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Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course

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Aims: To assess the pathological findings in lobectomy specimens, to correlate them with smoking history and postoperative course and to compare the findings with those in smoking-related interstitial lung disease.

Methods and results: Patients who had undergone lobectomy for lung cancer were reviewed. Subjects included 230 non-smokers and 587 smokers, of whom 572 had a known smoking index (SI). They were classified into mild, moderate and heavy smokers. Centrilobular emphysema (CLE), respiratory bronchiolitis, airspace enlargement with fibrosis (AEF), the presence of foci resembling usual interstitial pneumonia pattern (UIP/P) and the rate of postoperative respiratory failure were assessed. The incidence of AEF was 6.5% in mild smokers, and 17.7% in moderate smokers ($P < 0.01$) with lower lobe predominance. There were significant correlations ($P < 0.01$) between AEF and CLE and AEF and UIP/P. The rate of respiratory failure after lobectomy was 6%, and 10% in patients having UIP/P with or without AEF, but was not seen in patients with AEF alone ($P < 0.01$).

Conclusions: AEF is an important smoking-related change in the lung that appears to correlate with the smoking history, and its distinction from UIP/P may be important.

Keywords: lung, smoking, smoking-related interstitial lung disease, usual interstitial pneumonia pattern

Abbreviations: AEF, airspace enlargement with fibrosis; CLE, centrilobular emphysema; DIP, desquamative interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SI, smoking index; SR-ILD, smoking-related interstitial lung disease; UIP, usual interstitial pneumonia; UIP/P, UIP pattern

Introduction

Smoking is best known for causing chronic obstructive lung disease[1–3] and lung cancer.[4,5] It has also been associated with the development of interstitial lung disease; respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) was first described in 1986[6] with a subsequent report in 1989.[7] The frequent association of pulmonary Langerhans cell histiocytosis (PLCH) and desquamative interstitial pneumonia (DIP) with cigarette smoking has been known for years.[7,8] The concept of smoking-related interstitial lung disease

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(SR-ILD), including DIP, RB-ILD, and PLCH or combinations thereof, has been proposed.[9,10] Yousem recently described RB-ILD with fibrosis[11] and postulated that this was a smoking-related condition distinct from fibrotic non-specific interstitial pneumonia.[12,13] Some of the illustrations in the Yousem study appear to show airspace enlargement with fibrosis (AEF – see below).

In the current study, we assessed a large number of resected specimens of lung cancer to determine which histological changes are more frequent in smokers and if these correlate with histological features seen in clinical situations included under the heading of SR-ILD; i.e. could these be subclinical histological precursors of clinically manifest interstitial lung disease? We looked specifically for foci of AEF as well as the presence of regions of fibrosis similar to (but not always as extensive as) those seen in classical usual interstitial pneumonia (UIP)[13]and we have labelled these UIP pattern (UIP/P) fibrosis.[14–17]

Materials and methods

Histopathologic material from patients who had undergone lobectomy or pneumonectomy for lung cancer from April 1996 to December 2004 was reviewed. Those with central obstructing cancer or previously known pneumoconiosis were excluded. Clinical data including background diseases and smoking index (SI) were obtained from the patients' medical records. It could not be determined whether non-smokers were passively exposed to cigarette smoke or were concealing a history of smoking. All lungs were inflated intrabronchially with 20% formalin. On macroscopic examination, one of the authors (Y.K.) evaluated the presence and degree of centrilobular emphysema (CLE)[18,19] as 1+ (<10% of the cut surface), 2+ (10–30% of the cut surface) or 3+ (>30% of the cut surface). UIP/P was similarly assessed macroscopically as 1 + 10 mm thickness of subpleural fibrosis with honeycombing, Figure 1A) or 2+ (>10 mm in thickness, Figure 1B). Cases were scored according to the highest grade lesions identified. Y.K. also checked for

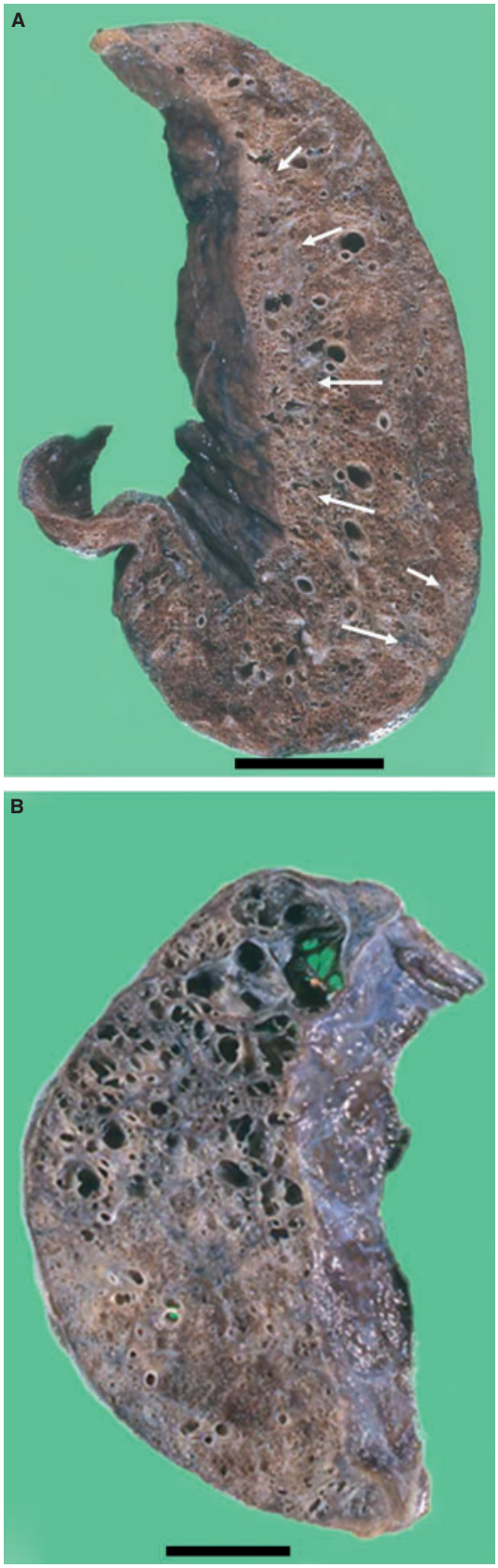

Figure 1. Macroscopic feature of usual interstitial pneumonia pattern (UIP/P) (bar 20 mm) **A,** Grade 1 UIP/P Zonal peripleural grey-coloured fibrosis of <10 mm depth seen in the basal area of the lower lobe with traction bronchioloectasis and tiny cysts in the fibrosis (areas of arrow) **B,** Grade 2 UIP/P Grey-coloured fibrosis and many thick-walled fibrous cysts (honeycombing) of >10 mm in depth seen in the lower lobe Histologically, both were confirmed to be UIP/P with dense fibrosis having structural remodelling and attachment of fibroblastic foci adjacent to the normal lung.

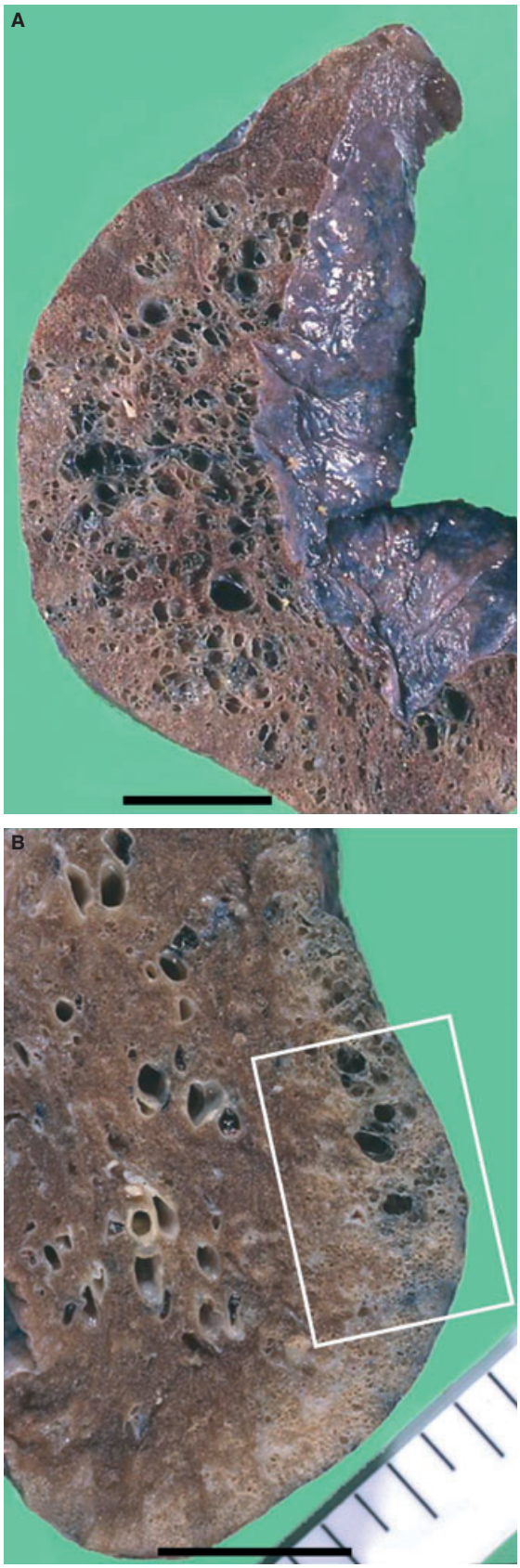

Figure 2. Macroscopic features of airspace enlargement with fibrosis (AEF) (bar 20 mm) **A,** Grade 2 AEF of thin-walled cysts Various sized thin-walled cysts seen slightly apart from pleura in the basal areas of the lower lobe **B,** Grade 2 AEF of mixtures of reticular lesion and thin-walled cysts Zonal reticular lesion and thin-walled cysts of about 10 mm in depth seen subpleurally in the lower lobe Box area is shown in Figure 4.

the presence of AEF grossly, seen as variously sized, thin-walled cysts (thinner than that of honeycombing, Figure 2A), reticular lesions or mixtures of both (Figure 2B), and graded the findings in a similar way to those of CLE. Lesions difficult to differentiate macroscopically between UIP/P and AEF were finally scored by microscopic examination.

Histological sections were prepared of the lung cancer itself, of grossly normal areas, and of the above lesions seen macroscopically; between five and 10 slides excluding those taken of the tumour were evaluated (mean 7.3). Haematoxylin and eosin and elastic-Van Gieson staining was used for histological evaluation. The following histological features were evaluated and scored together with confirmation of macroscopic diagnosis: CLE, RB and UIP/P. AEF was characterized as: (i) fibrous (frequently hyalinized) interstitium with structural remodelling; (ii) emphysematous change; (iii) frequent bronchiolocentric location; and (iv) absence of fibroblast foci (Figures 3 and 4). When there was a discrepancy between macroscopic diagnosis and histological diagnosis, the final diagnosis was based on histological findings. The score of the above histological features for the various clinical groups was calculated as follows: grade 1 × case no. + grade 2 × case no. + grade 3 × case no. ÷ total number of cases (e.g. 30 cases had grade 1 lesion, seven had grade 2 lesion and two cases had grade 3 lesion among 170 cases, then $30 + 7 \times 2 + 2 \times 3/170 = 0.29$). Two pathologists (Y.K. and T.V.C.) blindly evaluated slides (selected by Y.K.) of 18 cases showing UIP/P, 14 cases showing RB, 25 cases suspected of showing AEF alone, and 19 cases suspected of showing AEF and UIP/P. Discrepancies of interpretation between the two pathologists (three cases of suspected AEF alone and one case of suspected AEF and UIP/P) were excluded from the study.

Comparisons were made between non-smokers, mild, moderate and heavy smokers. In smokers, comparisons were also made between upper lobes and lower lobes. In smokers the interrelationships of CLE, AEF, RB and UIP/P were examined.

Statistical analysis was carried out by either χ^2 or Student's *t*-test. Non-smokers and mild smokers were not compared because of the significant sex differences.

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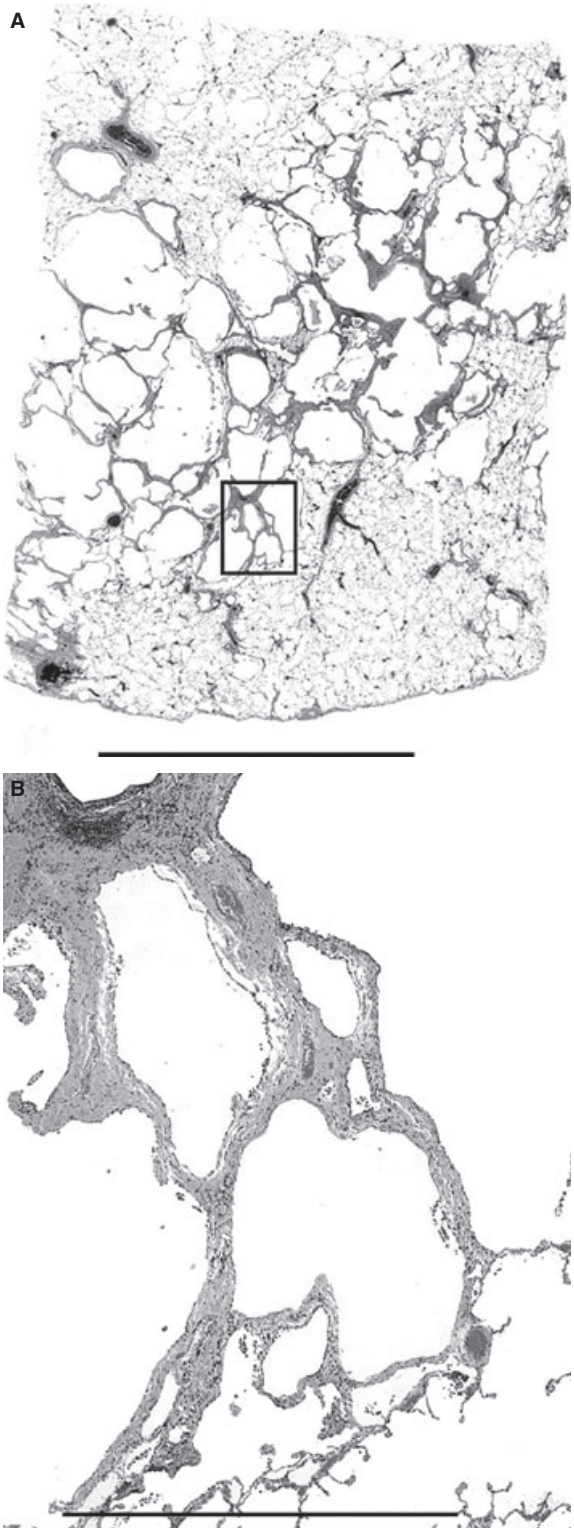

Figure 3. Histological features of airspace enlargement with fibrosis (AEF) (next slice of Figure 2A) **A,** Panoramatic view showing various sized cystic spaces in the lung slightly apart from pleura (bar 10 mm) (H&E) **B,** Low magnification showing fibrous wall of cysts (box of Figure 3A) (bar 015 cm, H&E).

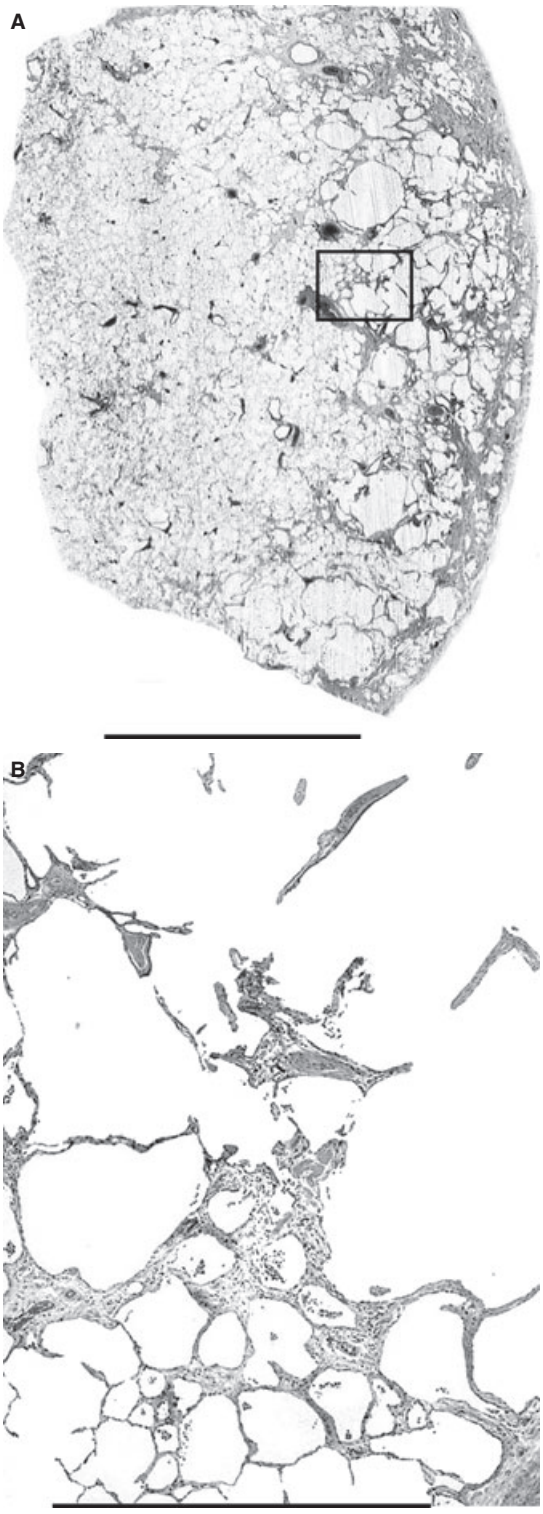

Figure 4. Histological features of airspace enlargement with fibrosis (AEF) (box of Figure 2B) **A,** Panoramatic view showing subpleural net-like fibrous interstitium without subpleural dense fibrosis (bar 10 mm, H&E) **B,** Low magnification showing peripheral area of Figure 4A (box) with mild fibrous interstitium and emphysematous change (bar 015 cm, H&E).

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The study was approved by the Ethics Committee of the Saitama Cardiovascular Respiratory Centre.

Results

Prior to surgery, 49 patients had a preoperative diagnosis of idiopathic pulmonary fibrosis (IPF). Of these patients, 48 had grade 2 UIP/P and one had grade I UIP/P on an upper lobe lobectomy specimen, one had UIP-type asbestosis (by the Helsinki criteria[20]), one had UIP associated with rheumatoid arthritis and one had DIP (on previous surgical lung biopsy). There were no cases of RB-ILD or PLCH. Lung function test results of smokers were as follows: vital capacity varied from 55% to 141% (mean 89%) and forced expiratory volume in 1 s varied from 41% to 99% (mean 70%). The clinical findings and demographics are included in Tables 1–4.

The incidence and degree of CLE, AEF, RB and UIP/P correlated with SI are shown in Table 1. For non-smokers the incidence of CLE was 9.5%, AEF 0.4%, RB 2% and UIP/P 3.5%. Among smokers the incidence and degree of CLE were 39.6% and 0.44 in mild smokers, and 57% and 0.68 in moderate smokers, respectively. Both of these differences were significant ($P < 0.01$).

The incidence and degree of AEF were 6.5% and 0.065 in mild smokers, 17.7% and 0.25 in moderate smokers, respectively, and these two findings were significantly different ($P < 0.01$). The incidence of RB was 9% in mild smokers and 33% in moderate smokers, and this difference was significant ($P < 0.01$). The degree of UIP/P was 0.2 in mild smokers and 0.34 in moderate smokers and this difference was statistically significant ($P < 0.05$).

There were no differences between moderate smokers and heavy smokers in any of the analyses.

On comparing findings in the upper lobes (either upper lobectomy or combined upper and middle lobectomies) with the lower lobes (lower lobectomy or combined lower lobe and middle lobectomies) among smokers, there was no difference in sex, age or SI

Table 1. Incidence and degree of CLE, AEF, RB and UIP/P related to SI by χ^2 test and Student's *t*-test

SI	Non-smokers	Mild smokers ≤25	Moderate smokers <25–≤50	Heavy smokers >50	Statistics
No (M:W)	230 (32:198)	91 (71:20)	254 (230:24)	227 (217:10)	
Age, M ± SD	64 ± 11	65 ± 13	66 ± 85	67 ± 85	
CLE					
Frequency	9.5%	39.6%	57%	60.8%	$P < 0.01$ between mild smokers and moderate smokers in both frequency and degree
Degree	0.05	0.44	0.68	0.81	
AEF					
Frequency	0.4%	6.5%	17.7%	21.1%	$P < 0.01$ between mild smokers and moderate smokers in both frequency and degree
Degree	0.004	0.065	0.25	0.25	
RB					
Frequency	2%	9%	33%	34%	$P < 0.01$ between mild smokers and moderate smokers in both frequency and degree
UIP/P					
Frequency	3.5%	15.4%	23.6%	22.4%	$P < 0.05$ between mild smokers and moderate smokers in degree
Degree	0.04	0.20	0.34	0.30	

SI, Smoking index; M, men; W, women; M ± SD, mean ± standard deviation; CLE, centrilobular emphysema; AEF, airspace enlargement with fibrosis; RB, respiratory bronchiolitis; UIP/P, usual interstitial pneumonia pattern.

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Table 2. Comparison between ULL and LLL among smokers (excluding MLL and pneumonectomy) by χ^2 test and Student's *t*-test

	ULL	LLL	Statistics
No (M:W)	282 (255:27)	231 (205:26)	
Age M ± SD	65 ± 10.1	67 ± 8.2	
CLE			
Frequency	7%	44%	$P < 0.01$ between ULL and LLL in both frequency and degree
Degree	0.86 ± 0.72	0.52 ± 0.65	
AEF			
Frequency	9%	28%	$P < 0.01$ between ULL and LLL in both frequency and degree
Degree	0.1 ± 0.34	0.37 ± 0.65	
UIP/P			
Frequency	9%	37.7%	$P < 0.01$ between ULL and LLL in both frequency and degree
Degree	0.1 ± 0.35	0.57 ± 0.79	

ULL, Upper lobe lobectomy or combined upper lobe and middle lobe lobectomies; LLL, lower lobe lobectomy or combined lower lobe and middle lobe lobectomies; MLL, middle lobe lobectomy; CLE, centrilobular emphysema; AEF, airspace enlargement with fibrosis; UIP/P, usual interstitial pneumonia pattern.

Table 3. Relationship of AEF, RB, CLE and UIP/P among 587 smokers by χ^2 test

	P
CLE versus AEF	0.001
AEF versus RB	0.0002
AEF versus UIP/P	0.000
CLE versus UIP/P	0.083

AEF, Airspace enlargement with fibrosis; RB, respiratory bronchiolitis; CLE, centrilobular emphysema; UIP/P, usual interstitial pneumonia pattern.

between the two groups. The incidence and degree of CLE were significantly higher in the upper lobe specimens ($P < 0.01$) and the incidence and degree of AEF and UIP/P were significantly higher in the lower lobe group ($P < 0.01$).

Among 587 smokers (Table 3), there were significant correlations ($P < 0.01$) between CLE and AEF, AEF and RB and AEF and UIP/P. AEF and UIP/P were co-existent in 69 cases (Table 4); however, macroscopically it was noted that AEF tended to be identified at costal regions of the lung, whereas UIP/P tended to be identified on the diaphragmatic surface. The coexistence of CLE, AEF and UIP/P was seen in 6.8% of patients. Coexistence of CLE and AEF was present in 32% of patients with UIP/P (40% if limited to 49 patients who had undergone pneumonectomy).

Table 4. Relationship between AEF and UIP/P and frequency of acute respiratory failure of unknown cause after lobectomy or pneumonectomy by χ^2 test

	UIP/P (−)	UIP/P (+)
AEF (−)		
No	431	56
Frequency	0.2%	11%
AEF (+)		
No	31	69
Frequency	0%	6%

AEF, Airspace enlargement with fibrosis; UIP/P, usual interstitial pneumonia pattern There was no acute respiratory failure of unknown cause after lobectomy or pneumonectomy in AEF alone patients One patient without UIP/P or AEF had a microscopic scar resembling UIP/P significant difference ($P < 0.01$) was seen between AEF alone and UIP/P with or without AEF.

The presence of AEF and UIP/P was evaluated in patients who developed acute respiratory failure of unknown cause following surgery (Table 4). The incidence of acute respiratory failure was 11% in patients with UIP/P without AEF, 6% in patients with UIP/P and AEF and 0% in patients with AEF without UIP/P. There was a significant difference ($P < 0.01$) between AEF alone and the presence of UIP/P with or without coexisting AEF.

Discussion

In this study of pathological changes in resection specimens from lung cancer patients, we have made a number of observations.

A dose relationship between SI and emphysema is well known and has been previously reported.[1] Fraig *et al.* studied the incidence of RB in surgical specimens and correlated it with smoking history: RB was found in current smokers in 100% of cases and in ex-smokers in 49%.[21] In this study SI correlated with degree of pigmented macrophage and peribronchiolar fibrosis.[21] Even though we have presented our findings somewhat differently (Table 1: RB incidence 9, 33 and 34% in mild, moderate and heavy smokers, respectively), there remains a discrepancy in the percentage of cases in which RB was identified. Some of this difference might be explained by formalin inflation of the lobectomy specimens and 'washing out' of the macrophages. Discrepancy may also be related to genetic differences, since our data came from an exclusively Japanese population. We do not know precisely why 2% of non-smokers showed RB; we suspect they were less than forthcoming concerning their smoking history.

The term AEF has been used as a form of emphysema.[18,19] We specifically addressed this change in the cases we examined. AEF was seen in only 0.4% of non-smokers. There were significant differences in the incidence and degree of AEF between mild smokers and moderate smokers. We have shown a definite correlation between AEF and smoking; however, we do not believe that AEF is a specific marker for smoking, because some non-smokers with various occupational exposures (mild pneumoconiosis) may also show AEF (Y.K., unpublished data).

Histologically, AEF shares some features with RB, and the fibrosis may resemble that seen in some cases of fibrotic non-specific interstitial pneumonia (NSIP). We suspect that some cases of fibrotic NSIP in smokers may include a significant component of AEF or may in fact be marked AEF producing interstitial lung disease. In his study of respiratory bronchiolitis associated with interstitial lung disease with fibrosis, Yousem has also suggested that some cases of fibrotic NSIP may actually represent examples of smoking-related changes (including AEF) producing a fibrotic interstitial pneumonia. Exact comparison of our findings with previous reports is difficult, since our study is unique, being an extensive macroscopic and microscopic study of inflated lobectomy specimens from patients who, for the most part, did not have clinical evidence of interstitial lung disease. We postulate that the AEF we have identified in lobectomy specimens may be a subclinical manifestation of a lesion that, when more widespread, may clinically manifest as interstitial lung disease.

AEF showed significant correlations with CLE and RB, both of which are caused by smoking, as well as correlating with the presence of UIP/P. Smoking is known to be a risk factor for UIP in the setting of idiopathic pulmonary fibrosis.[22,23] The coexistence of UIP/P and CLE and/or bullae was reported in 1992 as atypical IPF complicating emphysema, mainly bullae, from Japan.[24] More recently, this coexistence has been reported from aetiological and pulmonary physiological standpoints.[25–27] The coexistence of CLE and AEF was seen in 32% of our patients with UIP/P and in 40% of cases in which pneumonectomy was performed. The topological relationships are interesting, since AEF was located more in the upper portion of the lower lobe than UIP/P. The pathogenesis of AEF is not yet clarified, but smoking might cause destruction of lung tissue and an associated inflammatory reaction that is followed by organization in fibrosis, perhaps similar to that seen in DIP.[28,29] Topological differences of injury pattern related to smoking would also have to be considered.

It is noteworthy that cases showing only AEF were not associated with the development of acute respiratory failure of unknown cause following surgery. This is relatively frequent in patients with UIP as acute exacerbation.[30,31] The development of acute exacerbations, even in patients with histologically identifiable UIP/P (perhaps corresponding to subclinical UIP/IPF), has also been described.[14–17] The fact that such acute exacerbations do not occur in patients with AEF alone suggests that AEF and UIP/P may be fundamentally different, perhaps related to the fact that fibroblast foci[32] are not a feature of AEF.

In summary, we propose that AEF is a frequent finding of smoking-related pathological changes encountered in the lung. AEF shows a positive correlation with CLE, RB and UIP/P. AEF may be the histological basis for some cases of clinically manifest interstitial lung disease that could be included as part of the spectrum of SR-ILD. AEF appears to encompass cases described by Yousem as RB-ILD with fibrosis, and Yousem has proposed that these cases are distinct from fibrotic NSIP. The precise relationship(s) between fibrotic NSIP in a non-smoker and fibrotic NSIP in a smoker (RB with fibrosis or AEF) remains to be determined.

References

1. Anderson AE, Hernandez JA, Eckert P, Foraker AG. Emphysema in lung macrosections correlated with smoking habits. *Science* 1964; **144;** 1025–1026.

2. US Department of Health, Education, and Welfare. *Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service*. PHS Publication.No.:1103. Atlanta, GA: Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964.
3. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004; **328;** 1519–1528.
4. Minna JD, Pass H, Glatstein F, Ihde DC. Cancer of the lung. In Devita VT, Hellman S, Rosenberg SA eds. *Cancer: principles and practice of oncology*. Philadelphia: JB Lippincott, 1988; 591–705.
5. Parkin DM, Sasco AJ. Lung cancer: worldwide variation in occurrence and proportion attributable to tobacco use. *Lung Cancer (Elsevier)* 1993; **9;** 1–16.
6. Myers JL, Veal CF Jr, Sin MS, Katzenstein AL Respiratory bronchiolitis causing interstitial lung disease. A clinicopathological study of 6 cases. *Am. Rev. Respir. Dis.* 1987; **135;** 880–884.
7. Yousem SA, Colby TV, Gaensler EA Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia *Mayo Clin. Proc.* 1989; **64;** 1373–1380.
8. Friedman PJ, Liebow AA, Sokoloff J Eosinophilic granuloma of lung. Clinical aspects of primary histiocytosis in the adult. *Medicine (Baltimore)* 1981; **60;** 385–396.
9. Moon J, du Bois RM, Colby TV, Hansell DM, Nicholson AG Clinical significance of respiratory bronchiolitis on lung biopsy and relationship to smoking related interstitial lung disease *Thorax* 1999; **54;** 1009–1014.
10. Ryu JH, Colby TV, Hartman TE, Vassallo R. Smoking-related interstitial lung diseases: a concise review. *Eur. Respir. J.* 2001; **17;** 122–132.
11. 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.
12. Katzenstein AL, Fiorelli RF. Non-specific interstitial pneumonia/fibrosis, Histologic features and clinical significance. *Am. J. Surg. Pathol.* 1994; **18;** 136–147.
13. Travis WD, King TE Jr. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonia. *Am. J. Respir. Crit. Care Med.* 2002; **165;** 277–304.
14. Kawabata Y, Fukushima K, Uchiyama T, Sugita H, Kimura B. A focal usual interstitial pneumonia lesion: an important risk factor in diffuse alveolar damage–acute exacerbation of a focal usual interstitial pneumonia patient. *Nihon Kokyuki Gakkai Zasshi (J. Jap. Resp. Soc.)* 2001; **39;** 316–321. (with English abstract)
15. Kawabata Y, Aoyama K, Hoshi E, Ubukata M, Takayanagi N, Sugita Y. Pathological study of usual interstitial pneumonia in patients with lung cancer resection: with special reference to its relationship to subsequent acute exacerbation. *Haigan (JJLC)* 2005; **45;** 115–121 (with English abstract).
16. Fukushima K, Kawabata Y, Uchiyama T, Sugita H. Clinicopathologic study of 50 autopsy cases of idiopathic pulmonary fibrosis and non-diffuse usual interstitial pneumonia. *J. Jap. Resp. Soc.* 2005; **43;** 569–577. (with English abstract)
17. Araya J, Kawabata Y, Jinho P *et al.* Clinically occult subpleural fibrosis with acute interstitial pneumonia (AIP). *Respirology* 2008; **13;** 408–412.
18. Snider GL, Kleinerman J, Thurlbeck WM, Bengali ZH. The definition of emphysema, Report of National Heart, Lung, and Blood Institute, Division of Lung Diseases Workshop. *Am. Rev. Respir. Dis.* 1985; **132;** 182–185.
19. Snider GL. Emphysema: the first two centuries – and beyond a historical overview, with suggestions for future research: Part 1. *Am. Rev. Respir. Dis.* 1992; **146;** 1334–1344.
20. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand. J. Work Environ. Health* 1997; **23;** 311–316.
21. Fraig M, Shreesha U, Savici D, Katzenstein AL. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. *Am. J. Surg. Pathol.* 2002; **26;** 647–653.
22. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis Epidemiologic approaches to occupational exposure. *Am. J. Respir. Crit. Care Med.* 1994; **150;** 670–675.
23. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 1997; **155;** 242–248.
24. Homma Y, Saiki S, Doi O *et al.* Clinical criteria for definition of idiopathic interstitial pneumonia (IIP). *Nikkyousitu Kaishi (Jap. J. Resp. Dis.)* 1992; **30;** 1371–1377 (with English abstract).
25. Cottin V, Hunes H, Brillet PY *et al.* Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur. Respir. J.* 2005; **26;** 586–593.
26. Grubstein A, Bendayan D, Schactman I, Cohen M, Shitrit D, Kramer MR. Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. *Respir. Med.* 2005; **99;** 948–954.
27. Jankowich MD, Polsky M, Klein M, Rounds S. Heterogeneity in combined pulmonary fibrosis and emphysema. *Respiration* 2008; **75;** 411–417.
28. Craig PJ, Wells AU, Doffman S *et al.* Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. *Histopathology* 2004; **45;** 275–282.
29. Kawabata Y, Takemura T, Hebisawa A *et al.* Increased eosinophils in bronchoalveolar lavage fluid and lobule-based histologic lesions are characteristic features of desquamative interstitial pneumonia. *Histopathology* 2008; **52;** 94–202.
30. Kondo A, Saiki S. Acute exacerbation in idiopathic interstitial pneumonia. In Harasawa M, Fukuchi Y, Morinari H eds. *Interstitial pneumonia of unknown etiology*. Tokyo: University of Tokyo Press, 1989; 33–42.
31. Kondoh Y, Taniguchi H, Kawabata Y *et al.* Acute exacerbation in idiopathic pulmonary fibrosis. *Chest* 1993; **103;** 1808–1812.
32. Kawabata Y, Hoshi E, Ubukata M *et al.* Histological changes are background factors in acute exacerbation of usual interstitial pneumonia pattern/lesions following lung resection. *Haigan (JJLC)* 2006; **46;** 329–336 (with English abstract).