



Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature

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Summary

Introduction: Smoking can cause a variety of pulmonary interstitial diseases. Pulmonary fibrosis has traditionally been considered a non-smoking-related disease. Recently, however, evidence of smoking-induced fibrosis has emerged.

Subjects and methods: A group of eight patients from the pulmonary clinic in Rabin Medical Center with a combine presentation of fibrosis and emphysema was identified retrospectively. All patients underwent chest computed tomography and pulmonary function tests. One patient underwent lung–heart transplantation and a complete review of his lung pathology was obtained. Transbronchial biopsy was performed in 3 additional patients and echocardiography was performed to evaluate the pulmonary vasculature.

Results: Upper-lobe emphysema with bullous changes was found in all patients. In addition, a basal interstitial process was recognized, ranging from ground glass opacities to severe pulmonary fibrosis, with honeycombing. The radiological findings matched the pathological results of combined emphysema and usual interstitial pneumonia. Pulmonary function tests were also in accord, showing severe hypoxemia with mild obstruction, normal-to-mildly reduced lung volumes and a severe decrease in diffusion capacity. Most of the patients had moderate-to-severe pulmonary hypertension as well as diffuse coronary artery disease.

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Conclusion: Our findings are in line with emerging evidence that the spectrum of interstitial damage caused by smoke includes not only Langerhans cell histiocytosis, respiratory bronchiolitis or desquamative interstitial pneumonia but also advanced usual interstitial pneumonitis as well. We believe that in some patients smoking plays a destructive role by a variety of mechanisms and can cause emphysema, lung fibrosis as well as pulmonary vasculopathy and hypertension. Future studies are needed to define the genetics and pathophysiology of this uncommonly reported clinical syndrome.

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Introduction

Emphysema is a well-known consequence of heavy smoking. It more commonly affects the upper lobes with bullous formation. Smoking may also cause a spectrum of interstitial lung diseases, namely Langerhans cell histiocytosis, and respiratory bronchiolitis-associated interstitial pneumonia and desquamative interstitial pneumonia. Pulmonary fibrosis, in the forms of usual interstitial pneumonia or non-specific interstitial pneumonia has traditionally been considered as a separate entity and not a sequela of cigarette smoking.¹⁻³

Nevertheless, some researchers have suggested that tobacco smoking may be the common cause of both emphysema and pulmonary fibrosis. Indirect support for this hypothesis comes from studies showing that smoking may be an independent risk factor in some patients with idiopathic pulmonary fibrosis and that affected patients often have evidence of centrilobular emphysema on computed tomography (CT) scans.⁴⁻⁷

The aim of this work was to describe a cohort of heavy smokers who presented with concomitant upper-lobe bullous emphysema and lower-lobe usual interstitial pneumonia with honeycombing.

Subjects and methods

The study group consisted of eight patients, identified retrospectively, who presented with dyspnea and cough. All patients were heavy smoker and referred to our pulmonary clinic because of suspected emphysema or chronic obstructive lung disease. Assessment included pulmonary function tests, chest X-ray and chest CT. Transbronchial biopsy was performed in three patients. Echocardiography for the evaluation of pulmonary hypertension was performed in seven patients. One patient underwent heart-lung transplantation for end stage disease.

Results

Patient's characteristics (Table 1)

There were seven male and one female patient aged 62–76 years. All were heavy smokers (50–100 pack-years). The New York Heart Association (NYHA) classes ranged between 2 and 4.

Pulmonary function tests (Table 2)

Mean forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) were 86 ± 13.3 , 78.1 ± 20 , respectively, and mean FEV₁/FVC was 70 ± 7.9 , indicating mild obstruction combine with restriction. Mean residual volume (RV) and total lung capacity (TLC) were 98 ± 21 , 86 ± 10.9 , respectively, and mean RV/TLC was 44 ± 6.4 , indicating normal to reduced lung volumes with no significant hyperinflation. The most prominent feature in all patients was a very low diffusion capacity (mean 24 ± 5.65 ml/min/mmHg) and markedly reduced arterial oxygen saturation (mean 85 ± 4.8 on room air).

Radiological findings (Table 3)

Chest X-rays

Hyperlucency of the apexes was noted in all patients, combined with coarse reticular pattern at the bases and diminished lung volume (Fig. 1A and B).

Chest CT

The apexes showed bilateral upper-lobe emphysema in all cases. In four patients, large emphysematous, bullous changes were noted (Figs. 2A and 3A). The others showed small emphysematous cysts.

At the bases there was thickening and distortion of the interstitium, areas of honeycombing and traction bronchiectasis. These changes were typically located at the peripheral lung zones. Four

Table 1 Patient's characteristics.

Pt. no.	Sex/age (years)	Smoking (pack-years)	Symptoms	NYHA	PA	Comments
1	M/65	60	Dyspnea cough	4	55–80	Heart–lung transplantation Triple vessel CAD, NSCLC
2	F/71	50	Dyspnea cough	4	44	TBB
3	M/68	60	Dyspnea cough	4	80	Triple vessel CAD, Died
4	M/62	60	Dyspnea cough	2–3	40	NSCLC
5	M/76	60	Dyspnea cough	4	35	CAD
6	M/68	100	Dyspnea cough	3–4	80	CAD
7	M/71	50	Dyspnea	2–3	ND	
8	M/72	80	Cough	2–3	30	CAD

NYHA—New York heart association classification.

PA—estimated pulmonary artery (sys pressure mmHg).

CAD—coronary artery disease.

NSCLC—non-small cell lung cancer; ND—not done.

Table 2 Pulmonary function tests.

Pt. no.	FVC % (l)	FEV ₁ % (l)	FEV ₁ /FVC	FEF 50%	RV % (l)	TLC % (l)	RV/TLC	DLCO %	SAT % (RA)
1	106(3.7)	110(3)	81	87(3.4)	121(2.9)	104(6.4)	44	32	87
2	77(2.12)	65(1.42)	67	31(1/01)	105(2.3)	87(4.3)	53	25	90
3	68(2.61)	57(1.69)	65	25(1.04)	122(3.1)	85(5.74)	54	16	80
4	89(2.9)	65(1.69)	58	19(0.87)	82(1.55)	77(4.3)	36	22	88
5	98(2.8)	105(2.1)	80	109(3.6)	72(1.82)	85(4.83)	38	27	76
6	89(3.26)	77(2.16)	66	36(1.42)	92(2.32)	86(5.56)	42	20	88
7	70(2.47)	64(1.74)	70	35(1.34)	74(1.85)	68(4.33)	43	24	85
8	90(3.45)	87(2.59)	75	64(2.7)	118(2.51)	96(6.16)	41	74	88

FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; FEF 50 = forced expiratory flow in 50% of the volume; RV = residual volume; TLC = total lung capacity; DLCO = pulmonary diffusion capacity for carbon monoxide; SAT = oxygen saturation, room air.

patients had in addition ground glass opacities at the lung bases (Figs. 2B and 3B). In one of them the opacities and fibrosis had evolved over 6 years from delicate increased interstitial markings, distributed subpleurally. This patient underwent heart–lung transplantation with pathological confirmation of the radiographic findings of concomitant emphysema and usual interstitial pneumonia.

Two patients had mediastinal lymphadenopathy in addition to the parenchymal findings.

Pathological findings

In the patient after heart–lung transplantation, both lungs showed at the bases severe, diffuse fibrosing interstitial lung disease, most consistent with usual interstitial pneumonitis (UIP). Alveolar

septa were thickened by collagen fibrosis with inconspicuous lymphoid infiltrate. Focally bony metaplasia was seen, as well as alveolar macrophages accumulation resembling desquamative interstitial pneumonia in some areas. Most of the macrophages were pigmented (smoker's macrophages), and some contained large globules of hemosiderin. Scattered multinucleated giant cells were seen as well. Honeycombing was observed in the periphery of the lower lobes. The upper lobes on both sides showed severe emphysema with bullous formation (Fig. 4A and B). In the left lower lobe of the left lung, squamous cell carcinoma in the area of fibrosis was found, which was not known prior to the surgery.

Pathological study of the transbronchial biopsy specimens, although limited, revealed fibrosis in all patients, and accumulation of pigmented

Table 3 Radiological characteristic.

Case	Upper lobes	Lower lobes	Mediastinum
1	Bilateral emphysema with bulla formation	Septal thickening, architectural distortion honeycombing, traction bronchiectasis	
2	Bilateral emphysema with bulla formation	Septal thickening, architectural distortion honeycombing, traction bronchiectasis	
3	Bilateral emphysema with bulla formation	Ground glass opacities, mild septal thickening, architectural distortion, mainly subpleural distribution	Mediastinal lymphadenopathy
4	Bilateral emphysema with bulla formation	Ground glass opacities, mild septal thickening, architectural distortion, mainly subpleural distribution	Mediastinal lymphadenopathy
5	Bilateral emphysema	Septal thickening, architectural distortion honeycombing, traction bronchiectasis	
6	Bilateral emphysema	Ground glass, pleural effusion	
7	Bilateral emphysema with bulla formation	Ground glass opacities, mild septal thickening, architectural distortion, mainly subpleural distribution	
8	Bilateral emphysema	Septal thickening, architectural distortion honeycombing, traction bronchiectasis	

macrophages in one. In one patient, cytology exam of the transbronchial needle aspiration of subcarinal lymph node showed non-small cell lung cancer.

Echocardiography

Moderate-to-severe pulmonary hypertension was found in almost all patients 7/8 (ranged 44–80 mmHg) (Table 1). Coronary artery disease a common finding as well 5/8.

Discussion

Smoking-related lung diseases include emphysema, chronic bronchitis, and respiratory bronchiolitis alone or in association with interstitial pneumonia, desquamative interstitial pneumonia and Langerhans cell histiocytosis.^{2,8} Not infrequently, however, more than one pattern can be seen in a single patient on biopsy, lung function tests and imaging.

Emphysema is characterized by permanent, abnormal enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls. The destructive mechanisms that cause emphysema do not, by definition, include thickening of the alveolar septa and fibrosis. Accordingly, pulmonary function tests in emphysema show obstruction, hyperinflation and decreased diffusion capacity, whereas in interstitial lung disease and fibrosis lung volumes are reduced.⁹

In smoking-related respiratory bronchiolitis, the damage to small airways is manifested by the accumulation of pigmented macrophages within the respiratory bronchiole and adjacent's alveoli. Desquamative interstitial pneumonia occurs more peripherally and is characterized by the accumulation of macrophages within the alveoli. In between exists respiratory bronchiolitis-associated interstitial lung disease. These pathological entities can be considered as part of the spectrum of the same disease process.^{2,8}

In all our patients the pathology, imaging and lung function tests found coexistent bullous emphysema on the upper lobes and interstitial fibrosis on the lower lobes. In none of the patients did the biopsy show bronchial or peribronchial interstitial fibrosis to suggest respiratory bronchiolitis-associated interstitial pneumonia (although a small transbronchial biopsy can miss this diagnosis). In the first case (post-lung-heart transplantation) multiple foci of pigmented macrophages were noticed microscopically. The same picture was found in another patient on transbronchial biopsy, again pointing to smoking the probable cause.

In desquamative interstitial pneumonia, there is relatively little fibrosis compared with usual interstitial pneumonia. Although desquamative interstitial pneumonia with fibrosis is well recognized, it is not considered to be an earlier (cellular) stage of cryptogenic fibrosing alveolitis.^{2,3,8} The most common radiological findings are bilateral ground-glass opacities distributed in the middle and lower

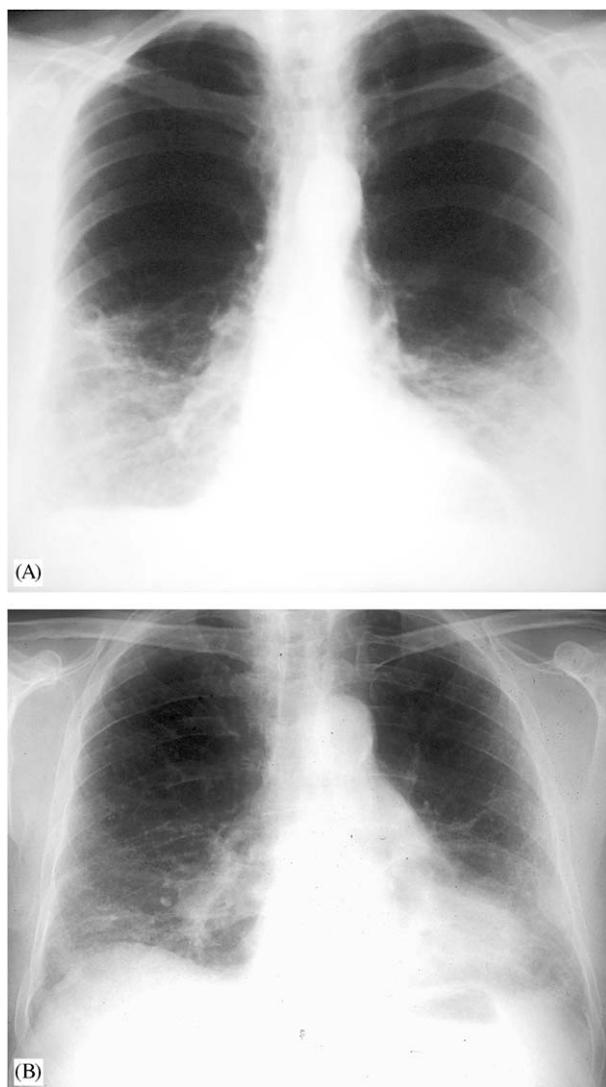


Figure 1 (A,B). Posteroanterior chest radiographs from (A) a 71-year old female and (B) 60-year old male, both heavy smokers. Hyperlucency of both upper lung zones combine with reticular pattern at the bases is seen.

zones. In patients with respiratory bronchiolitis-associated interstitial pneumonia, high-resolution CT may show centrilobular nodules. Emphysema, if present, is rarely extensive. Thickening of interlobular septa may also be present, but again, not as a dominant feature.^{12,6,8}

Ninety percent of all cases of Langerhans cell histiocytosis are smokers. The disease is characterized by nodular lesions that evolve into cysts, with sparing of the costophrenic recesses and the tip of the lingula.⁸ In all our patients, the fibrotic changes were predominantly basal, mostly peripheral, and the costophrenic recesses and the tip of the lingula were involved. Moreover, the bullous changes in the upper lobe are distinct from the thin-wall cyst typically seen in Langerhans cell histiocytosis.

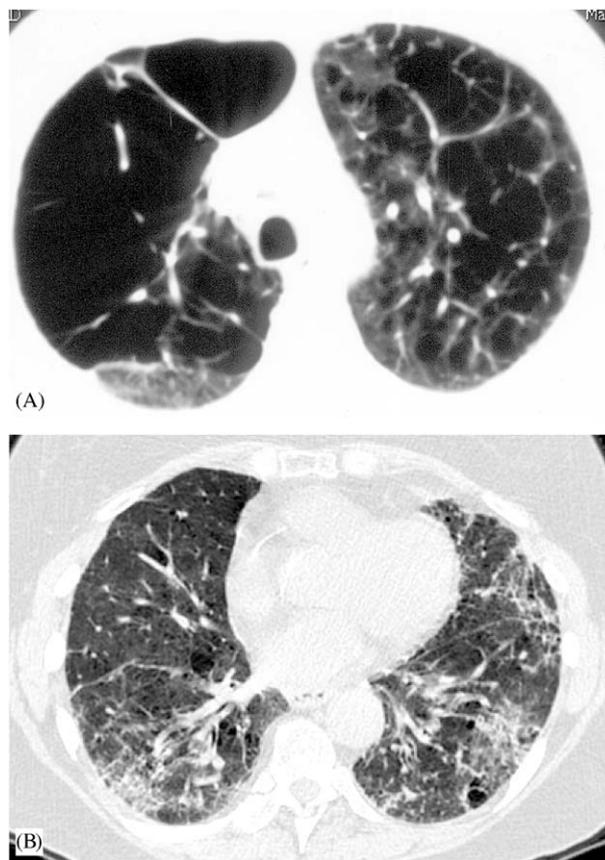


Figure 2 (A,B). CT sections showing marked bullous formation in the apices (A) and architectural distortion with honeycombing and ground glass opacities at the bases (B).

The radiological appearance of upper-lobe bullous emphysema is well known. The lower lobes are typically compressed, with apparently increased interstitial markings. In our patients, however, there was a genuine interstitial process with a basal distribution. This finding was confirmed on the pathology examination. Moreover, in upper-lobe emphysema, there is a severe obstructive pattern and hyperinflation on pulmonary function tests, unlike our patients, who had reduced or preserved lung volumes, restriction and severe reduction in diffusion capacity.

Can smoking cause both pathological changes in the same patient, namely, destruction of the alveoli wall on the one hand, and fibrosis on the other? In a histopathologic study of autopsied lungs from 1824 subjects, Auerbauch et al.¹⁰ reported that smoking could induce, indeed, both these processes. Wiggins et al.⁶ in a study of patients with cryptogenic fibrosing alveolitis and preserved lung volumes suggested that in many of these cases, this combination appears to reflect coincidental

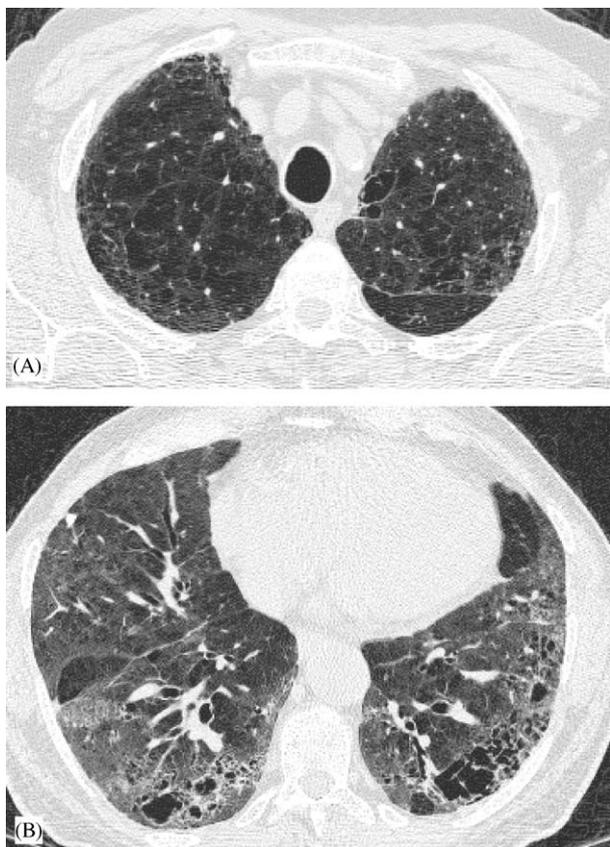


Figure 3 (A,B). CT section showing emphysema at the apices (A) and traction bronchiectasis, honeycombing as signs of fibrosis at the bases (B).

emphysema. Doherty et al.⁷ adopted the same concept for their findings of upper-lobe emphysema on high-resolution CT in eight patients proven lung fibrosis but with preserved lung volumes. These reports agree with ours, of severe interstitial fibrosis and normal lung volumes caused by upper-lobe bullous emphysema.^{6,7} A similar report by Hanninghake et al.¹² showed a high-resolution CT picture of basal fibrosis and apical emphysema in a patient with usual interstitial pneumonia.

Another puzzling feature is the moderate-to-severe pulmonary hypertension in most of our patients. Both chronic obstructive pulmonary disease as well as interstitial fibrosis may cause secondary pulmonary hypertension.¹¹ However, in the setting of combined emphysema/fibrosis, the presence of pulmonary hypertension could suggest severe, smoking-related damage to the pulmonary capillaries. Pulmonary hypertension tends to be of moderate severity and progress slowly, and is associated with shorter survival and worse clinical evolution.¹³ The vasculopathy is involving both pulmonary arteries, as well as the coronary

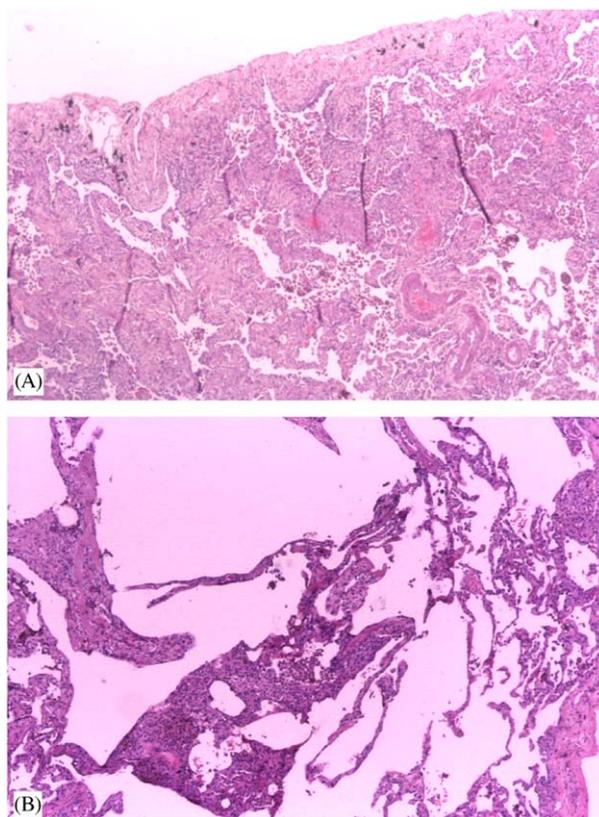


Figure 4 (A,B). Post heart–lung transplantation pathology. *Bases*: Severe fibrosing interstitial lung disease. Alveolar septa thickened by collagen fibrosis. Macrophages accumulation (A). *Upper lobes*: Severe emphysema with bullous formation (B).

arteries, as is seen by the high incidence of severe coronary artery disease in our patients.

In summary, the apparent contradictory coexistence of emphysema and pulmonary fibrosis is reported here in eight heavy smokers and is in accordance with several emerging reports. Although smoking seems to be able to induce both pathologies, the question of whether, in these cases, it is directly responsible for the interstitial lung disease or whether the combined disorder is coincidental findings, is still unresolved. We believe that in some patients, smoking is destructive at several levels, and leads to simultaneous emphysema and lung fibrosis, as well as pulmonary hypertension and coronary artery disease. As the association between smoking and fibrosis continue to unfold, we suggest that the spectrum of respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial pneumonia and desquamative interstitial pneumonia should be expanded to include pulmonary fibrosis (usual interstitial pneumonitis). Further studies are needed to explore the

possible genetic and pathophysiology mechanisms of this unusual syndrome.

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