Background

Destruction of subepithelial basement membrane is a key event in in parenchymal remodeling.
To evaluate the pathogenetic role of MMP-2 and MMP-9 expression and activity, were studied in bronchoalveolar lavage fluid (BALF) and in lung tissue of **26 IPF-UIP, 11 NSIP, and 6 COP**

Suga et al. AJRCCM, 2000

UIP cases showed predominant expression of MMP-9, whereas NSIP and BOOP cases showed predominant MMP-2 expression in both BALF and tissues.

MMP-9 are in tensely expressed in UIP by regenerated cells, alveolar macrophages, and neutrophils; absent in NSIP/OP



MMP-2 is widely detected in regenerated epithelial cells, macrophages and fibroblasts of UIP.

MMP-2 is intensely expressed by regenerated cuboidal epithelial cells in NSIP/OP

Suga et al. AJRCCM, 2000

MMP-9 activity correlated with an increase of neutrophils in BALF of UIP and were characteristically detected in BALF from rapidly progressive IPF-UIP cases.

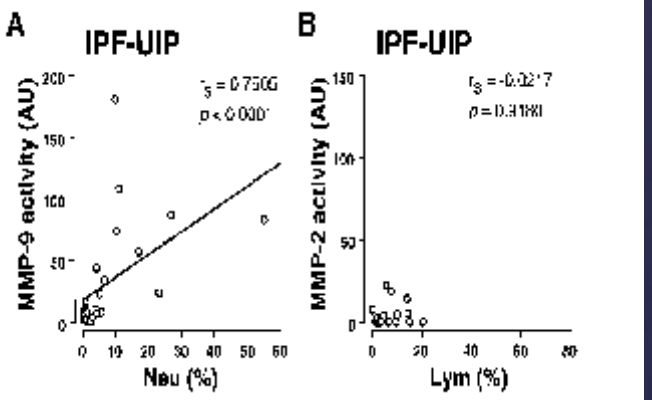


Figure 5. Correlation between MMP-2 or MMP-9 activity and BAL cell constituents from patients with IPF-UIP. MMP-9 activity correlates significantly with the percentage of neutrophils (r_s 5 0.7505, p , 0.0001) (*A*), whereas no correlation is observed between MMP-2 activity and the percentage of lymphocytes (r_s 5 0.0217, p 5 0.918) (*B*). Neu 5 neutrophils; Lym 5 lymphocytes.

MMP-2 activity associated with NSIP and BOOP correlated with an increase of lymphocytes.

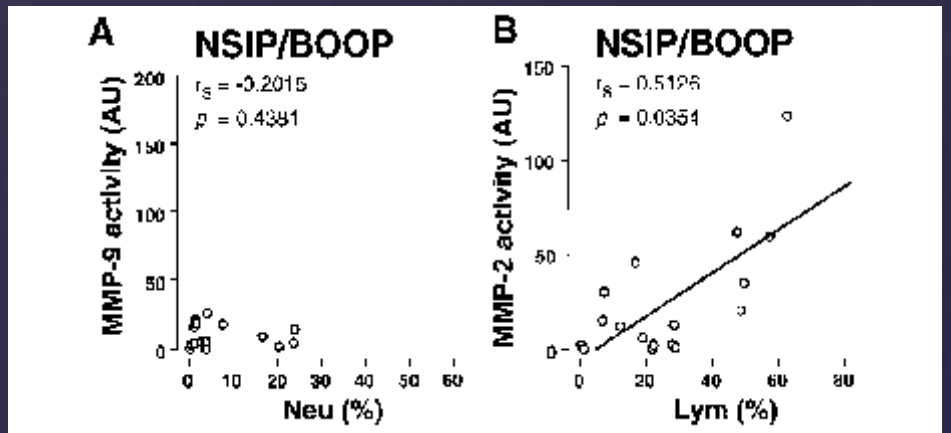


Figure 6. Correlation between MMP-2 or MMP-9 activity and BAL cell constituents from patients with NSIP and BOOP. MMP-2 activity correlates significantly with the percentage of lymphocytes (r_s 5 0.5126, p 5 0.0354) (*B*), whereas no correlation is observed between MMP-9 activity and the percentage of neutrophils (r_s 5 2 0.2015, p 5 0.4381) (*A*). Neu 5 neutrophils; Lym 5 lymphocytes.

Suga et al. AJRCCM, 2000

These results indicate that MMP-9 in IPF-UIP and MMP-2 in NSIP and BOOP

1. may contribute to pulmonary structural remodeling through type IV collagenolytic activity;
2. the characteristic contributions of matrix-degrading proteins may relate to the distinct prognostic features of these diseases.

The greater VEGF-A and MMP-2 expression may play a role in the pathogenesis of neovascularization in early intra-alveolar fibrotic lesions in f-NSIP.

Authors observed a a considerable degree of neovascularization in iNSIP compared to UIP:

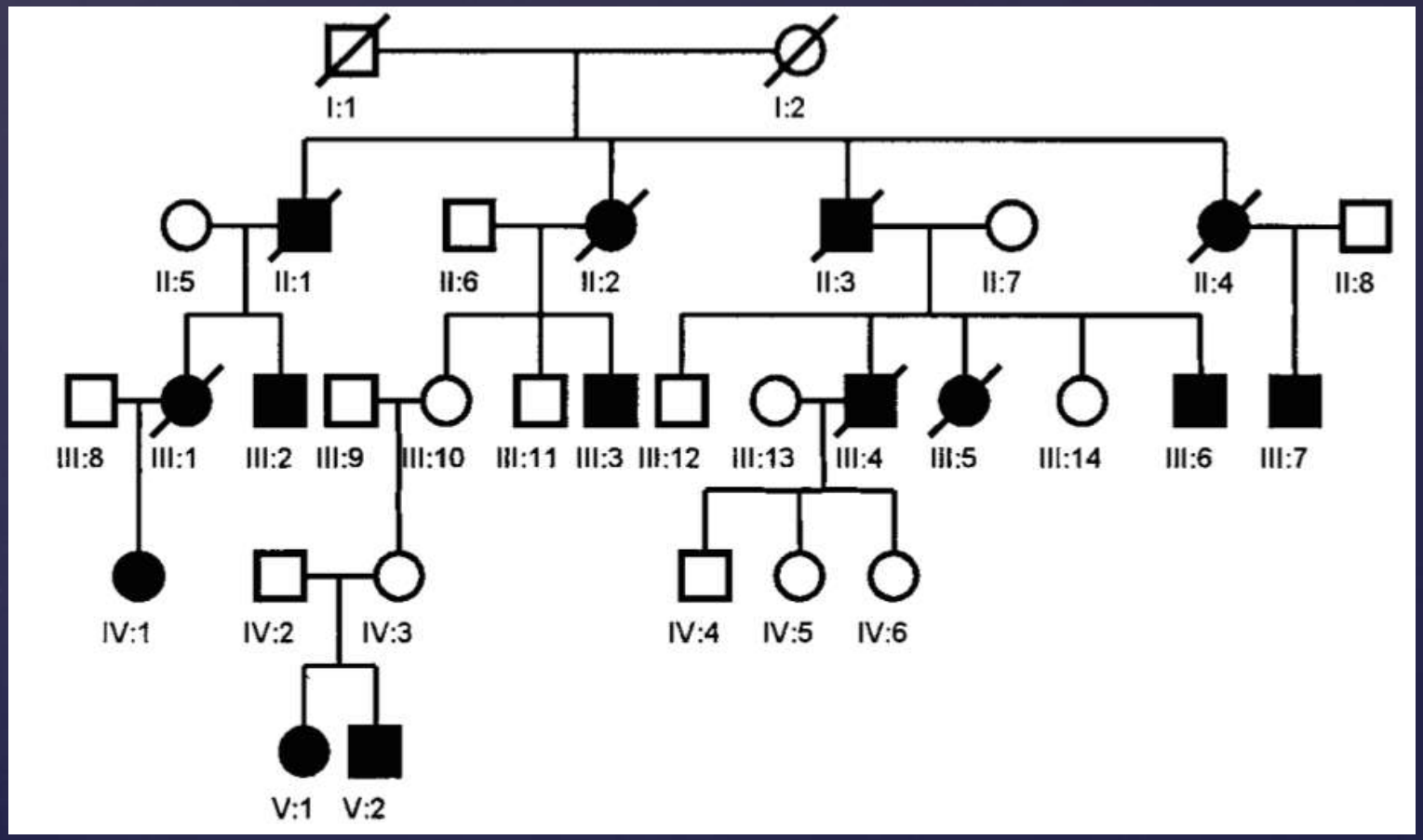
1. The expression of MMP-2 mRNA was significantly higher in f-NSIP than UIP

2. Real-time reverse transcription polymerase chain reaction revealed a significantly greater expression of VEGF-A mRNA in f-NSIP than in UIP.

Takahashi, Pathol Int. 2013

The lesson from FPF:
Are NSIP and UIP pleiotropic manifestation of the same initial pathogenetic defect?

A heterozygous exon 5 + 128 T→A transversion of *SFTPC* in a large familial pulmonary fibrosis kindred



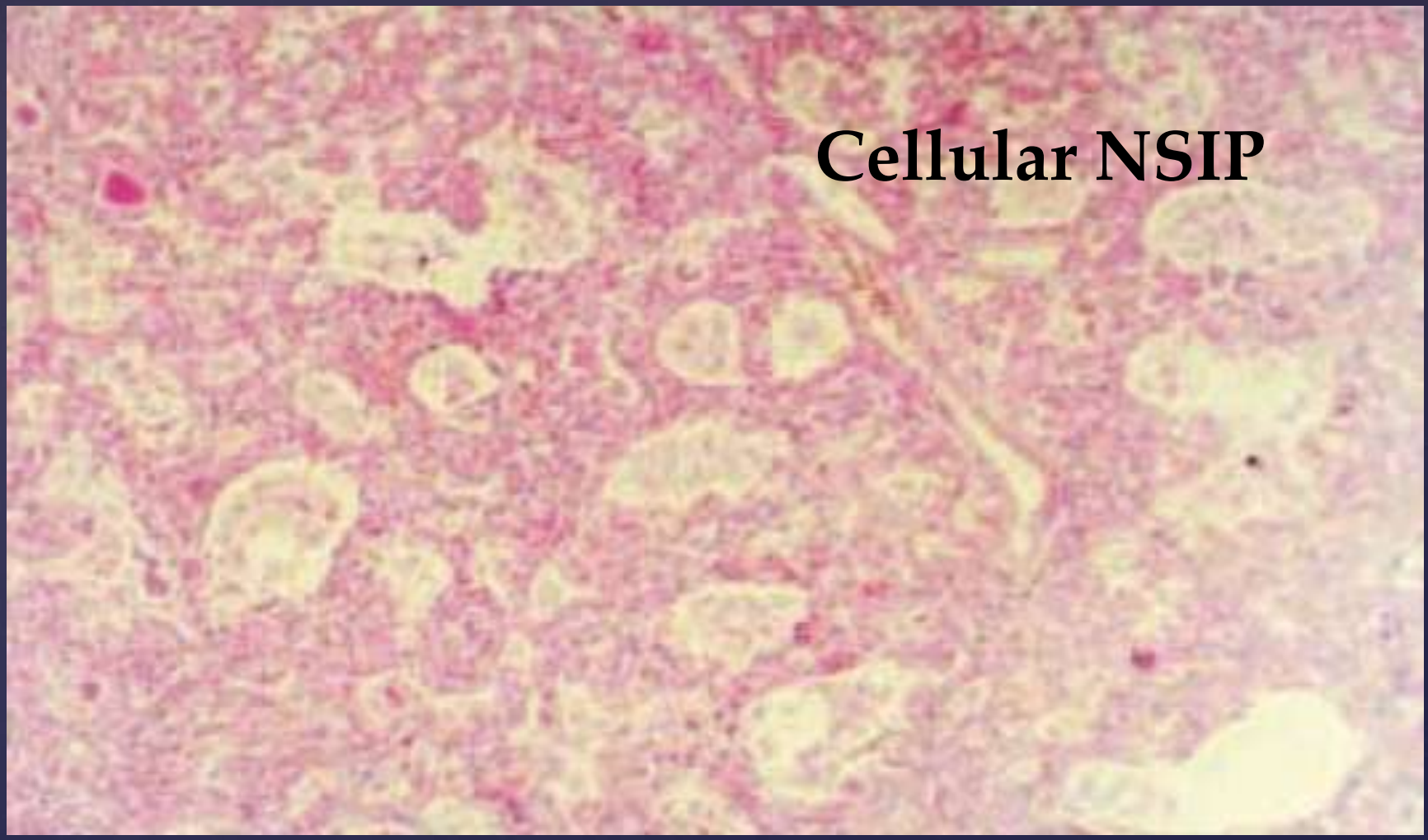
Thomas et al. AJRCCM, 2002

TABLE 1. CLINICAL AND PATHOLOGIC DATA FROM AFFECTED INDIVIDUALS

Patient	Sex	Age at Dx	Year of Dx	Year of Death	Clinical and Pathologic Descriptors
II:1	M	29	1942	1952	Dyspnea, cough, clubbing; CXR with "diffuse granular infiltration"; path report "fibrocystic pulmonary dysplasia."
II:2	F	57	1976	1986	Dyspnea, cough; cause of death "pulmonary fibrosis."
II:3	M	20	1945	1990	Dyspnea, cough, clubbing; CXR with "bilateral interstitial fibrosis"; TLC 52%, D_{LCO} 51%.
II:4	F	41	1967	1986	Dyspnea, clubbing; cause of death "pulmonary fibrosis."
III:1	F	17	1959	1964	Dyspnea, cough, clubbing; CXR "extensive, scattered nodular infiltrations throughout both lungs"; FVC 21%; Asian influenza pneumonia before onset; path report "interstitial pulmonary fibrosis (Hamman-Rich Disease)."
III:2	M	20	1965	1991	Dyspnea, cough; path report UIP.
III:3	M	32	1986	Alive	Dyspnea; CXR "diffuse coarse reticulation with multiple lucencies"; DLT 2000; path UIP by slide review.
III:4	M	34	1989	2000	Dyspnea, cough, clubbing; TLC 60%, D_{LCO} 41%; CXR "diffuse interstitial infiltrates, worse at bases"; DLT 2000; path UIP by slide review.
III:5	F	6 mo	1952	1953	Failure to thrive, cough, cyanosis; CXR "ground glass appearance with fine fibrillary infiltration through both lungs"; path NSIP by slide review.
III:6	M	40	2001	Alive	Pulmonary fibrosis diagnosed as a child; mild dyspnea in adulthood; age 40 CXR "worsening reticulonodular interstitial infiltrates."
III:7	M	44	1990	Alive	Diagnosed as "environmental lung scarring"; CXR "bilateral scarring."
IV:1	F	37	1999	Alive	Dyspnea, cough; TLC 70%, D_{LCO} 60%; chest CT "bilateral patchy interstitial opacities and honeycombing"; path report UIP.
V:1	F	17 mo	1997	Alive	Respiratory failure; RSV pneumonia before disease onset; path report NSIP.
V:2	M	4 mo	1998	Alive	Respiratory failure; influenza B pneumonia before disease onset; path report NSIP.

Definition of abbreviations: CT = computed tomography; CXR = chest X-ray; D_LCO = diffusion capacity of carbon monoxide (% predicted); DLT = double lung transplantation; Dx = diagnosis; FVC: = forced vital capacity (% predicted); N/A = not available; NSIP = nonspecific interstitial pneumonitis; Path = pathology; RSV = respiratory syncytial virus; TLC = total lung capacity (% predicted); UIP = usual interstitial pneumonitis.

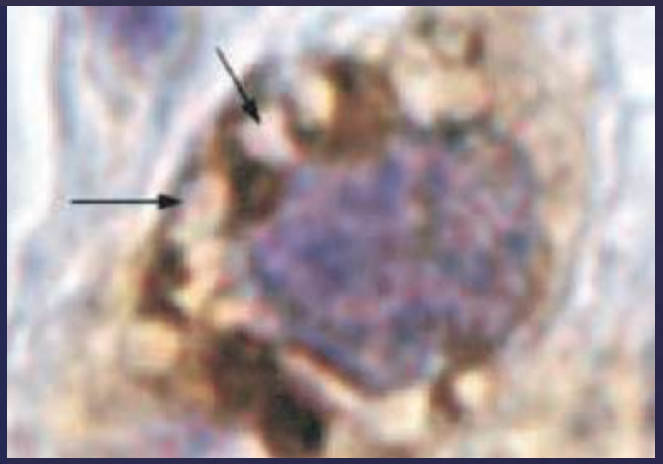
Thomas et al. AJRCCM, 2002



Thomas et al. AJRCCM, 2002

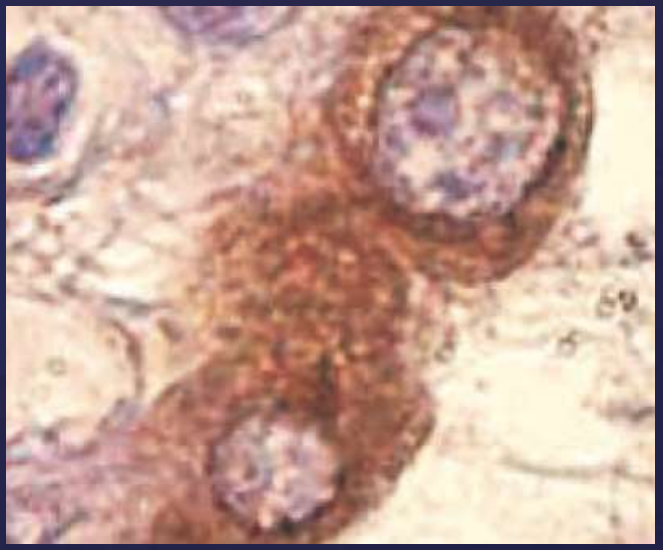
Mutated SP-C precursor protein displays aberrant subcellular localization by immunostaining.

Lung of a normal adult subject immunostained for proSP-C. Type II cell shows predominately focal brown staining of the cytoplasm adjacent to lamellar bodies, which are evident as clear vesicles



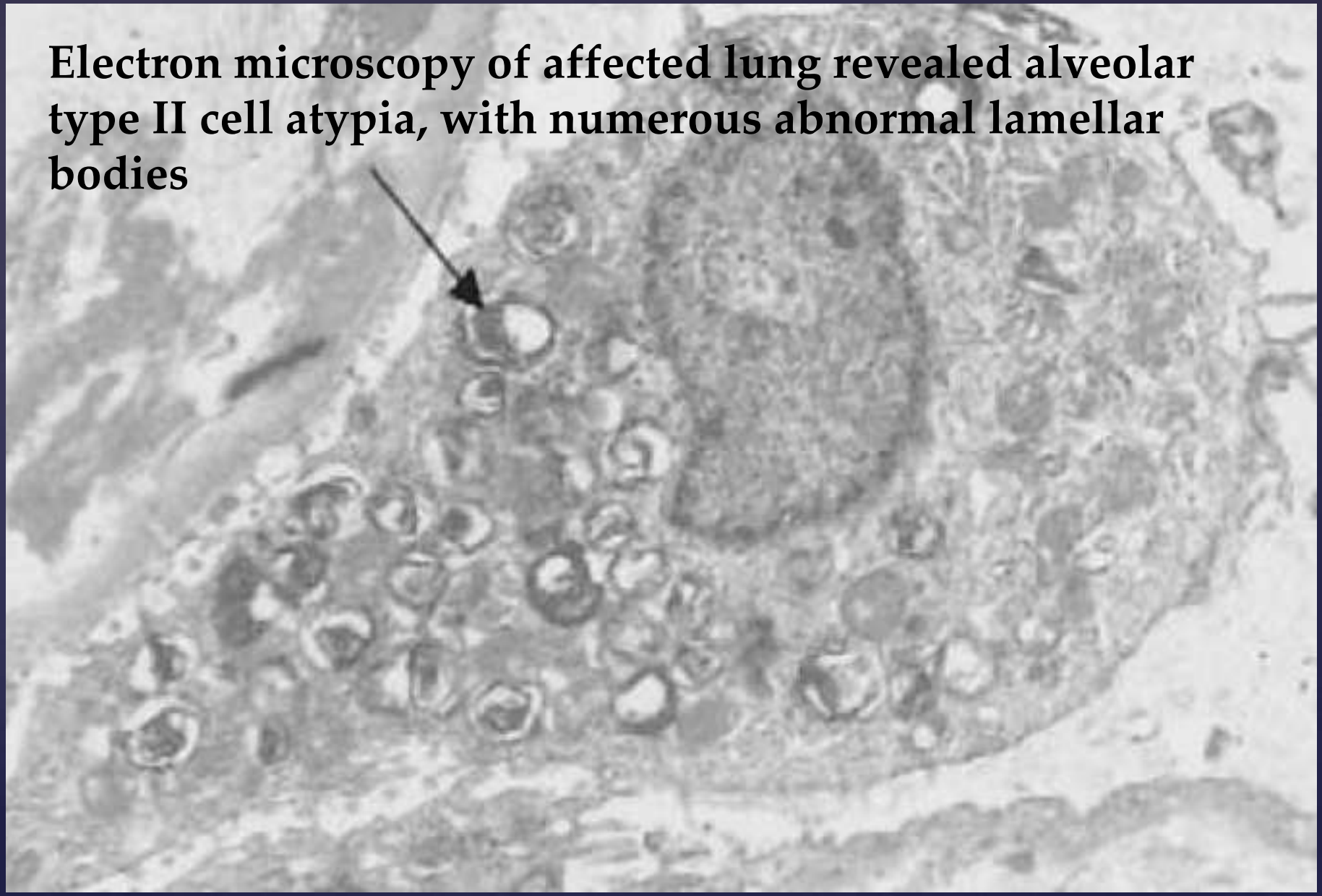
unstained
Explanted lung from FPF patient.
Two cuboidal type II cells show diffuse brown cytoplasmic staining.

No obvious lamellar bodies are seen.

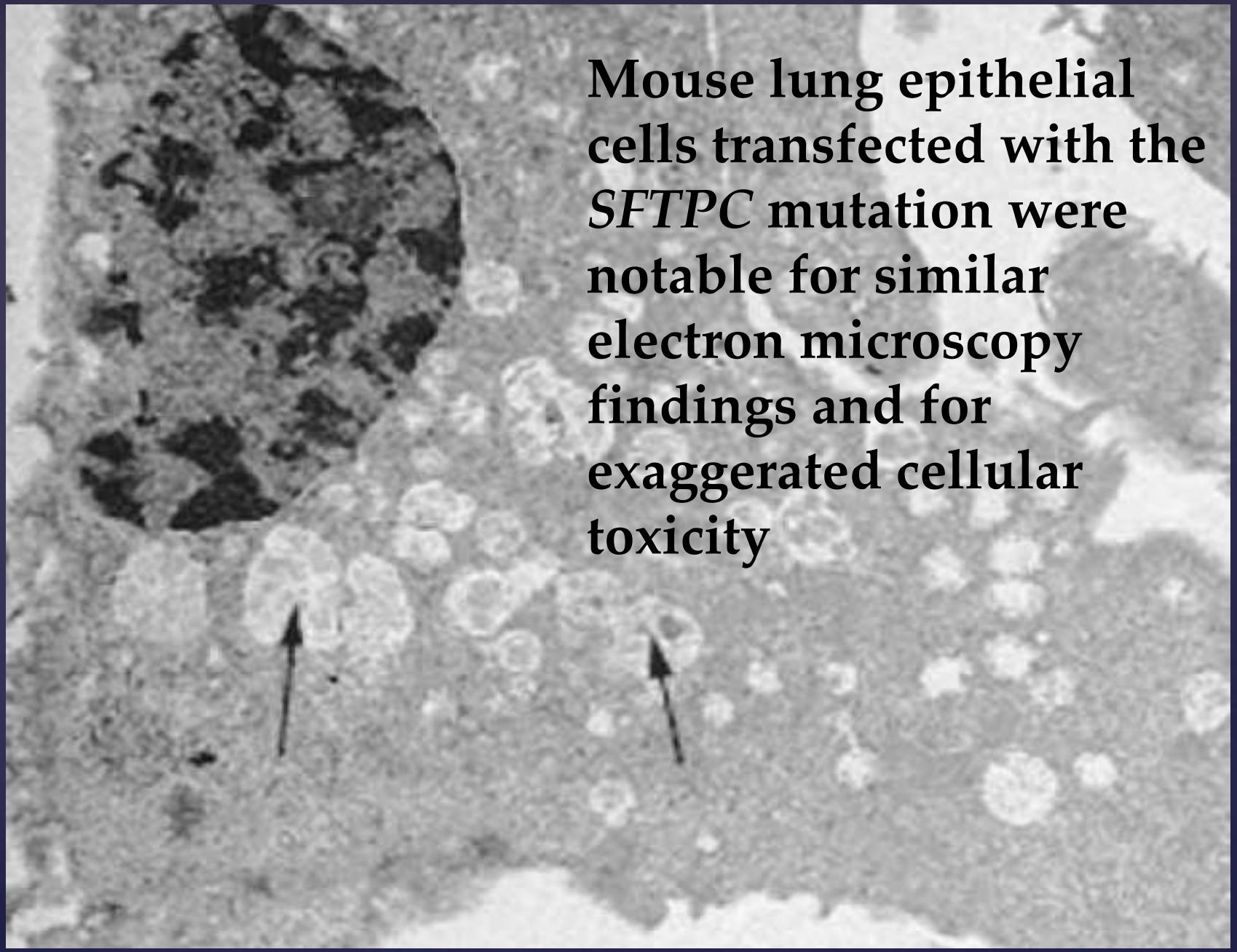


Thomas et al. AJRCCM, 2002

Electron microscopy of affected lung revealed alveolar type II cell atypia, with numerous abnormal lamellar bodies



Thomas et al. AJRCCM, 2002



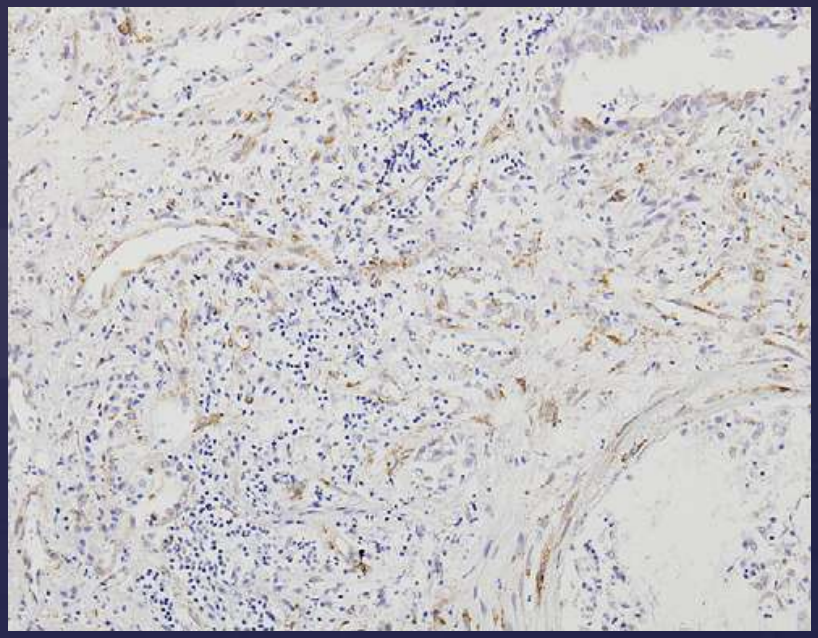
Thomas et al. AJRCCM, 2002

Conclusions :

1. *SFTPC* mutation segregates with the pulmonary fibrosis phenotype in this kindred
2. SFTPC mutation may hinder processing of SP-C precursor protein and cause type II cellular injury
3. UIP in the adults and cellular NSIP in the pediatric patients share the same genetic background and initial cellular toxicity pathogenetic mechanisms, envinronmental triggers may diverge

Heat shock protein 47

Heat shock protein (HSP) 47, a collagen-specific molecular chaperone, is involved in the processing and/or secretion of procollagen. HSP47 is increased in various fibrotic diseases.



Fibroblast expression of HSP47 in iNSIP [Amenomori 2010]

The serum levels of autoantibodies to HSP47 in patients with idiopathic NSIP were significantly higher

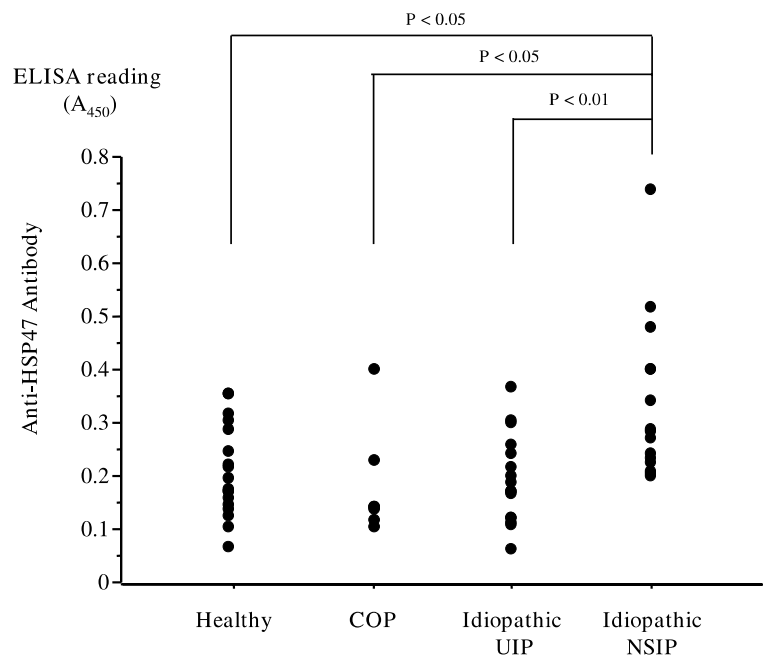


Figure 1
Scattergram of IgG titers to HSP47 in patients with cryptogenic organizing pneumonia (COP), idiopathic usual interstitial pneumonia (UIP), idiopathic non-specific interstitial pneumonia (NSIP) and healthy volunteer. Antibody titers are expressed as absorbance at 450 nm.

In fibrosing NSIP were significantly higher than those of cellular and fibrosing NSIP ($p < 0.05$).

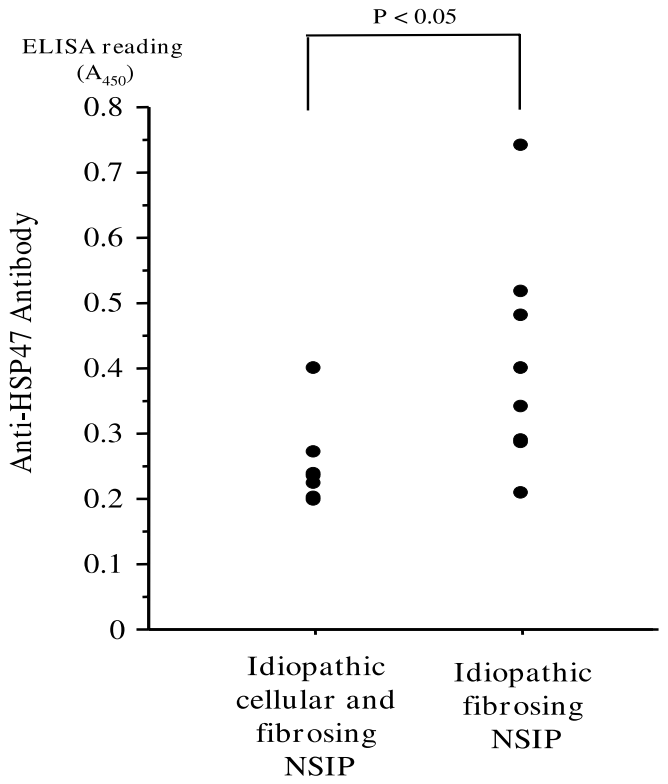


Figure 2
Scattergram of IgG titers to HSP47 in patients with idiopathic cellular and fibrosing nonspecific interstitial pneumonia (NSIP) and idiopathic fibrosing NSIP. Antibody titers are expressed as absorbance at 450 nm.

Kakugawa, Resp Res 2005

HSP47 in lung fibroblasts is a predictor of survival in fibrotic nonspecific interstitial pneumonia

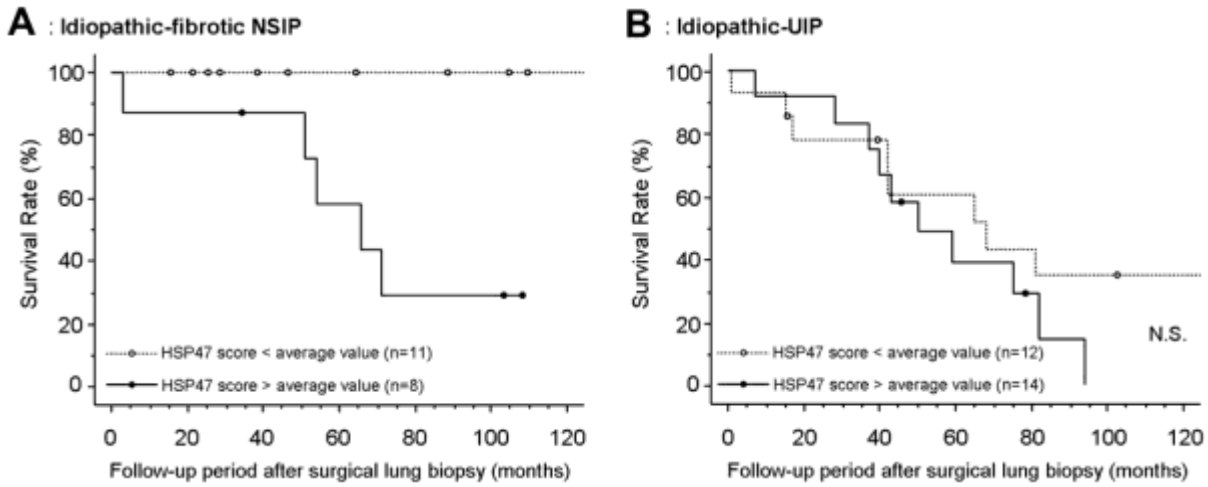


Figure 4 The survival curves of the idiopathic—fibrotic NSIP (A) and idiopathic-UIP (B) groups, divided into two subgroups based on the average fibroblast HSP47 score (1.19 and 1.36, respectively).

Amenomori, Resp Res 2010

Serum HSP47 levels are elevated in patients with AIP and AE-IPF = DAD. This finding suggests that the underlying fibrogenic mechanisms affecting HSP47 levels might differ between AIP and other IIPs.

Kakugawa, Resp Res 2014

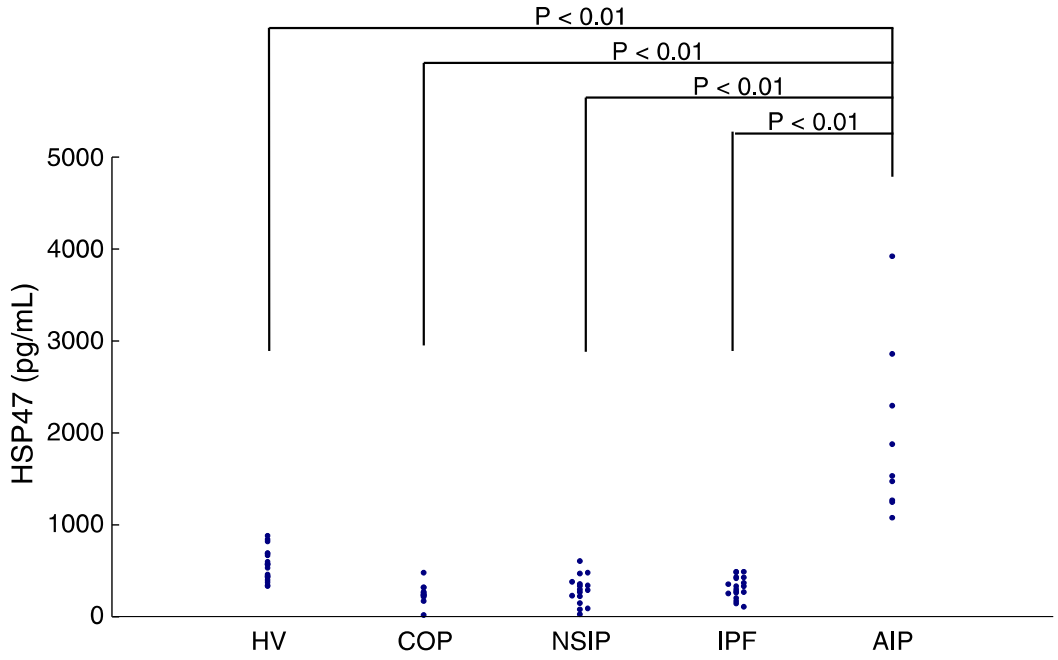


Table 2 Serum concentrations of HSP47, KL-6, SP-A, SP-D, and LDH

	Healthy volunteer (N = 19)		[n]	COP (N = 12)		[n]	NSIP (N = 16)		[n]	IPF (N = 19)		[n]	AIP (N = 9)		[n]	p value
HSP47 (pg/mL)	565.8	(332.1-879.8)	[19]	239.1	(166-476.6)	[12]	290.7	(24.8-603.0)	[16]	330.9	(105.1-487.6)	[19]	1530.2*	(1075.1-3919.9)	[9]	<0.001
KL-6 (U/mL)	193.0	(144-322)	[19]	427.5	(172-1310)	[10]	1568.5¶	(192-4745)	[14]	1460¶	(444-4340)	[15]	332.5	(201-2200)	[8]	<0.001
SP-A (ng/mL)	22.7	(12.1-60.8)	[19]	52.8	(20.6-129)	[8]	48.9	(20.3-127)	[12]	103§	(62.4-355)	[15]	138£	(43.8-148)	[6]	<0.001
SP-D (ng/mL)	17.3	(17.3-58.6)	[19]	105.7	(27.8-247)	[8]	477.0	(17.2-942)	[13]	316.0	(93.1-721)	[14]	417#	(72.1-4510)	[8]	<0.001
LDH (IU/L)	124.5	(20-246)	[19]	164.0	(132-236)	[12]	212.5#	(135-738)	[14]	233#	(113-416)	[15]	380*	(231-736)	[9]	<0.001

Data presented as median (range).

Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is a proinflammatory cytokine that can induce interferon-γ (IFN-γ), and it plays an important role in T-helper 1 responses.

Solution structure of human IL-18

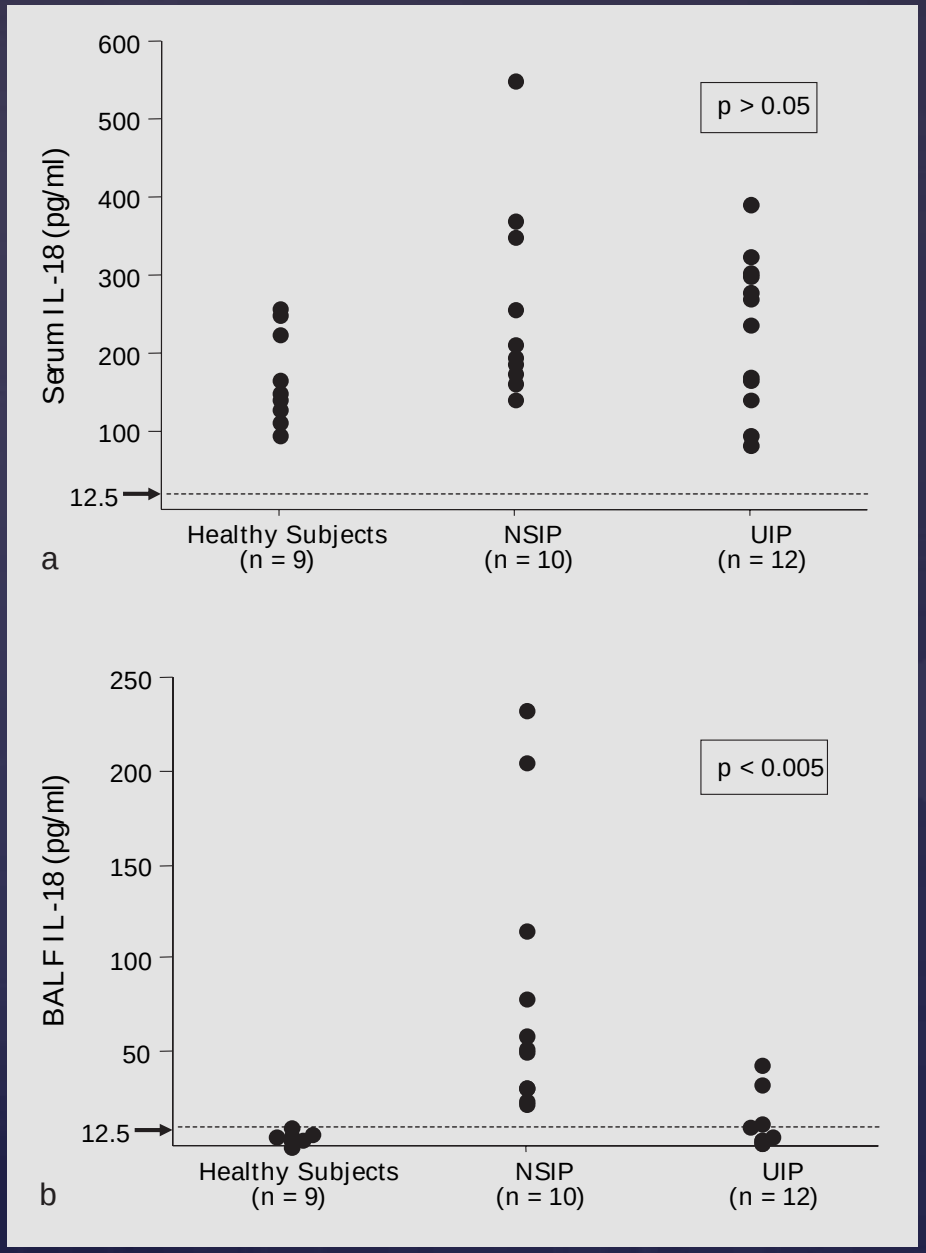
Lymphocyte proportions in BALF were significantly higher in NSIP than in UIP

Variables	n	Total cells[a] 10^5/ml	Macrophages[b] %	Neutrophils[c] %	Eosinophils %	Lymphocytes[a] %	Lymphocytes[c] 10^4/ml	CD4/CD8 ratio
Patients	22							
UIP	12	4.3 (10.6)	74.0 (13.7)	7.4 (7.5)	3.1 (5.6)	14.1 (9.5)	6.6 (4.5)	1.9 (1.5)
NSIP	10	3.1 (0.9)	58.5 (19.9)	2.5 (2.2)	2.1 (1.7)	36.6 (19.0)	11.7 (8.2)	0.7 (0.8)
Healthy subjects	9	1.3 (0.7)	86.9 (2.9)	2.1 (1.5)	1.0 (1.5)	10.0 (2.7)	1.3 (0.8)	1.3 (0.6)

Data are expressed as means (SD).

[a] p ! 0.001, [b] p ! 0.001, and [c] p ! 0.05 for the overall comparison of all three groups (one-way analysis of variance).

Ishii, Respiration 2005



The authors found increased BALF IL-18 levels in patients with NSIP in comparison with those in UIP patients ($p = 0.003$) and healthy subjects (0.002).

Ishii, Respiration 2005

Conclusion :

the level of IL-18 at a local inflammatory site may play an important role in the pathogenesis of NSIP, which reveal increased lymphocyte numbers in BALF and that elevated local production of IL-18 may reflect circulating IL-18 levels.

Ishii, Respiration 2005

The data reported by Ishii et al. suggest the potential role of IL-18 as an inflammatory marker in the pathogenetic pathway of IIPs and its different expression among them.

Since immunohistochemical studies have not been performed using tissue sections, it is unknown which cell is the source of IL-18. In addition, the expression of this proinflammatory cytokine has not been evaluated in tissue or BALF, such as its role in the balance of Th1/Th2 cytokines or in the balance of angiogenesis in IIPs.

Bouros and Antoniou, Respiration 2005

B cell immunity and iNSIP

AJSP 2000

Cellular NSIP		Fibrotic NSIP	
Organizing pneumonia	58%	Organizing pneumonia	32%
Lymphoid aggregates	**71%**	**Lymphoid aggeragtes**	**86%**
Chronic pleuritis	71%	Pleural fibrosis/pleuritis	84/64%
Bronchiolar inflammation	86%	Bronchiolar inflammation	86%
Bronchiolar fibrosis	14%	Bronchiolar fibrosis	77%

CONCLUSION -1

iNSIP pathogenetic mechanisms seems to be driven by:

1. Specific gene mutations in familial cases
2. “Autoimmune background” in a large proportion of cases*
3. Smoking and environmental exposure drive the disease in a very minority of cases

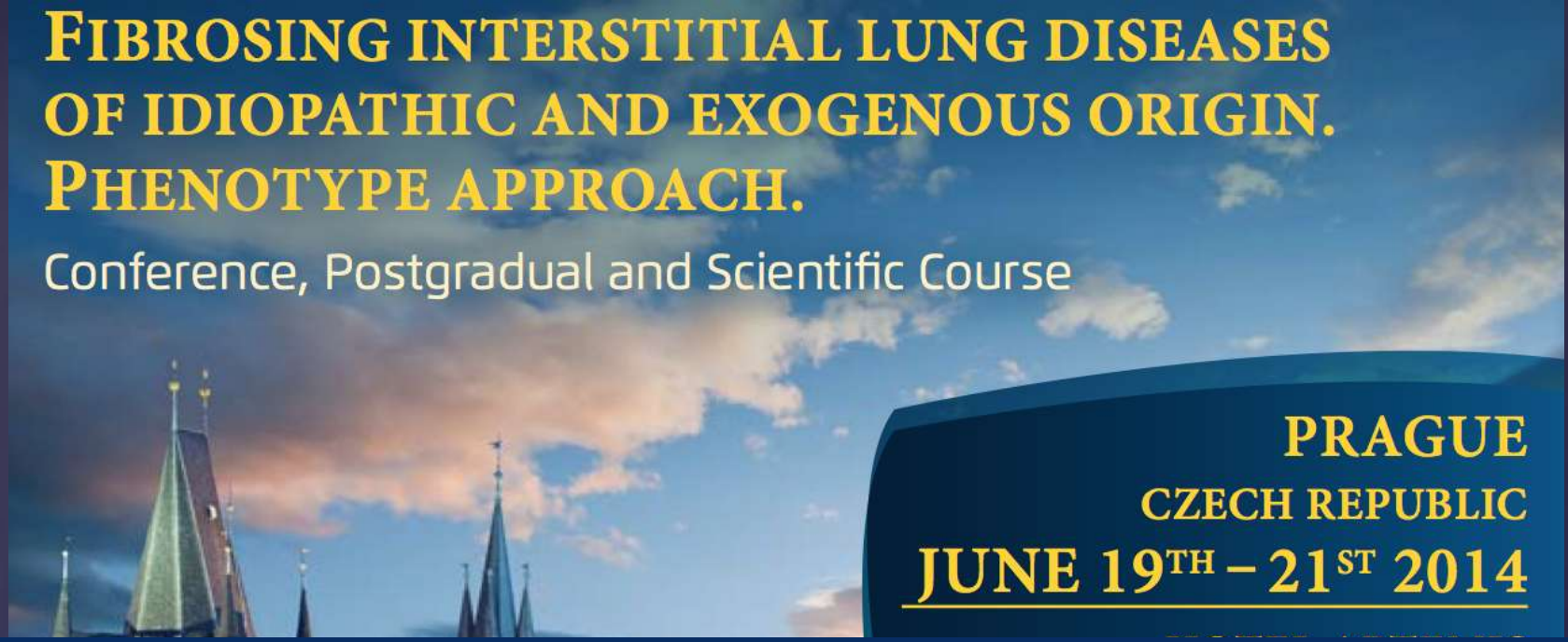
**Interstitial Pneumonitis with autoimmune features (IPAF)*

CONCLUSION 2

In all cases of iNSIP (particularly in the cellular form) a Th-1 driven inflammatory process seems to play a role and INFLAMMATORY PATHWAYS seem to be crucial in the pathobiology of this entity. B cell immunity could also have a pathogenetic role.

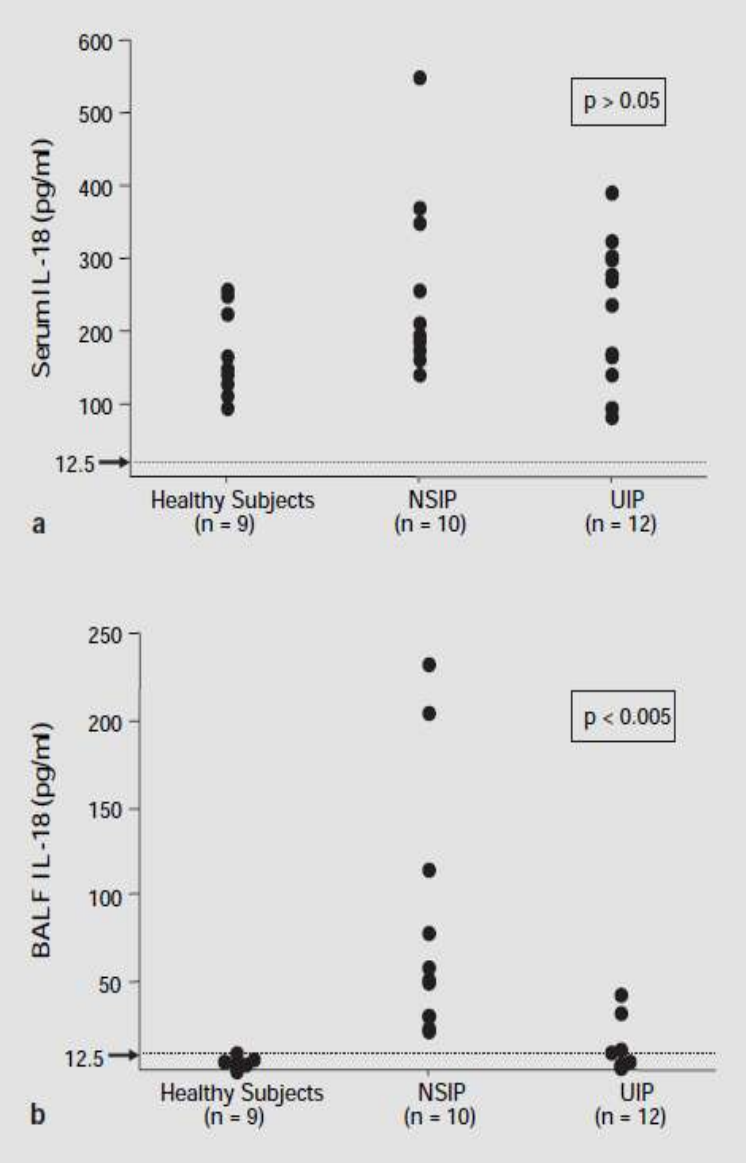
The pathogenetic profile of iNSIP seems very different form IPF

Chilosi M, et al. Transl Res 2013


FIBROSING INTERSTITIAL LUNG DISEASES
OF IDIOPATHIC AND EXOGENOUS ORIGIN.
PHENOTYPE APPROACH.
Conference, Postgradual and Scientific Course
PRAGUE
CZECH REPUBLIC
JUNE 19TH – 21ST 2014

THANK YOU

Increased levels of IL-18 in BAL fluid of patients with idiopathic NSIP

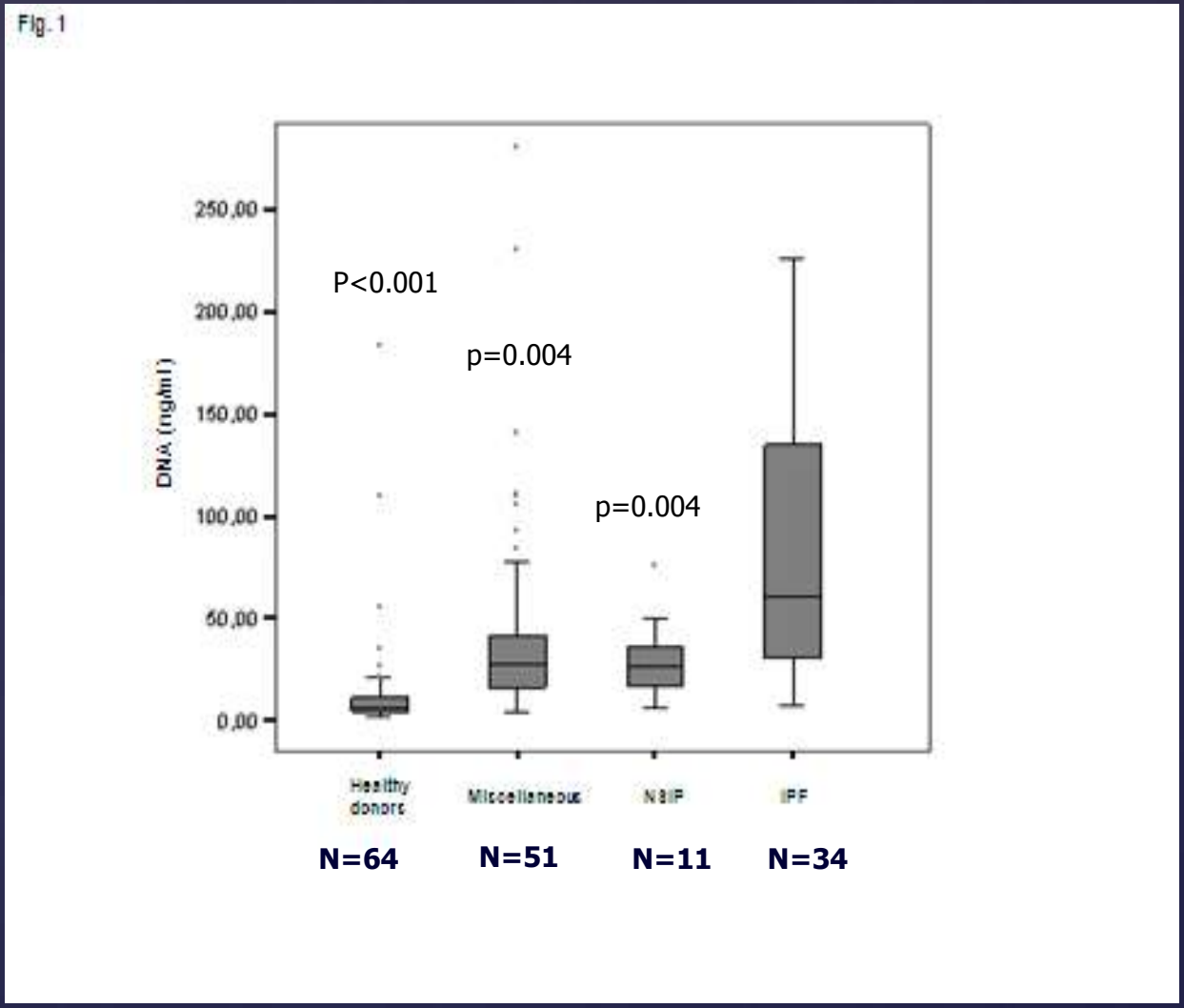


12 patients with UIP
10 with iNSIP:

- Lymphocytes in BALF were significantly higher in NSIP than in UIP
- BALF levels of IL-18 in NSIP were higher than in UIP

Ishii H et al. Respiration, 2005

Free circulating DNA levels in ILD



Casoni GL et al. Int J Biol Markers. 2010

Respiratory Medicine (2005) 99, 234–240

ELSEVIER

respiratoryMEDICINE

Idiopathic non-specific interstitial pneumonia: as an "autoimmune interstitial pneumonia"

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Forty-six patients:

-24 patients had underlying diseases

(12 polymyositis/dermatomyositis, 5 systemic sclerosis, 2 rheumatoid arthritis, 2 Sjogren's syndrome, 1 ulcerative colitis, 1 primary biliary cirrhosis, and 1 multiple myeloma).

- 22 of the 46 patients had no underlying diseases (idiopathic NSIP).

Idiopathic non-specific interstitial pneumonia: as an ''autoimmune interstitial pneumonia''

- CONCLUSIONS:
- Clinical and pathologic features of patients with idiopathic NSIP and those with CTD-associated NSIP were qualitatively similar.

Fujita J et al, Respir Med 2005

DOES NSIP EVOLVE INTO UIP?

We do not know the answer to this with certainty, but probably not. No reports have documented the progression of NSIP to UIP (or vice versa). Katzenstein and co-workers suggested that the initial injury in UIP could itself cause secondary inflammation and fibrosis that resemble NSIP, thus explaining the finding of NSIP-like areas in UIP.[12] In support of this hypothesis, they showed that areas resembling NSIP were present in the majority of UIP cases in both biopsy and explant specimens and were extensive in some.[12] In addition, no explant that showed UIP was found to show NSIP in the preceding biopsy, and the one patient with NSIP who underwent transplantation had a biopsy specimen and explant that showed similar features. In the authors' view, the observation that a cluster of patients with apparently NSIP dies at a rate that matches that of IPF is insufficient to draw this conclusion.