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Combined Pulmonary Fibrosis and Emphysema Syndrome

A Review

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There is increasing clinical, radiologic, and pathologic recognition of the coexistence of emphysema and pulmonary fibrosis in the same patient, resulting in a clinical syndrome known as combined pulmonary fibrosis and emphysema (CPFE) that is characterized by dyspnea, upper-lobe emphysema, lower-lobe fibrosis, and abnormalities of gas exchange. This syndrome frequently is complicated by pulmonary hypertension, acute lung injury, and lung cancer. The CPFE syndrome typically occurs in male smokers, and the mortality associated with this condition, especially if pulmonary hypertension is present, is significant. In this review, we explore the current state of the literature and discuss etiologic factors and clinical characteristics of the CPFE syndrome.

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Abbreviations: CPFE = combined pulmonary fibrosis and emphysema; DLCO = diffusing capacity of lung for carbon monoxide; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test

Emphysema and pulmonary fibrosis have dissimilar physiologic effects. Emphysema causes reduced lung elastic recoil, increased lung compliance, and increased lung volumes with reduced maximal expiratory flow rates, whereas pulmonary fibrosis results in increased lung elastic recoil, decreased lung compliance, and reduced lung volumes with preserved or even increased maximal expiratory flow rates at a given lung volume. Clinically, either emphysema or fibrosis typically predominates, and individual patients are rarely recognized as having both disorders simultaneously. However, pathologic changes of coexisting emphysema and fibrosis are common in smokers.[1,2] The presence of pulmonary fibrosis may not be appreciated in patients with advanced emphysema, and patients with a combination of pulmonary emphysema and other pulmonary parenchymal disease may be at increased risk of postoperative complications.[3] Patients with both pulmonary fibrosis and emphysema have different pulmonary function tests (PFTs) and outcomes than patients with pure emphysema or pure fibrosis. Therefore, the traditional clinical dichotomy between emphysema and pulmonary fibrosis and the limitation of traditional diagnostic tests used to identify the simultaneous occurrence of these disorders may result in an underappreciation of the frequent coexistence of these entities in individual patients.

High-resolution CT (HRCT) scanning has enhanced clinical recognition of the simultaneous occurrence of emphysema and pulmonary fibrosis.[4,5] Patients with both processes have been described, with a resulting physiologic profile generally characterized by relatively normal spirometry and lung volumes in the setting of severely impaired gas exchange, a condition known as combined pulmonary fibrosis and

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emphysema (CPFE) syndrome,[6] and their clinical characteristics have been delineated in case series.[7-9] Radiographic characteristics include the presence of upper-lobe emphysema and lower-lobe pulmonary fibrosis (Fig 1); clinical characteristics include a smoking history and the presence of dyspnea, pulmonary hypertension, and hypoxemia; and pathologic characteristics include a predominance of usual interstitial pneumonia.

Whether CPFE represents a unique disease entity or a coincidence of two pulmonary diseases related to cigarette smoking is as yet unclear. In this review, we explore the current state of literature on CPFE and discuss etiologic factors and clinical characteristics of CPFE.

A MEDLINE search was performed using the terms "pulmonary fibrosis" and "emphysema" and the term combined "pulmonary fibrosis and emphysema." Abstracts of all studies were then reviewed, with human studies included for consideration if they included information on subjects with the combination of both emphysema and pulmonary fibrosis; studies of patients categorized as having either pulmonary fibrosis or emphysema were excluded. References of included studies also were reviewed to capture any additional studies not identified in the MEDLINE searches.

Diagnosis of the CPFE Syndrome

The diagnosis of the CPFE syndrome is established after HRCT imaging, sometimes in conjunction with pathology. A consensus definition of CPFE syndrome does not currently exist. In the broadest sense, this term should include all patients with coexistent emphysema and pulmonary fibrosis pathology, although current methods of detection, such as HRCT scanning, likely allow identification of a portion of this larger group. The combination of emphysema and pulmonary fibrosis detectable on HRCT scan initially was reported in the setting of apparent idiopathic pulmonary fibrosis (IPF),[4] and in this setting, emphysema is a relatively common finding on CT scan (Table 1). However, although a pattern of usual interstitial pneumonia/IPF appears to be the most common imaging or pathologic findings in the setting of CPFE, other patterns of fibrotic interstitial lung disease have been reported in conjunction with emphysema,[7,9] and the presence of IPF, therefore, is not necessary for the diagnosis of CPFE. Most reported cases of CPFE (Table 2) seem to share certain characteristics, including male sex, a history of cigarette smoking, relatively preserved spirometric values, and decreased diffusing capacity of lung for carbon monoxide (Dlco). These common factors have led to the description of a CPFE syndrome,[6] which denotes the subgroup of patients with coexistent pulmonary fibrosis and emphysema who present with dyspnea, often in the setting of a history of smoking; who have the characteristic physiologic abnormalities; and who frequently also have pulmonary hypertension. Classification of this group of patients under the CPFE syndrome label is important because as discussed later, these patients have a different natural history, complications, and mortality than those with pulmonary fibrosis or emphysema alone. What remains unclear is what extent of emphysema and fibrosis is needed to distinguish the patient with CPFE from patients with predominant emphysema or predominant fibrosis.

The diagnosis of the CPFE syndrome should be considered in a variety of settings. PFTs demonstrating normal or near-normal spirometry and lung volumes but a severely diminished Dlco should suggest the possibility of CPFE, especially in a current or former smoker. In a study by Aduen et al,[31] only 179 of 38,095 PFTs (0.47%) reviewed had an isolated reduction in diffusing capacity, and of 27 patients in this subgroup with comprehensive data, including HRCT scans, six with both emphysema and pulmonary fibrosis were identified. In a retrospective review of patients with severe abnormalities in gas exchange on PFTs, defined as a carbon monoxide transfer coefficient of $<40\%$ predicted (present in 195 of 5,576 [3.5%] PFTs reviewed), 16% had CPFE, with the remainder having emphysema, interstitial lung disease, or pulmonary arterial hypertension.[32] These PFT patterns, although uncommon, should raise suspicion for CPFE syndrome but may also be explained by other abnormalities, including pulmonary vascular disease, emphysema, and some forms of interstitial lung disease.

The CPFE syndrome is a consideration in the patient with pulmonary hypertension and abnormal lung function on PFTs, especially with a mixed obstructive/restrictive abnormality.[33] CPFE also has been recognized in the lung cancer population, being present in 101 of 1,143 (8.9%) consecutive patients with lung cancer in a study by Usui et al.[34] Other patients in whom this diagnosis should be considered are those with severe breathlessness and normal or near-normal spirometry and those with oxygen requirements out of proportion to spirometric abnormalities. In such cases, full PFTs and chest imaging can establish the presence of CPFE syndrome.

Etiology

Cigarette Smoking

Recent studies of CPFE consistently have revealed a strong association with cigarette smoking. Of the

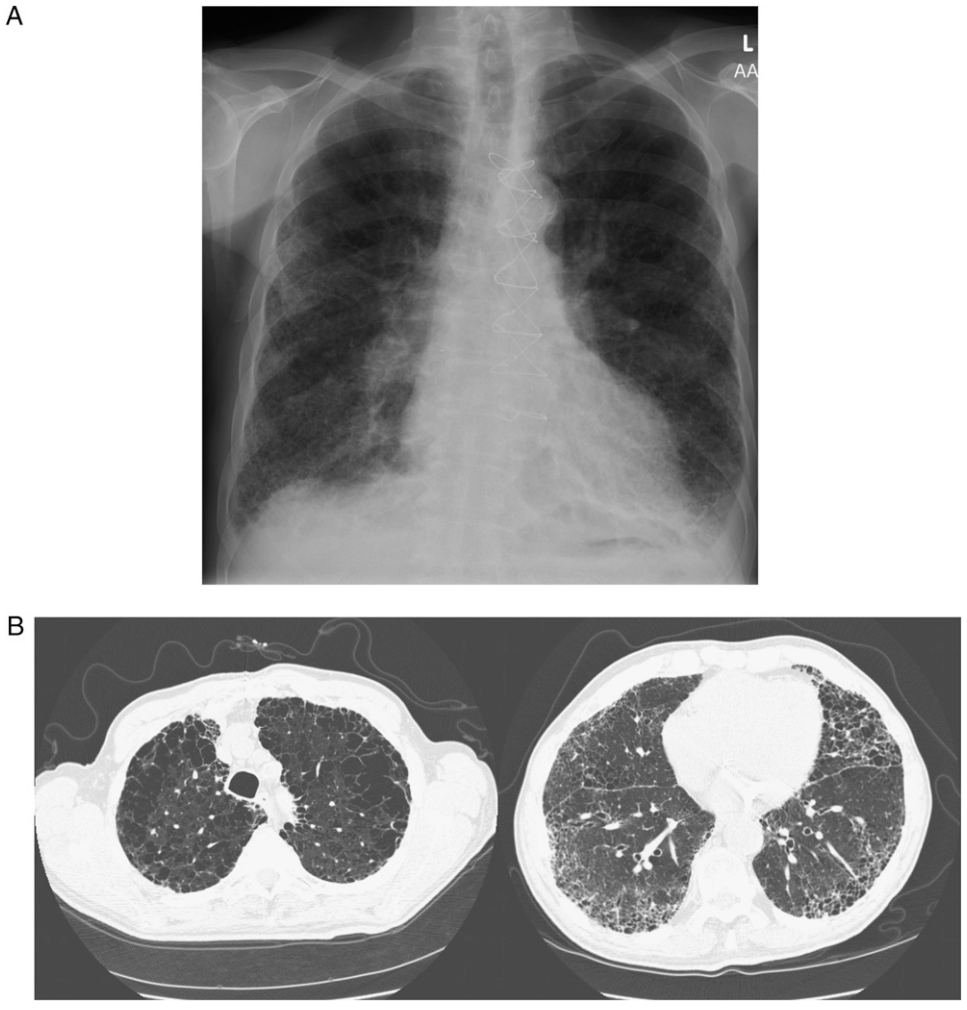

FIGURE 1. Images from a male smoker aged 77 years with combined pulmonary fibrosis and emphysema demonstrating upper-lobe emphysema and lower-lobe pulmonary fibrosis. A, Chest radiograph. B, CT image. Pulmonary function tests showed an FEV_1 of 108% predicted, FVC of 107% predicted, total lung capacity of 121%, and diffusing capacity of lung for carbon monoxide of 36% predicted. Echocardiography demonstrated grade I diastolic dysfunction and estimated pulmonary artery pressure of 30 to 40 mm Hg.

607 total patients with CPFE for whom smoking status was recorded in the published studies summarized in Table 2, 592 (98%) were either current or former smokers. These results are not surprising given the relationships between emphysema/COPD[35] and IPF[36] and smoking. Interstitial lung abnormalities visible by HRCT scan have been observed in 8% of HRCT scans in a cohort of 2,416 smokers.[37] In this study, interstitial abnormalities were positively associated with the extent of tobacco exposure, although only a minority of smokers (0.49%) had radiographic characteristics diagnostic of interstitial lung disease. The relationship between CPFE and smoking, therefore, may be explained by the associations between smoking and both diseases. However, we speculate that a unique subset of patients exposed to cigarette smoke is vulnerable to developing the typically extensive emphysema and pulmonary fibrosis characteristic of clinical CPFE syndrome.

Male Sex

Studies of CPFE syndrome have reported a male predominance. Excluding 20 Veterans Administration cases,[13] of the 587 patients with CPFE in the published studies summarized in Table 2, 529 (90%) were men. The male preponderance of cases of CPFE could be explained by greater exposure to smoking and other CPFE risk factors (discussed in this article) in men than women. However, smoking rates in men vs women do not completely explain the sex differences.

Emphysema has been reported to be more common in male smokers than in female smokers.[38] Most

Table 1—*Proportion of Patients With CT Scan Evidence of Emphysema in the Setting of Pulmonary Fibrosis*

Study	Proportion of Patients With Pulmonary Fibrosis and Emphysema	%
Akira et al[10]	15/80	18.8
Copley et al[11]	76/212	35.8
Doherty et al[12]	9/23	39.1
Jankowich and Rounds[13]	20/44	45.5
Kurashima et al[14]	221/660	33.5
Mejía et al[15]	31/110	28.2
Schmidt et al[16]	86/169	50.9
Todd et al[17,a]	28/102	27.4

[a]Twenty-eight of 102 patients had advanced emphysema, 26 of 102 had trivial emphysema, and 48 of 102 had no emphysema.

studies of sex and emphysema have focused on the relative extent of emphysema in men and women, with slightly more extensive emphysema in male smokers on CT imaging.[39,40] However, these minor differences in extent of emphysema do not clearly indicate the basis for the significant male preponderance of CPFE cases.

IPF also is more common in men than in women, especially in older age groups.[41] A male:female ratio of 2:1 was reported in a study of 220 patients with IPF.[42] A similar sex ratio was seen in a recent study of interferon γ-1b in IPF, where 70.8% of subjects were men and 29.2% women.[43] However, the association between male sex and IPF would not necessarily explain the disproportionate male predominance noted in CPFE studies (9:1 male:female ratio).

We speculate that men are more susceptible to smoking-induced emphysema and pulmonary fibrosis because of greater vulnerability to abnormal lung aging in men. Both emphysema and pulmonary fibrosis are associated with chronologic aging. In an autopsy study of smokers and nonsmokers, the burden of both emphysema and pulmonary fibrosis increased with increasing chronologic age, whereas smoking synergistically increased these effects within each age group.[1] Both COPD and pulmonary fibrosis have been associated with telomere length shortening, a biologic marker of aging of research interest.[44,45] Future research in the pathogenesis of CPFE should include assessment of lung tissue samples for biologic markers of aging, such as telomere length.

Asbestos and Other Mineral Dust Exposures

Emphysema occurs in individuals with asbestosis. In HRCT scan studies of patients with asbestosis, emphysema was present in 10% to 36%.[10,11,46] Although the presence of emphysema in asbestosis may be related to cigarette smoking, emphysema has been described in never smokers with asbestosis and with silicosis.[47] Emphysema and fibrosis CT scan scores in asbestosis are positively, but weakly correlated.[48] Emphysema and fibrosis also may occur simultaneously in the lung following coal dust exposure.[49,50] The extent of emphysema is directly related to lung coal content as well as to extent of pneumoconiosis.[50] Pulmonary talcosis also may result in a mixture of emphysema and granulomatous pulmonary fibrosis.[51] These findings suggest that both emphysema and fibrosis may coexist with or without concomitant smoking history, and mineral dust exposure may account for some cases of the CPFE syndrome.

Other Associations

Hypersensitivity pneumonitis/farmer lung may result in both pulmonary fibrosis and emphysema. In this case, emphysema has been reported in the absence of cigarette smoking.[52,53] Emphysema and interstitial lung disease may coexist in the setting of connective tissue diseases, including rheumatoid arthritis and systemic sclerosis.[22,54,55] A case of CPFE syndrome in a patient with surfactant protein C mutation as well as positive antinuclear antibodies has been reported, suggesting a potential contribution of inherited or acquired abnormalities of surfactant proteins in the pathogenesis of this disorder.[56] A case of extensive upper-lobe emphysema and lower-lobe pulmonary fibrosis consistent with classic clinical CPFE syndrome was described in a movie projectionist exposed to rare earth elements as well as to tobacco.[57] These examples illustrate that the coexistence of emphysema and pulmonary fibrosis may occur in a variety of clinical settings.

Pathogenesis

A single gene defect responsible for most cases of CPFE has not been established in humans. The best established environmental insult in the CPFE syndrome is cigarette smoking, which is associated with the majority of reported cases. Cigarette smoking exposure induced a combination of pulmonary fibrosis and emphysema in a canine model.[58] A variety of genetically altered animal models have demonstrated incidental lung morphologic changes, including both pulmonary emphysema and fibrosis, thus highlighting the potential role of individual molecular pathways in the development of CPFE. Potential roles for surfactant protein D, tumor necrosis factor-α, IL-1β, and neutrophil elastase in formation of both emphysema and pulmonary fibrosis have been seen in various animal models.[59-64] However, it is not clear whether any of these models represent typical CPFE syndrome in

Table 2—*Summary of Reports of Characteristics of Patient With CPFE*

Study/Year	No.	Age, y	Male/Female Sex	Ever Smokers/Total Patients	FEV_1/FVC	Vital Capacity, %	Total Lung Capacity, %	Dlco, %
Akagi et al[18]/2009	26	65 ± 9	23/3	24/26	0.77 ± 0.09	87 ± 24	78 ± 17	44 ± 15
Arce et al[19]/2009	2	52 ± 10	2/0	2/2	0.72 ± 0.01	76 ± 1	85	31 ± 10
Casas et al [20]/2008	4	67 ± 6	4/0	4/4	0.75 ± 0.05	97 ± 16	97 ± 18	NA
Cottin et al[7]/2005	61	65 ± 10	60/1	61/61	0.69 ± 0.13	90 ± 18	88 ± 17	37 ± 16
Cottin et al[21]/2010	40	68 ± 9	38/2	39/40	0.75 ± 0.18	86 ± 18	84 ± 23	24 ± 14
Cottin et al[22]/2011	34	57 ± 11	23/11	30/34	0.73 ± 15	85 ± 24	82 ± 17	46 ± 16
Daniil et al[23]/2006	9	NA	9/0	9/9	NA	NA	NA	NA
Grubstein et al[8]/2005	8	69 ± 4	7/1	8/8	0.70 ± 0.08	86 ± 13	98 ± 21	30 ± 18
Hiwatari et al[24]/1993	9	67 ± 2	9/0	9/9	0.65 ± 0.17	95 ± 15	NA	45 ± 21
Jankowich and Rounds[13]/2010	20	69 ± 10	20/0	20/20	0.67 ± 0.12	77 ± 14	76 ± 11	29 ± 11
Kitaguchi et al[25]/2010	47	70 ± 1	46/1	46/1[a]	0.72 ± 0.02	95 ± 4	NA	40 ± 3
Kosacka et al[26]/2009	1	61	1/0	1/1	0.66	118	NA	27
Kurashima et al[14]/2010	221	71 ± 8	209/12	221/221	0.70 ± 12	87 ± 17	94 ± 17	65 ± 21
Lim[5]/1993	1	72	1/0	1/1	0.80	78	92	28
Mejía et al[15]/2009	31	67 ± 7	30/1	24/31	0.91 ± 0.09	62 ± 16	NA	NA
Mura et al[27]/2006	21	66 ± 10	20/1	21/21	0.74 ± 18	77 ± 20	95 ± 25	48 ± 26
Rogliani et al[28]/2008	9	71 ± 3	6/3	9/9	0.85 ± 0.02	82 ± 6	76 ± 6	NA
Schmidt et al[16]/2001[b]	42	64 ± 10	33/9	42/42	0.78 ± 0.07	76 ± 15	NA	42 ± 16
Silva et al[29]/2008	11	71 ± 7	8/3	11/11	0.74 ± 0.11	72 ± 13	92 ± 19	28 ± 13
Todd et al[17]/2011	28	57 (51, 62)[c]	17/11	28/28	0.81 (72, 86)[c]	60 (55, 73)[c]	64 (57, 73)[c]	27 (20, 37)[c]
Tsushima et al[30]/2010[d]	14	62 ± 10	14/0	13/14	0.69 ± 11	117 ± 14	NA	102 ± 31
Wiggins et al[4]/1990	8	68 ± 6	7/1	8/8	NA	94 (57-129)[e]	93 (88-121)[e]	32 (9-35)[e]
Totals[f]	607		549/58	592/607 (98%)				

Data are presented as mean ± SD or SE, unless otherwise indicated. CPFE = combined pulmonary fibrosis and emphysema; NA = not available.
[a]The one never smoker had significant passive smoking exposure (K. Fujimoto, MD, personal communication, April 2011).
[b]Moderate or severe emphysema in conjunction with pulmonary fibrosis.
[c]Median (first, third quartile).
[d]This study was focused on early diagnosis of interstitial lung disease and CPFE by CT scan, which may account for the relatively preserved gas exchange values reported.
[e]Median and range.
[f]Totals include all studies except Cottin et al[21] because of overlap of three patients in this study with Cottin et al.[7]

human smokers, and CPFE is unlikely to result from a defect in a single signaling pathway.

Physiologic Consequences

The physiologic consequences of the CPFE syndrome include preservation of spirometric values and lung volumes despite extensive radiographic evidence of lung disease as well as marked impairment of gas exchange manifested as a reduction in Dlco.[4,12] Mean values for vital capacity and total lung capacity frequently are in the normal range, whereas values for gas exchange are nearly always abnormal (Table 2). To account for the effects of emphysema on lung function parameters in the setting of pulmonary fibrosis, a composite physiologic index was developed that is a better predictor of prognosis in IPF than individual pulmonary function parameters.[65] The relatively normal lung volumes in CPFE usually are attributed to the counterbalancing effects of the restrictive defect of pulmonary fibrosis and the propensity to hyperinflation seen in emphysema. The normal spirometric values seen in some patients with CPFE also may be explained by increased traction caused by pulmonary fibrosis, preventing the typical expiratory airway collapse seen in emphysema,[66] and contributing to stiffening/support of the small airways by peribronchial fibrosis,[67] resulting in the preservation of FEV_1. The severe impairment of gas exchange in CPFE is likely due to reduced vascular surface area and pulmonary capillary blood volume plus alveolar membrane thickening resulting from the two coexistent disease processes.

Resting and exertional hypoxemia is common in CPFE syndrome. In the series by Cottin et al[7], mean Pao_2 at rest on room air was 63 ± 14 mm Hg, with an elevated average A-a gradient of 41 ± 16 mm Hg and average exertional desaturation of 8.9% during 6-min walk testing. In a study of 20 patients with CPFE over a 5-year period, 80% required an oxygen prescription, with mean resting flow rates of 3.3 ± 1.9 L/min.[13] Hypercarbia does not appear to be as frequent as hypoxemia in CPFE, with normal mean levels of $Paco_2$ in patients with CPFE in two studies.[7,25]

Radiology

Characteristic radiologic findings in the CPFE syndrome include upper-lobe emphysema and lower-lobe interstitial fibrotic changes (Fig 1). The emphysema in CPFE includes bullous, paraseptal, and centrilobular changes[7,13,25] and is typically distributed in the upper lobes.[7,25] Kitaguchi et al[25] found that paraseptal emphysema was more common in the CPFE population than in a control group of patients with COPD (33.3% vs 8.5%, respectively). Honeycombing and reticular abnormalities are frequent, but areas of ground glass attenuation also are commonly present, as in 66% of subjects with CPFE in a series by Cottin et al.[7] Occasionally, ground glass attenuation is the exclusive abnormality suggesting the possibility of interstitial lung disease, and in this setting, biopsy is essential.[9] Because smoking is almost universal in reported cases of CPFE, ground glass attenuation may be indicative of smoking-related interstitial lung diseases, such as desquamative interstitial pneumonia. Incidental lung nodules or masses may be found in patients with CPFE because the prevalence of lung cancer in this population appears to be high.[25,68] The overall sensitivity of CT imaging, even HRCT imaging, for findings consistent with CPFE is unclear and may not be high when pathologic findings are compared with imaging.[2] More-sensitive imaging techniques may be needed in diagnosing small regions of CPFE in at-risk populations, but the clinical significance of small regions of emphysema and fibrosis is presently unknown.

Pathology

A variety of pathologic patterns of pulmonary fibrosis have been reported in conjunction with emphysema in the CPFE syndrome, including usual interstitial pneumonia,[7] airspace enlargement with fibrosis,[69] nonspecific interstitial pneumonia,[7] respiratory bronchiolitis-associated interstitial lung disease with alveolar septal fibrosis,[70] desquamative interstitial pneumonia with extensive fibrosis,[9] and unclassifiable smoking-related interstitial fibrosis.[2]

Natural History and Mortality

The significance of changes in lung function over time appears to differ in patients with isolated IPF compared with patients with CPFE syndrome. Akagi et al[18] reported that patients with CPFE experience a slower decline in FVC and Dlco over time than do patients with isolated IPF. Because decline in FVC and Dlco are important prognostic factors in IPF, lack of recognition of concomitant emphysema in these patients may result in errors in prognostication. This has been highlighted by Schmidt et al,[16] who found that longitudinal decline in FEV_1 was more predictive of mortality in patients with CPFE than other pulmonary function parameters or a composite physiologic index, whereas a composite physiologic index was a better predictor of mortality in the isolated IPF group.

Mortality in patients with the CPFE syndrome is significant (Table 3). Median survival in reported series has ranged from 2.1 to 8.5 years, excluding a series by Usui et al[34] in which all patients had previously been given a diagnosis of lung cancer. If pulmonary hypertension confirmed by right heart catheterization is present, 1-year survival is only 60%.[21] Whether patients with CPFE syndrome have worse survival than patients with pulmonary fibrosis alone is unclear. A study by Mejía et al[15] found worse survival in a group with both emphysema and IPF compared with a group with isolated IPF, a finding related to pulmonary hypertension. Interestingly, the group with emphysema and IPF described by Mejía et al[15] had lower vital capacities than other reported cases of the CPFE syndrome (Table 2), and may not reflect the typical patient with CPFE syndrome. In contrast to the results of Mejía et al,[15] other studies[12-14,17,18] have found comparable or better survival in CPFE cohorts than in groups with isolated pulmonary fibrosis. The basis for these conflicting results is unclear and may include the relative proportion of non-IPF pathology in patients with CPFE syndrome in individual studies,[13,17] influence of emphysema subtypes,[17] retrospective study design,[13,15] inclusion and exclusion criteria,[14] and control group selection. However, these results raise significant questions about whether patients with characteristics of the CPFE syndrome should be included in trials of therapy in IPF[6] because they may not share the same pathogenetic factors or natural history as patients with IPF. An improved understanding of the natural history of the CPFE syndrome based on prospective cohort studies is needed

Table 3—*Mortality of CPFE*

Study/Year	No.	5-y Survival, %	Median Survival, y
Akagi et al[18]/2009	26	50	5
Cottin et al[7]/2005	61	55	6.1
Jankowich and Rounds[13]/2010	20	35	4
Kurashima et al[14]/2010	129	80	8.5
Mejía et al[15]/2009	31	NR	2.1
Todd et al[17]/2011	28	>50	5.25
Usui et al[34]/2011[a]	101	NR	0.9

NR = not reached. See Table 2 legend for expansion of other abbreviation.

[a]Patients with CPFE with concomitant lung cancer.

because these patients may not benefit from or may be harmed by therapies developed specifically for IPF. Subgroup analysis of completed IPF drug therapy trials stratified by presence or absence of emphysema may be informative.

Complications of CPFE

Pulmonary Hypertension

Pulmonary hypertension is a well-described complication of advanced lung disease in patients with CPFE syndrome. Pulmonary hypertension appears to be more frequent and more severe in the CPFE population than in patients with IPF alone.[15] Cottin et al[21] reported right heart catheterization findings in 40 patients with CPFE and pulmonary hypertension, with a mean pulmonary artery pressure of 40 ± 9 mm Hg. In this cohort, a reduced cardiac index (< 2.4 L/min/m^2) or elevated pulmonary vascular resistance (> 485 dyne/s/cm^5) were predictors of poor prognosis (median survival, 7.5 and 6.6 months, respectively).[21] No significant effect of medical therapy was observed,[21] and controlled studies are needed. Therefore, at present, oxygen therapy and, if appropriate, referral for lung transplantation would appear to be the most reasonable measures for the management of pulmonary hypertension in CPFE syndrome.

Lung Cancer

Patients with CPFE may be at significantly increased risk of lung cancer. Odani et al[68] found lung cancer prevalent in 13 of 31 (42%) CPFE cases. Kitaguchi et al[25] also found a significantly increased prevalence of lung cancer in a cohort with CPFE compared with a cohort with COPD alone (46.8% vs 7.3%, respectively), although this result may be affected by referral bias at a lung cancer treatment center. Kurashima et al[14] found a significantly higher proportion of deaths due to lung cancer in a cohort with CPFE (12 of 36 deaths, 33.3%) compared with a cohort with IPF alone (eight of 66 deaths, 12.1%). In a large cohort with lung cancer, Usui et al[34] found that CPFE was a significantly more frequent imaging finding (101 of 1,143 patients, 8.9%) than isolated pulmonary fibrosis (15 of 1,143 patients, 1.3%). Survival was significantly worse for CPFE and lung cancer than for emphysema and lung cancer.[34] These results need to be replicated in more-diverse patient populations at other centers. However, they suggest that chronic lung injury occurring in CPFE may influence the development and progression of lung cancer, which may be related to the "triple hit" effects of smoking, emphysema, and pulmonary fibrosis, all factors associated with lung cancer development, in CPFE. Additionally, an oncogene-based predisposition to the development of CPFE syndrome is possible.

Acute Lung Injury

CPFE may increase the risk of acute lung injury after lung resection surgery. In a retrospective study of 487 patients undergoing lobectomy for lung cancer, Saito et al[71] found 10 cases of postlobectomy ARDS. Seven of the 10 patients (70%) with postlobectomy ARDS had CPFE.[71] By contrast, Kawabata et al[69] found that smokers with usual interstitial pneumonia had a higher incidence of post-lung resection respiratory failure than smokers with a mixture of emphysema/airspace enlargement with fibrosis and usual interstitial pneumonia. Keller et al[3] observed more prolonged chest tube drainage and longer hospital stay in patients with emphysema and other histologic findings, including interstitial fibrosis, undergoing lung volume reduction surgery compared with a cohort with emphysema alone. Postoperative complications in the group with emphysema and another unexpected histologic finding included respiratory failure requiring reintubation in 17%.[3] Chemotherapy also may induce lung injury in CPFE. Usui et al[34] reported that 20 of 101 patients (19.8%) with CPFE and lung cancer developed severe acute lung injury during treatment, which included surgery, radiation, and chemotherapy. These studies and reports highlight the potential vulnerability of the CPFE population to additional lung insults. Therefore, preoperative identification of vulnerable hosts based on PFTs and chest CT scan is important.

Treatment of CPFE

There is no specific treatment of the CPFE syndrome. Smoking cessation, of course, should be encouraged and supported. Immunosuppressive therapy in conjunction with smoking cessation may be reasonable in select patients with evidence of active inflammation, such as ground glass infiltrates,[9] but is unlikely to be helpful in the setting of emphysema plus end-stage usual interstial pneumonia/IPF. Oxygen therapy is appropriate for management of hypoxemia. However, use of specific pulmonary hypertension therapies for CPFE-associated pulmonary hypertension requires further study.[21] Lung transplantation should be considered for patients with CPFE, given the significant mortality associated with this disorder. The relatively preserved spirometry associated with CPFE may disfavor such patients for lung allocation.

Conclusions

The CPFE syndrome illustrates the limitations of a simplistic diagnostic dichotomy between lung emphysema and fibrosis. Tobacco smoking may cause emphysema-dominant, fibrosis-dominant, or CPFE pathology, with differing implications for treatment, complications, and prognosis. We should take a broad view of the mixture of lung pathologies in patients and avoid single-minded application of classification schemes that have great usefulness in categorizing large groups of patients for clinical trials but that sometimes hobble our appreciation of the complexity of the individual patient. Biomarkers and more-sensitive imaging techniques are needed to better define the CPFE syndrome. While this article was in press, Alder et al[72] reported on a family with lung disease, including a member with onset of CPFE at age 34 years, harboring a mutation in telomerase component hTR. This is important evidence of a possible contribution of telomerase abnormalities and abnormal aging to the CPFE syndrome.

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