Title
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Journal
European Respiratory Journal, 44(3)

ISSN
0903-1936

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Publication Date
2014-09-01

DOI
10.1183/09031936.00166813

Peer reviewed

Published in final edited form as:

Eur Respir J. 2014 September ; 44(3): 594–602. doi:10.1183/09031936.00166813.

Smoking related idiopathic interstitial pneumonia: Results of an ERS/ATS Task Force

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Abstract

Background—Cigarette smoking is a key factor in the development of numerous pulmonary diseases.

Methods—An international group of clinicians, radiologists, and pathologists evaluated patients with previously identified idiopathic interstitial pneumonia (IIP) to determine unique features of cigarette smoking. Phase 1 (derivation group) identified smoking related features in patients with a history of smoking (n=41). Phase 2 (validation group) determined if these features correctly predicted the smoking status of IIP patients (n=100) to participants blinded to smoking history. Finally, investigators sought to determine if a new smoking-related interstitial lung disease phenotype could be defined.

Results—Phase 1 suggested that preserved forced vital capacity with disproportionately reduced DL_{CO}, various radiographic and histopathologic findings were smoking related features. In Phase 2 the kappa among clinicians was 0.16 (95% CI 0.11 – 0.21), among the pathologists 0.36 (95% CI 0.32 – 0.34) and among the radiologists 0.43 (95% CI 0.35 – 0.52) for smoking related features. Eight of the 100 cases were felt to represent a potential smoking related interstitial lung disease.

Conclusion—Smoking related features of interstitial lung disease were identified in a minority of smokers and are not specific for smoking. This study is limited by its retrospective design and the potential for recall bias of smoking history and lack of information on second had smoke exposure. Further research is needed to understand the relationship between smoking and interstitial lung disease.

Keywords

computed tomography; histopathology; interstitial lung disease; smoking

INTRODUCTION

Cigarette smoking is the leading cause of chronic obstructive pulmonary disease in developed countries [1]. Smoking is also associated with diffuse parenchymal lung diseases such as respiratory bronchiolitis interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), idiopathic pulmonary fibrosis (IPF) and pulmonary Langerhans' cell histiocytosis (PLCH) [2–6]. Growing interest has developed around the idea that there may be a smoking-related interstitial lung disease phenotype. In particular, combined lower lobe

pulmonary fibrosis and upper lobe emphysema (CPFE) has been reemphasized as a distinct entity [7–17] and smoking-related interstitial fibrosis may be associated with a specific histopathological pattern [18, 19].

This study was performed by an international group of pulmonary physicians, radiologists, and pathologists who retrospectively evaluated the clinical history, radiographic and histopathologic materials from patients initially presenting with suspected idiopathic interstitial pneumonias. An initial derivation phase sought to identify smoking related features from patients with a history of smoking. A second validation phase sought to determine if investigators could utilize these features to correctly predict the smoking status of patients (when the smoking history was withheld) and thus provide at least indirect evidence that unique smoking related features are present in patients with idiopathic interstitial pneumonia. Finally, investigators sought to determine if a new smoking-related interstitial lung disease phenotype (S-ILD) could be defined. This study is limited by its retrospective design and the potential for recall bias of smoking history and lack of information on second had smoke exposure.

METHODS

Organization of the Expert panel

The primary goal of this project was to define the clinical, radiologic, and pathologic features of smoking-related interstitial pneumonia based on a pooled dataset of cases with clinical, high-resolution chest computed tomography (HRCT), and surgical lung biopsy (SLB) data. To develop a broad consensus on this complicated topic, an international panel of expert clinicians, radiologists and pathologists was organized (from Canada, Germany, Italy, Japan, Korea, Mexico, United Kingdom and the United States). This project was organized in two phases. Phase 1 consisted of initial review of selected cases with a history of smoking to determine a consensus for specific smoking–related features. In Phase 2 we employed the criteria developed in phase I to determine if the criteria allowed for the identification of cases with a history of smoking. Not all experts participated in both phases (see below). This project was sponsored by the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Korean Academy of Tuberculosis and Respiratory Diseases. Institutional review board approval was granted to review the case material for this study.

Collection of the Cases and Data reviewed

A total of 141 cases of IIP were reviewed during the course of this study. This project was organized in two phases. The Phase 1 derivation stage consisted of initial review of selected cases (n = 41) with a history of smoking to determine a consensus for specific smoking–related features. In Phase 2 validation stage (n = 100) we employed the criteria developed in phase I to determine if the criteria allowed for the identification of cases with a history of smoking. For purposes of this study a smoker was considered as any subject with any history of smoking. Former smokers were subjects that had a history of smoking but had quit prior to surgical lung biopsy. Not all experts participated in both phases (see below).

In each phase of the study available clinical data included age, presence and duration of symptoms (cough, dyspnea, fever, weight loss, myalgias, arthritis, rash, Raynaud's), physical exam findings (crackles, clubbing, other), occupational/hobby exposures, pulmonary function, arterial blood gas, and serological test results. A high resolution computed tomography (HRCT) study within six months of a surgical lung biopsy was available in all patients.

Phase 1 - derivation group

Forty-one cases of idiopathic interstitial pneumonia (IIP) with a known positive smoking history were selected by investigators from the United States, Great Britain, Mexico, and Korea. The groups initially worked independently with clinicians (n=8) reviewing clinical data and HRCTs, radiologists (n=3) reviewing HRCTs, and pathologists (n=6) reviewing histopathology. Clinicians initially recorded diagnostic impressions for each case as well as comments about the clinical and HRCT features present and the possibility of certain features being attributable to smoking. Radiologists and pathologists used a score sheet to note the presence/absence of pre-specified features as well as a graded impression of relatedness to smoking. Radiologists scored the presence/absence of honeycombing, reticular thickening, cysts, nodules, ground glass, consolidation, emphysema, mosaic attenuation, disease distribution, other features as well as the overall diagnostic impression. Pathologists scored the presence/absence of emphysema, emphysema-like airspace enlargement with fibrosis, acellular hyaline fibrosis of alveolar walls, pigmented macrophages, respiratory bronchiolitis, desquamative interstitial pneumonia-like foci, bronchiolocentric stellate scarring, other features as well as overall diagnostic impression. Radiologists utilized a three tier system (0 – none, 1 – mild, 2 – definite related to smoking) while pathologists used a 5 tiered system (1 – definite, 2 – probable, 3 – possible, 4 – definitely not, 5 – don't know if related to smoking).

Phase 2 – validation group

In the second phase of this study, five expert clinicians, three thoracic radiologists, and five pulmonary pathologists individually reviewed 100 cases of IIP (48 never smokers, 52 former/current smokers) to determine the diagnosis, smoking status, and contribution of smoking changes (if any) to the primary pathologic process. We also attempted to determine if a unique S-ILD existed and could be culled from the current IIP classifications. Some, but not all, physicians had participated in phase 1 of the study. All physicians were blinded to the smoking history of the patients. Cases were selected from Great Britain, Germany, Korea, Japan, Mexico, and the United States. Each individual classified features present and utilized the presence or absence of features to predict the patients' smoking status.

Following individual review, all physicians collectively reviewed the 100 cases and determined if any met the predefined criteria from Phase 1 for S-ILD. A consensus diagnosis of "S-ILD", "ILD in a Smoker" or "ILD in Non-Smoker" was assigned to each case. Assignment to each group was made by general consensus using features in Table 2; a specific definition of each group was not specified. A subject was considered to be a probable smoker if the majority of clinicians (3 of 5), radiologists (2 of 3), or pathologists (3 of 5) classified that subject as a smoker.

Statistical Analysis

Descriptive statistics were used to characterize the demographic characteristics for subjects in phase 1 and 2. Differences between groups were tested with student's t test and chi^2 statistics. Kappa coefficients of inter-rater agreement were determined for each type of physician (n=500 observations each for the clinicians and pathologists, and 300 observations for the radiologists). Data are expressed as mean ± SD or frequency (percent). Tests were significant when $p<0.05$. Statistical analysis was performed with SPSS 14.0 (Chicago, Il, USA) and SAS 9.1 (Cary, NC, USA) software packages.

RESULTS

A total of 141 cases of IIP were reviewed during the course of this study. Forty-one subjects were evaluated in the Phase 1 definition stage and 100 subjects in the Phase 2 validation stage.

Phase 1

Demographic characteristics of the cases are shown in Table 1. All of the cases had a history of smoking. There were no differences in age, gender, or clinical features between the former and current smokers. Lung function was also similar between the two groups; however, former smokers had a lower diffusion capacity for carbon monoxide (DL_{CO}) % predicted compared to current smokers. Pathologic patterns included usual interstitial pneumonia (UIP; n=10), NSIP (n=11), RBILD/DIP (n=14), cryptogenic organizing pneumonia (COP; n=4), and non-classifiable (n=3).

Clinical, radiographic, and histopathologic features that were felt by consensus discussion during case review to be attributable to smoking and thus representative of a S-ILD phenotype were identified (Table 2). These included preserved pulmonary mechanics with disproportionately reduced DL_{CO}, radiographic evidence of emphysema, centrilobular nodules, cysts in ground glass opacity (Figure 1A–B) and histopathologic features of emphysema, emphysema-like airspace enlargement, respiratory bronchiolitis, DIP-like foci, and bronchiolocentric stellate scars, i.e. a lesion suggestive of healed PLCH lesions (Figure 2A–C).

Phase 2

Demographic and known clinical characteristics of the patients (n = 100; 48 never smokers and 52 ever smokers) are outlined in Table 3. Never smokers were younger, more likely to be female, and had lower forced vital capacity (FVC) % predicted than current or former smokers. Pathologic patterns included UIP (n=44), NSIP (n=21), RBILD/DIP (n=18), hypersensitivity pneumonia (n=5), end-stage lung (n=4), acute lung injury (n=1), COP (n=1), and pulmonary venous occlusive disease (n=1). A consensus pathologic pattern was not reached in 4 cases.

The ability of participants to agree on the presence of smoking-related features determined from Phase 1 (Table 2) was fair to moderate as assessed by the kappa coefficient. The kappa among clinicians was 0.16 (95% CI 0.11 – 0.21), among the pathologists 0.36 (95% CI 0.32

– 0.34) and among the radiologists 0.43 (95% CI 0.35 – 0.52). Furthermore, the overall ability of participants to correctly classify subjects as smokers/non-smokers utilizing features from Phase 1 was poor (Table 4).

All members of the panels met collectively to review the 100 cases analyzed in Phase 2 and determined if any met predefined criteria from Phase 1 for S-ILD (Table 5). Eight of the 100 cases were felt to represent a potential S-ILD, thirteen cases were deemed ILD in smokers (patients with clinical, radiographic, and/or histopathologic evidence of smoking) and 79 cases were not otherwise reclassified (Table 5). Cases reclassified as a potential S-ILD were predominantly of British origin and all had a numerically greater pack year history of smoking. Interestingly, one case classified as S-ILD was a never smoker which even retrospectively was felt to represent an inaccurate history by the study group. There were no significant differences in overall symptoms. The group of subjects classified as S-ILD had more preserved FVC compared to other groups although other measures of lung function were similar (Table 5).

DISCUSSION

Smoking, either directly or through second hand smoke exposure, has been implicated in numerous pulmonary diseases including the diffuse parenchymal lung disorders. The histopathologic features attributed to cigarette smoke may exist across specific diagnostic disorders and can be seen in cases that fail to fit into currently described diagnostic patterns. Although abnormalities attributed to cigarette smoking are common, a distinct S-ILD phenotype has not been defined. This study tested the hypothesis that changes attributed to smoking can be identified in patients with suspected IIP and be used to predict a history of smoking. We also explored if a unique S-ILD phenotype could be culled from the larger group of IIPs. Data from this study document that although distinct clinical, radiological and pathological findings were felt to suggest an association between smoking and ILD, these features are diverse and nonspecific and could not be reliably used by physicians to accurately identify if cases under review truly had a history of smoking. A S-ILD phenotype may be present, however, it is found in a minority of ILD cases with documented smoking history. A S-ILD phenotype may be sufficiently uncommon (no more than 8% of IIP) that our case numbers were too small to confidently identify and characterize such a subgroup.

Features attributed to smoking in this study extend previously published descriptions of smoking related features of ILD. Clinicians in this study identified relatively preserved pulmonary mechanics with disproportionately reduced DL_{CO} as suggestive of smoking related ILD. This supports previously published data regarding the superimposition of emphysema and IPF [20–22]. Radiologists identified emphysema, centrilobular nodules, respiratory bronchiolitis, and changes suggestive of NSIP (ground glass attenuation with or without intra-pulmonary cystic areas). These findings are similar to those reported in other settings [23, 24]. Pathologists identified emphysema and emphysema-like airspace enlargement with fibrosis, respiratory bronchiolitis, DIP-like foci, and bronchiolocentric stellate scars indicative of healed PLCH lesions as suggestive of smoking related ILD [19, 23, 25]. These findings are not all-inclusive to changes that could occur with cigarette

smoking but seemed to best fit as smoking related cases when cases with and without a history of smoking were reviewed knowing a priori the smoking history.

Although several clinical, radiographic, and histopathologic features were felt to represent changes attributable to smoking, the identification of these features failed to accurately represent the true smoking history in a significant number of subjects. There was significant disagreement between the true smoking history and the assignment of smoking history by all observers. Features attributable to smoking were seen in non-smokers and patients with a history of smoking often lacked 'attributable' features of smoking. This was particularly evident in the assignment by clinicians but also applied to radiologists who used a broad spectrum of features including the presence of emphysema, interlobular septal thickening and centrilobular nodules [23]. Pathologists also used a broad range of features including the presence of emphysema, acellular hyaline fibrosis, respiratory bronchiolitis, pigmented macrophages, DIP foci, bronchiolocentric scars and the presence and distribution of fibroblastic foci [19, 23]. Two investigative groups have recently documented the frequent finding of smoking related fibrosis in patients undergoing lobectomy for presumed malignancy [18, 19, 26]. A correlation between smoking history and airspace enlargement with fibrosis was suggested by one of these groups [19] while the other group felt the findings suggested a specific smoking related pattern of fibrosis [18]. Importantly, in our group of subjects, 'smoking-related' pathological changes were identified in some non-smokers. This may relate to a common mechanism of injury and repair, as opposed to a common toxicological form of injury. For example, RB and RB-ILD are seen in smokers but DIP may be seen in smokers and non-smokers (due to drugs, infection, or other insults). In RB and RB-ILD, cigarette smoke is the common injury, whereas DIP may represent manifestations of a common injury/repair mechanism. It is also possible that changes in our non-smoking subjects that were attributed to smoking could relate to second hand smoke or pollution, factors that could not be verified in our subjects.

At consensus review of the derivation cohort only eight of the 100 cases were felt to represent a S-ILD phenotype utilizing features from phase I with an additional 13 cases showing strong evidence for smoking in addition to underlying ILD. The majority of patients in the second phase cohort had idiopathic pulmonary fibrosis as the final diagnosis. Those patients with a possible S-ILD were more likely to be from Great Britain but otherwise exhibited similar demographic, clinical and physiological features to the other patient groups. One patient classified in the S-ILD group was a non-smoker. There are numerous possibilities for these discrepancies. The first is related to the retrospective nature of the study. The possibility for misclassification of smoking status either through deception or recall bias is clearly possible. In addition, we did not have access to detailed information about second hand smoke or levels of environmental pollution so it is possible that some of our non-smoking subjects actually had significant smoke exposure. Second, the definition of S-ILD features from phase I were purposefully restrictive in hopes of being specific. We tended to identify the patients with emphysema and coexistent ILD. There is clearly the potential for other manifestations of smoking injury including patients with more restrictive or mixed obstructive/restrictive physiology, diffuse ground glass on HRCT, or overlaps between cysts/emphysema/ground glass. It is also possible that features attributed to smoking such as centrilobular nodules and respiratory bronchiolitis may be recognized in

patients without smoking related lung injury. It is well-established that similar histopathologic patterns (such as usual interstitial pneumonia, organizing pneumonia, etc.) can be seen in response to numerous types of injury or diseases and thus histopathologic patterns are rarely, if ever, specific for a disease without clinical and pathologic correlation [27]. Finally, an individual patient's response to injury is likely to be different to responses identified in a population; in large groups of smokers it is possible to identify patients with normal lung function, emphysema, and chronic bronchitis. Thus, the possibility for a differential response to injury clearly exists.

Strengths of this study include the large number of well-characterized patient samples evaluated as well as the participation of a large group of international experts with a broad range of experience. The diverse patient population is also considered a strength although different environmental factors, practice patterns (when to get pulmonary function, HRCT, or biopsy), or genetic/racial responses to injury could influence the smoking-ILD relationship. The inclusion of derivation and validation groups with blinding of the participants during the second phase also adds strengths to the observations. The lack of a prospectively assigned treatment regimen and long-term follow up are weaknesses. Another potential weakness is the study population size if a putative S-ILD is relatively rare (and would require an even larger study sample to confidently identify).

In summary, a large international cohort of clinicians, radiologists, and pathologists with expertise in interstitial lung disease retrospectively reviewed a collection of clinical, radiographic, and histopathologic data to establish if specific smoking related features of ILD and a specific S-ILD could be identified. These features were identified in a minority of heavy smokers; however, these features were absent in some patients with a history of smoking and present in some patients without a history of smoking. The finding that one of the eight patients regarded by all specialists to have S-ILD was a never smoker without passive smoke exposure suggests that other causes exist for this phenotype. Thus, smoking is strongly associated with ILD but it is difficult to distinguish S-ILD from non-smoking ILD unless the smoking history is available to the clinician. Further research is needed to better understand the clinical manifestations of smoking and interstitial lung disease as well as implications for treatment and prognosis.

Acknowledgments

Funding Sources:

This study was supported by the grants from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Korean Academy of Tuberculosis and Respiratory Diseases and the Alberta Heritage Foundation for Medical Research.

The authors gratefully thank Dr. Ken Guire, Dept of Biostatistics, School of Public Health, University of Michigan, for his assistance analyzing data for this project. In addition, the authors wish to gratefully thank Drs. Gary Hunninghake, Roland du Bois, and Andrew Flint for their aid during the data collection phase of the study.

List of Abbreviations

IIP	Idiopathic interstitial pneumonias

RB-ILD	Respiratory bronchiolitis – interstitial lung disease
DIP	Desquamative interstitial pneumonia
RB	Respiratory bronchiolitis
fNSIP	Fibrosing form of NSIP
NSIP	Non-specific interstitial pneumonia
UIP	Usual interstitial pneumonia
COP	Cryptogenic organizing pneumonia
ILD	Interstitial lung disease
HRCT	High resolution computed tomography
IPF	Idiopathic pulmonary fibrosis
S-ILD	Smoking-related interstitial lung disease, a proposed new entity
SD	Standard deviation
PLCH	Pulmonary Langerhans' cell histiocytosis
BALF	Bronchoalveolar lavage fluid
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 second
DL_{CO}	Diffusion capacity for carbon monoxide

References

1. Fromer L, Cooper C. A review of the gold guidelines for the diagnosis and treatment of patients with copd. Int J Clin Pract. 2008; 62:1219–1236. [PubMed: 18547365]
2. American Thoracic Society, European Respiratory Society. 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. [PubMed: 11790668]
3. Ryu J, Colby TV, Hartman T, Vassallo R. Smoking-related interstitial lung diseases: A concise review. Eur Respir J. 2001; 17:122–132. [PubMed: 11307741]
4. Ryu J, Myers J, Capizzi S, Douglas W, Vassallo R, Decker P. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease. Chest. 2005; 127:178–184. [PubMed: 15653981]
5. Steele MP, Speer MC, Loyd JE, Brown KK, Herron A, Slifer SH, Burch LH, Wahidi MM, Phillips JA 3rd, Sporn TA, McAdams HP, Schwarz MI, Schwartz DA. Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med. 2005; 172:1146–1152. [PubMed: 16109978]
6. Vassallo R, Ryu J. Smoking-related interstitial lung diseases. Clin Chest Med. 2012; 33:165–178. [PubMed: 22365253]
7. Cottin V, Cordier J. The syndrome of combined pulmonary fibrosis and emphysema. Chest. 2009; 136:1–2. [PubMed: 19584202]
8. Hiwatari N, Shimura S, Takishima T. Pulmonary emphysema followed by pulmonary fibrosis of undetermined cause. Respiration. 1993; 60:354–358. [PubMed: 8290801]
9. Millar A, Denison D. Verticxal gradients of lung density in supine subjects with fibrosing alveolitis or pulmonary emphysema. Thorax. 1990; 45:602–605. [PubMed: 2402722]

10. Wiggins J, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: The value of high resolution computed tomography in assessment. Respir Med. 1990; 1990:5.
11. Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, Barrientos E, Gaxiola M, Navarro C, Selman M. Idiopathic pulmonary fibrosis and emphysema: Decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009; 136:10–15. [PubMed: 19225068]
12. Oliva I, Cortopassi F, Rochester C, Rubinowitz A. Combined pulmonary fibrosis and emphysema syndrome: A radiologic perspective. Monaldi Arch Chest Dis. 2011; 75:220–234. [PubMed: 22462310]
13. Portillo K, Morera J. Combined pulmonary fibrosis and emphysema syndrome: A new phenotype within the spectrum of smoking-related interstitial lung disease. Pulm Med. 2012; 2012:867870. [PubMed: 22448331]
14. Jankowich M, Rounds S. Combined pulmonary fibrosis and emphysema syndrome: A review. Chest. 2012; 141:222–231. [PubMed: 22215830]
15. Samara K, Maragitopoulos G, Wells A, Siafakas N, Antoniou K. Smoking and pulmonary fibrosis; novel insights. Pulm Med. 2011; 2011:461439. [PubMed: 21766018]
16. Lee C, Kim H, Park C, Lim K, Lee J, Kim D, Yeon J, Hwang S, Kim D, Lee S, Yim J, Yang S, Yoo C, Chung H, Kim Y, Han S, Shim Y. The impact of combined pulmonary fibrosis and emphysema on mortality. Int J Tuberc Lung Dis. 2011; 15:1111–1116. [PubMed: 21740677]
17. Todd N, Jeudy J, Lavania S, Franks T, Galvin J, Deepak J, Britt E, Atamas S. Centrilobular emphysema combined with pulmonary fibrosis results in improved survival. Fibrogenesis Tissue Repair. 2011; 4:6. [PubMed: 21324139]
18. Katzenstein A, Mukhopadhyay S, Zanardi C, Dexter E. Clinically occult interstitial fibrosis in smokers: Classification and significane of a surprisingly common finding in lobectomy specimens. Hum Pathol. 2010; 41:316–325. [PubMed: 20004953]
19. Kawabata Y, Hoshi E, Murai K, Ikeya T, Takahashi N, Saitou Y, Kurashima K, Ubukata M, Takayanagi N, Sugita H, Kanauchi S, Colby T. Smoking-related changes in the background lung of specimens resected for lung cancer: A semiquantitative study with correlation to postoperative course. Histopathology. 2008; 53:707–714. [PubMed: 19102010]
20. Cherniack RM, Colby TV, Flint A, Thurlbeck WM, Waldron JA, Ackerson L, Schwarz MI, King TE. Correlation of structure and function in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1995; 151:1180–1188. [PubMed: 7697250]
21. Cottin V, Nunes H, Brillet P, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune K, Valeyre D, Cordier J. Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: A distinct underrecognised entity. Eur Respir J. 2005; 26:586–593. [PubMed: 16204587]
22. Doherty MJ, Pearson MG, O'Grady EA, Pellegrini V, Calverley PM. Cryptogenic fibrosing alveolitis with preserved lung volumes. Thorax. 1997; 52:998–1002. [PubMed: 9487350]
23. Attili A, Kazerooni E, Gross B, Flaherty K, Myers J, Martinez F. Smoking-related interstitial lung disease: Radiologic-clinical-pathologic correlation. RadioGraphics. 2008; 28:1383–1398. [PubMed: 18794314]
24. Lederer D, Enright P, Kawut S, Hoffman E, Hunninghake G, van Beek E, Austin JHM, Jiang R, Lovasi G, Barr R. Cigarette smoking is associated with sublinical parenchymal lung disease. The multi-ethnic study of atherosclerosis (mesa)-lung study. Am J Respir Crit Care Med. 2009; 180:407–414. [PubMed: 19542480]
25. Vassallo R, Ryu J. Tobacco smoke-related diffuse lung diseases. Sem Respir Crit Care Med. 2008; 29:643–650.
26. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: A proposal. Mod Pathol. 2006; 19:1474–1479. [PubMed: 16951670]
27. Maher T, Wells A, Laurent G. Idiopathic pulmonary fibrosis: Multiple causes and multiple mechanisms? Eur Respir J. 2007; 30:835–839. [PubMed: 17978154]

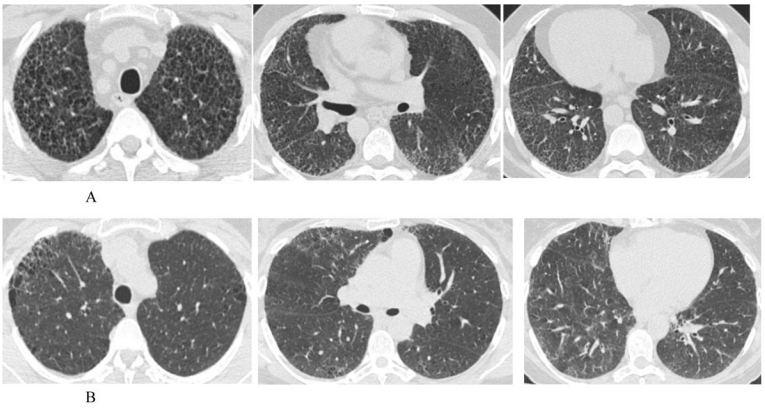

Figure 1. HRCT images of patients classified as S-ILD

A: Case BR-8 showing emphysema and reticulation;

B: Case BR-11 showing cysts in areas of ground glass opacification.

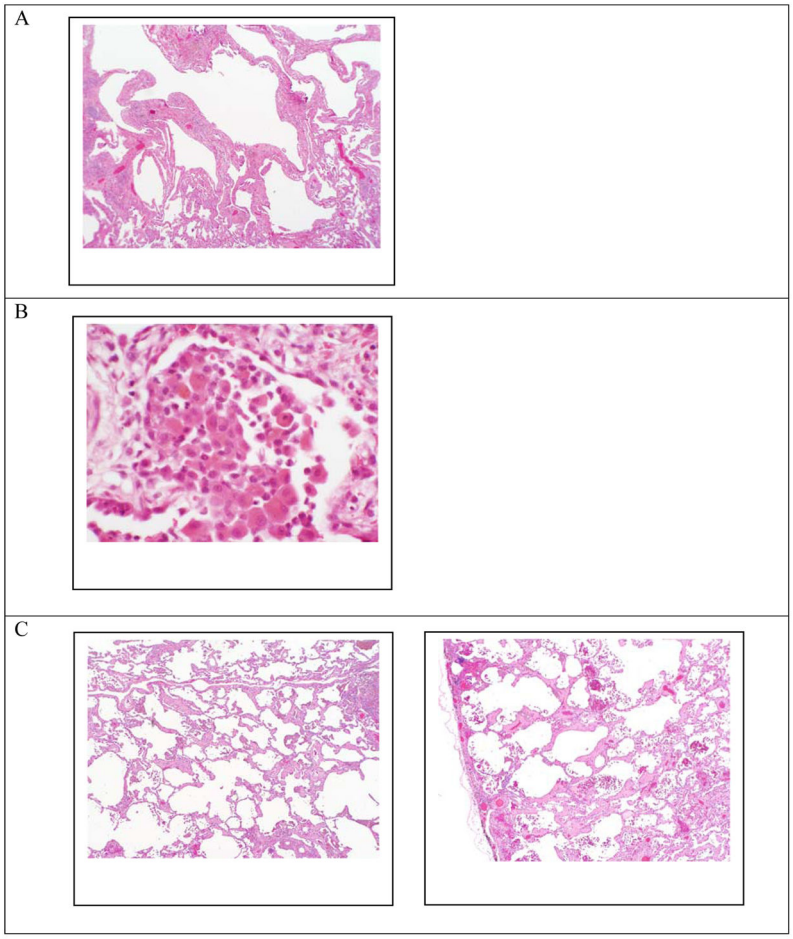

Figure 2. Histopathologic features associated with smoking in patients with ILD

A. Fibrosis and emphysema in a patient with UIP.

B. RB-ILD changes in a patient with NSIP.

C. Respiratory bronchiolitis vs. NSIP in a smoker

Table 1

Demographic and physiologic data from 41 cases of smokers with idiopathic interstitial pneumonia from Phase I (Derivation).

	Former Smokers (n=14)	Current Smokers (n=27)	p value
Age (years)	55.1 ± 8.7	52.7 ± 11.2	0.49
Gender (Men/Women)	11/3	20/7	0.23
Pack-years of smoking	34.5 ± 24.59	38.4 ± 19.3	0.59
Clinical History			
Cough (Yes/No)	13/1	24/2	0.96
Duration of cough (months)	18.5 ± 18.3	12.4 ± 16.7	0.30
Dyspnea (Yes/No)	14/0	26/1	0.75
Duration of dyspnea (months)	18.9 ± 17.0	13.1 ± 17.2	0.31
Pulmonary Function			
FVC % predicted	71.7 ± 22.6	77.0 ± 19.3	0.44
FEV_1 % predicted	76.4 ± 18.2	75.5 ± 18.8	0.89
FEV_1/FVC	81.3 ± 8.9	77.1 ± 12.5	0.28
DLCO % predicted	46.1 ± 18.1	57.0 ± 12.5	0.03

Continuous variables compared with student's t test; categorical variables with Chi^2 test.

Abbreviations: FVC=forced vital capacity; FEV_1=forced vital capacity in one second; DL_{CO}=diffusion capacity for carbon monoxide.

Table 2

Clinical, radiographic, and histopathologic features attributed to smoking in patients with idiopathic interstitial pneumonia.

Clinical Features
Preserved pulmonary function with decreased gas transfer
HRCT Features
Emphysema
Centrilobular nodules
Cysts in areas of ground glass opacity
Histopathologic Features
Emphysema
Emphysema-like airspace enlargement with fibrosis
Respiratory bronchiolitis
DIP-like foci
Bronchiolocentric stellate scars (± smooth muscle) (simulating healed Pulmonary Langerhans' cell histiocytosis)

Table 3

Demographic and physiologic data for 100 cases of idiopathic interstitial pneumonia presented in phase II (Validation).

	Never Smokers (n = 48)	Current/Former Smokers (n = 52)	p value
Age	53.0 ± 10.7	55.6 ± 12.2	0.259
Gender (Men/Women/NA)	(18/27/3)	(33/18/1)	0.013
Pack-Years of smoking	0	31.4 ± 32.8	<0.005
Clinical History			
Cough (Yes/No/NA)	38/6/4	37/14/1	0.100
Duration of cough (months)	28.2 ± 42.3	22.4 ± 27.0	0.479
Dyspnea (Yes/No)	46/2	47/5	0.286
Duration of dyspnea (months)	21.2 ± 35.3	27.2 ± 31.2	0.399
Pulmonary Function:			
FVC % predicted	61.9± 15.9	70.5 ± 21.9	0.028
FEV_1 % predicted	68.5 ± 16.3	74.7 ± 21.3	0.106
FEV_1/FVC	96.7 ± 16.4	89.6 ± 17.2	0.043
TLC %predicted	67.0±14.148.9 ±	75.8±17.6	0.01
DL_{CO} % predicted	18.2	50.4 ± 19.8	0.711

Abbreviations: NA=not available; FVC=forced vital capacity; FEV_1=forced vital capacity in one second; DL_{CO}=diffusion capacity for carbon monoxide.

Table 4

Classification of patients with idiopathic interstitial pneumonia as ever smokers and never smokers stratified by actual history of smoking.

	Never Smokers (n = 48)	
	No Smoke	**Yes Smoke**
Clinicians	27	21
Radiologists	40	8
Pathologists	37	11

	Current Smokers (n = 20)	
	No Smoke	**Yes Smoke**
Clinicians	6	14
Radiologists	6	14
Pathologists	5	15

	Former Smokers (n = 32)	
	No Smoke	**Yes Smoke**
Clinicians	11	21
Radiologists	21	11
Pathologists	14	18

p = 0.008 (Chi-square)

p = 0.92 (Chi-square)

p = 0.037 (Chi-square)

Table 5

Demographic and clinical features of cases labeled by study participants as smoking related interstitial lung disease (S-ILD), interstitial lung disease in a smoker, or other.

	S-ILD (n=8)	ILD in Smokers (n=13)	Others (n=79)	P value
Age	47.00 ± 5.00	54.64 ± 10.93	54.98 ± 11.82	0.211
Gender (Men/Women/NA)	4/3/1	5/8	42/34	0.520
Smoking History				0.103
Never	1	6	41	
Former/current	7	7	38	
Pack years	34.17 ± 29.90	17.83 ± 22.69	13.73 ± 28.19	0.215
Clinical History				0.642
Cough (Yes/No/NA)	5/1/2	9/4/0	61/15/3	
Cough duration (month)	16.2 ± 11.14	31.00 ± 41.53	24.80 ± 35.88	0.737
Dyspnea (Yes/No)	8/0	13/0	72/7	0.368
Dyspnea duration (months)	20.62 ± 16.31	31.08 ± 39.46	23.48 ± 33.76	0.732
Pulmonary Function:				
FVC % predicted	81.90 ± 19.09	69.38 ± 9.05	64.33 ± 20.38	0.045
FEV_1 % predicted	79.75 ± 18.28	77.38 ± 10.94	69.90 ± 20.15	0.202
FEV_1/FVC	74.50 ± 9.93	93.50 ± 14.50	94.33 ± 17.17	0.02
TLC % predicted	91.17±10.98	74.92±10.59	68.9±16.67	0.0039
DL_{CO} % predicted	48.87 ± 13.72	46.08 ± 19.28	50.39 ± 19.47	0.750

Abbreviations: S-ILD: smoking related ILD, a proposed new entity; ILD=interstitial lung disease; NA=not available; FVC=forced vital capacity; FEV_1=forced vital capacity in one second; DL_{CO}=diffusion capacity for carbon monoxide.