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IPF, comorbidities and management implications

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a complex disease that is associated with various respiratory and non-respiratory comorbidities. The most common comorbidity is cardiovascular disease (CVD), which increases in incidence with increasing duration of IPF and is associated with a higher risk of mortality. The direction of causality between CVD and IPF is unclear. There is evidence that IPF is associated with a prothrombotic state; however, warfarin is not beneficial in IPF patients. Lung cancer is another common comorbidity, being present in more than 50% of IPF patients at 10 years after diagnosis. IPF and lung cancer share several risk factors and pathogenic pathways and also show a similar anatomic distribution; this can make radiological diagnosis difficult. As with CVD, lung cancer in IPF patients is associated with a significantly worse prognosis and treatment options are limited. Surgery, chemotherapy, and radiotherapy have all been associated with an increased risk of morbidity and mortality. However, treatment may be considered in selected patients with less advanced cancer and less advanced IPF. Emphysema may occur in patients with IPF and is believed to represent a distinct clinical syndrome, known as the combined pulmonary fibrosis and emphysema (CPFE) syndrome. CPFE has a strong male predominance, is strongly linked with smoking, and has distinct radiographic features. CPFE is also associated with a very high frequency of pulmonary hypertension, which is associated with a poor prognosis. There are no specific treatments for CPFE and evaluation of IPF therapies in CPFE patients is urgently needed. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32; Suppl 1: 17-23)*

Key words: idiopathic pulmonary fibrosis; comorbidity; cardiovascular disease; lung cancer; pulmonary hypertension

Introduction

Idiopathic pulmonary fibrosis (IPF) is associated with a wide range of respiratory and non-respiratory conditions, such as gastroesophageal reflux, cardiovascular disease (CVD), pulmonary hypertension, lung cancer, obstructive sleep apnea, depression and diabetes (1). The presence of IPF comorbidities can significantly influence prognosis and inform management strategies, so it is important that clinicians recognise the potential for these concurrent conditions and be able to identify and manage them. Here we focus on three common IPF comorbidities: CVD, lung cancer, and emphysema, including the clinical syndrome known as combined pulmonary fibrosis and emphysema (CPFE).

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Cardiovascular disease

CVD is the most frequent comorbidity in patients with IPF. In a Danish cohort study, CVD, arterial hypertension, ischaemic heart disease, and pul-

monary hypertension were present in 20%, 15%, 13%, and 10% of IPF patients, respectively (Table 1) (1). Significantly, patients who developed CVD during follow-up were at increased risk of mortality compared with those who did not develop this comorbidity.

An earlier UK population-based study assessed the prevalence of vascular disease in people with IPF (2). It found that acute coronary syndrome (ACS), angina, atrial fibrillation, and deep vein thrombosis (DVT) were all significantly more prevalent among IPF patients than in the general population. These differences were present at the time of IPF diagnosis and became more pronounced during follow-up. As IPF progressed, there was a steady increase in the occurrence of vascular events, with the most marked increase seen for ACS and DVT (Figure 1).

While there is no doubt that IPF and CVD are correlated, the direction of causality is less clear. Does IPF favour the onset of a prothrombotic state or does a prothrombotic state favour the onset of IPF? There are several possible mechanisms by which IPF might lead to a prothrombotic state. For instance, hypoxia can lead to angina and arrhythmias; decreased mobility in patients with IPF is a risk factor for DVT; and the presence of IPF might distract medical attention from assessment of CV risk. Arguing against these putative mechanisms is the fact that patients with chronic obstructive pulmonary disease – another major respiratory disease that is also associated with hypoxia and decreased mobility – have a much lower annual risk of venous thromboembolic disease than patients with IPF (3).

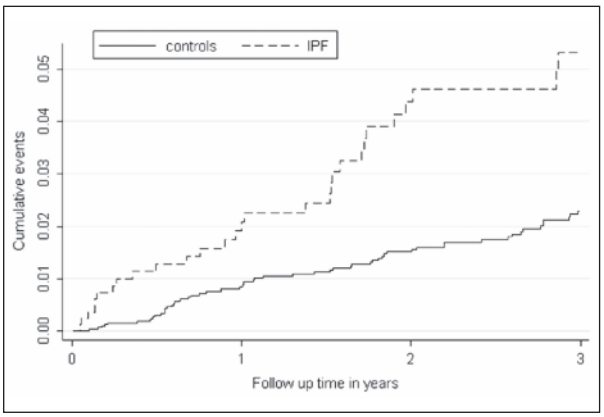

Fig. 1. Cumulative incidence of acute coronary syndromes in IPF and control subjects (2)

What is the evidence that a prothrombotic state favours the onset of IPF? We already know that the coagulation cascade is very important in the process of wound healing and that abnormal wound healing is a fundamental defect in IPF. Following injury, the coagulation cascade is activated, leading to production of fibrin, plasminogen and plasminogen inhibitors and the formation of a reticulum, with subsequent recruitment of fibroblasts. In normal wound

Table 1. Comorbid diseases in patients with IPF (1)

Comorbid diagnosis	At time of inclusion n (%)	Diagnosed during follow-up n (%)	Total n (%)
Cardiovascular disease	24 (20%)	9 (7%)	33 (27%)
Arterial hypertension	18 (15%)	4 (3%)	22 (18%)
Ischaemic heart disease	16 (%)	6 (5%)	22 (18%)
Pulmonary hypertension	12 (10%)	14 (11%)	26 (21%)
Diabetes	11 (9%)	10 (8%)	21 (17%)
Gastroesophageal reflux	10 (8%)	0	10 (8%)
Depression	8 (7%)	20 (17%)	25 (21%)
Osteoporosis	8 (7%)	10 (8%)	18 (15%)
Cerebral infarction	8 (7%)	3 (2%)	11 (9%)
Atrial fibrillation	5 (4%)	6 (5%)	11 (9%)
Lung cancer	0	7 (6%)	7 (6%)
Other cancers	0	4 (3%)	4 (3%)

[a]Ischaemic heart disease, cerebral infarction, peripheral arteriosclerosis. Some patients had more than one diagnosis. B (n-1), rectum (n-1), prostate (n-2)

healing, a point is reached where fibrinolysis increases and fibrin disappears; this does not occur in patients with IPF.

There is clinical evidence that IPF is associated with a prothrombotic state. In a case–control study, 80% of patients with IPF had a prothrombotic state (defined as the presence of at least one inherited or acquired clotting defect or marker of fibrinolytic dysfunction) (4). IPF patients were nearly five times more likely than general population controls to have a prothrombotic state; furthermore, IPF patients with a prothrombotic state tended to have more severe disease at diagnosis and a three-fold greater mortality during follow-up compared with IPF patients with no clotting defects. Thus, a profibrotic state in patients with IPF is highly relevant to disease progression and outcomes.

How might this occur? Thrombin is a potent promoter of fibroblast proliferation and extracellular matrix deposition; it also promotes the differentiation of fibroblasts into myofibroblasts. Thrombin and the coagulation cascade are therefore highly involved in the fibrotic process (5). There is evidence for this *in vivo*: studies show that fibrinolytic activity is reduced in the lungs of people with IPF (6). It has also been demonstrated *in vivo* that plasminogen activator inhibitor-1 is overexpressed by type-2 pneumocytes within honeycomb lesions (7).

Given the high prevalence of a prothrombotic state observed in people with IPF, it seems rational to use anticoagulants in these individuals. Yet, surprisingly, a trial of warfarin in IPF patients who lacked other indications for anticoagulation found that treatment did not reduce all-cause mortality or hospitalisation compared with placebo. Conversely, warfarin was actually associated with an increased risk of mortality in this population (8). A similar result was seen in a Danish IPF cohort, in which patients receiving anticoagulation had significantly higher mortality than their non-anticoagulated counterparts (1). Therefore, the issue of causality relating to IPF and a vascular disease remains unresolved.

Lung cancer

Lung cancer is a frequent comorbidity in IPF, with a higher incidence and reduced survival in IPF compared to other IIPs (9). Estimates of the prevalence of lung cancer in IPF vary widely, from 5% to 20%, and depends on the duration of follow-up and therefore on survival. In a population of Italian IPF patients, 13% had lung cancer; the most frequent histologic subtypes were peripheral squamous cell carcinoma and adenocarcinoma (10). Interestingly, the cumulative incidence of lung cancer increases strikingly over time, from around 3.3% at 1 year after IPF diagnosis to 15.4% at 5 years and 54.7% at 10 years (11). In this study, age at initial IPF diagnosis was a significant independent factor predicting the development of lung cancer.

IPF and lung cancer share many of the same risk factors – older age, male sex, and smoking. They also share many pathogenic pathways, including genetic and epigenetic alterations, tissue invasion, uncontrolled proliferation, and activation of specific signal transduction pathways (Figure 2) (12). In IPF patients with lung cancer, tumours are typically subpleural or peripheral and close to or within honeycomb and fibrotic areas. Less often, the appearance is of isolated areas of ground glass. This can make radiological diagnosis of lung cancer difficult, especially at the time of the first high-resolution computed tomography (HRCT) scan (Figure 3).

The development of lung cancer in patients with IPF heralds a significantly worse prognosis. In a recent study, survival at 1 and 3 years after IPF diagnosis was 78% and 52%, respectively, in patients with lung cancer versus 92% and 70%, respectively, in those without lung cancer (Figure 4) (10). Despite the poor prognosis, the decision about whether and how to treat lung cancer in IPF is extremely difficult since any lung cancer treatment is associated with significant toxicity (9). Surgery has been shown not to improve survival (13). Furthermore, acute exacerbations of IPF are a well-described complication following lung resection, with an incidence of approximately 15% and mortality of 100% in some studies (14).

The role of chemotherapy in IPF is controversial. A paclitaxel/carboplatin regimen has been evaluated in patients with idiopathic interstitial pneumonias and advanced non-small-cell lung cancer and found to be as effective and well tolerated as in patients without idiopathic interstitial pneumonia (15). In this study, the overall response rate was 61%, median progression-free survival was 5.3 months, and just one patient (5.3%) experienced an acute exacerbation of idiopathic interstitial pneumo-

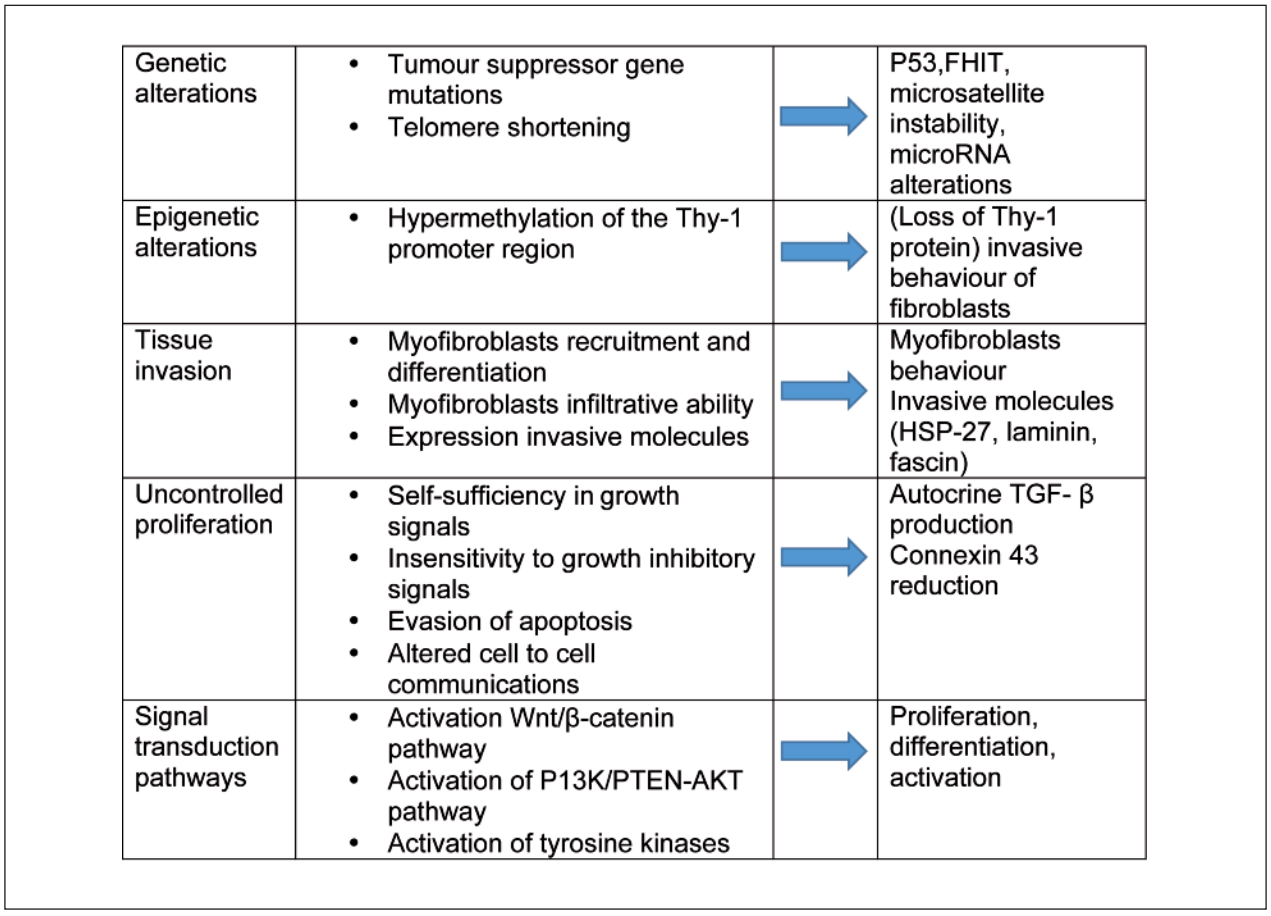

Fig. 2. Cancer and IPF share common pathogenic pathways (12)
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nia following treatment. However, another study reported an acute exacerbation rate of 30% together with a high rate of grade 5 pulmonary toxicity (16). Acute exacerbations of IPF have also been reported following radiotherapy for lung cancer (17).

In the absence of effective and safe treatment options, the management of patients with IPF and lung cancer should comprise annual HRCT imaging; advice on reducing risk factors (e.g., smoking); regular evaluation of lung function and performance status; and accurate cancer staging. Treatment of lung cancer may be considered in a small group of patients – typically those with less advanced cancer and less advanced IPF, in whom surgery or radiotherapy may be helpful. Unfortunately, the 2011 ATS/ERS/JRS/ALAT guidelines offer no practical guidance on this issue, citing lack of evidence (18).

Emphysema and CPFE

The co-occurrence of emphysema and IPF is believed by some to be a distinct entity that represents a clinical syndrome, termed the combined pulmonary fibrosis and emphysema (CPFE) syndrome (19). This view is challenged by others, who argue that comorbid emphysema and IPF simply represent the co-occurrence of two separate diseases.

A syndrome may be defined as a collection of signs and symptoms that are associated with certain clinical manifestations and disease behaviours. Using these criteria, comorbid emphysema and IPF is indeed a syndrome: it has a high male predominance and a strong link with smoking, it exhibits radiographic diagnostic features (namely, emphysema of the upper lobes and opacities suggesting fibrosis),

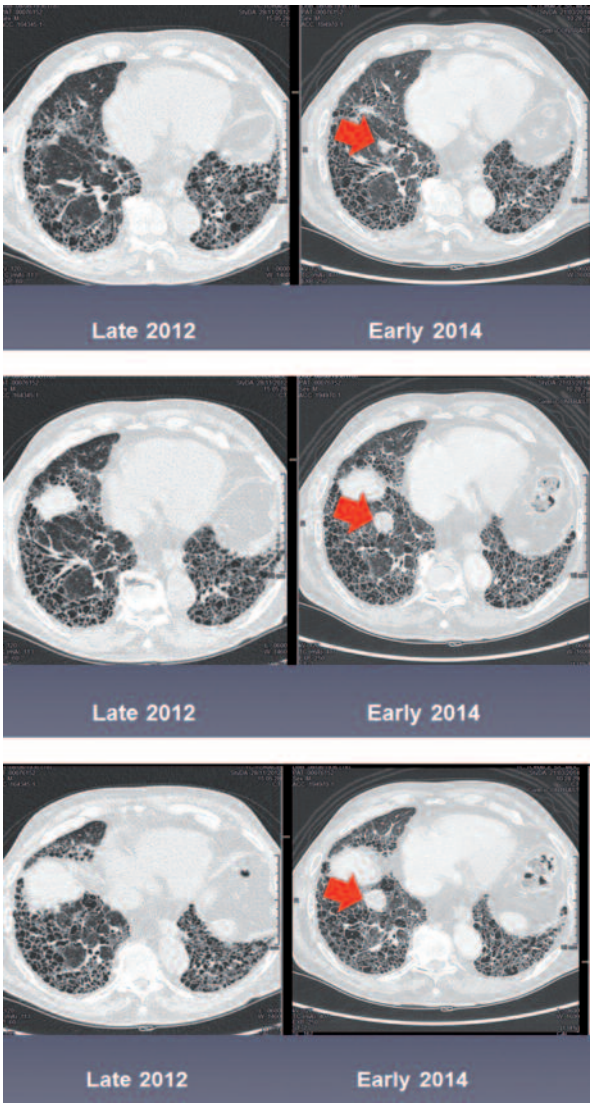

Fig. 3. Lung cancer and IPF (12)

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and there is high prevalence of comorbid pulmonary hypertension (19).

In a study of 365 patients with IPF, several clinical characteristics differed according to the presence or absence of emphysema. Patients with emphysema were significantly more likely to be current or former smokers, had higher lung volumes and lower DL_{CO}, lower fibrosis scores, and were much more likely to have pulmonary hypertension and to need long-term oxygen therapy (20).

Importantly, the aetiology of CPFE is heterogeneous. As well as male sex and smoking, CPFE

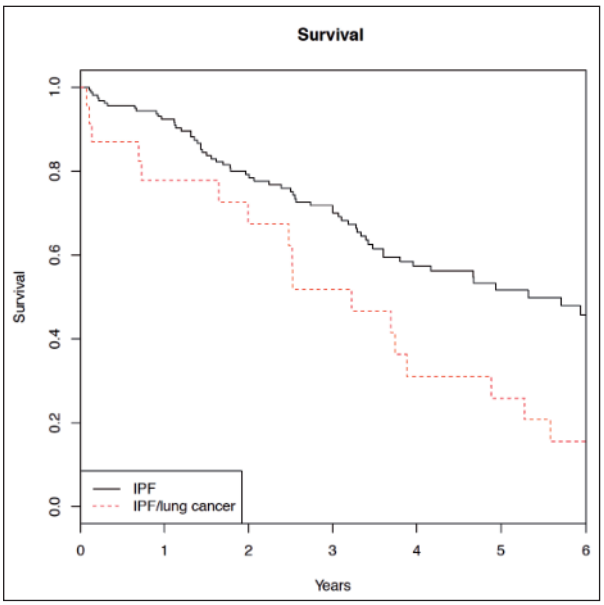

Fig. 4. Survival of IPF patients with and without lung cancer (time 0 is diagnosis of IPF for both groups) (10)

Reproduced with permission from the American College of Chest Physicians. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest 2015 Jan 1; 147 (1): 157-64.

may occur in people with systemic diseases (such as connective tissue disease and vasculitis) and there may be a genetic predisposition. CPFE has also been described in other contexts, in the presence or absence of tobacco smoking, such as in people with occupational exposure to agrochemical compounds, coal dust, talc or asbestos (21,22).

There is emerging evidence that CPFE has a genetic component. This is supported by the epidemiology, which shows a strong male predominance with a male to female ratio of 9 to 1 (23). There has been a case report of a heterozygous mutation in the surfactant protein-C (*SFTPC*) gene in a woman with CPFE (24). In addition, both fibrosis and emphysema are associated with shorter telomeres, and CPFE has recently been reported in a family with a mutation in the telomerase (*TERT*) gene (25).

Imaging patterns in patients with CPFE differ from those with IPF, being characterised by very tight interconnections between areas of fibrosis and emphysema. Both the honeycombing and the emphysema seen in CPFE are unlike those seen in the lone diseases (Figure 5). Furthermore, smoking-related interstitial fibrosis has a distinctive pathologic

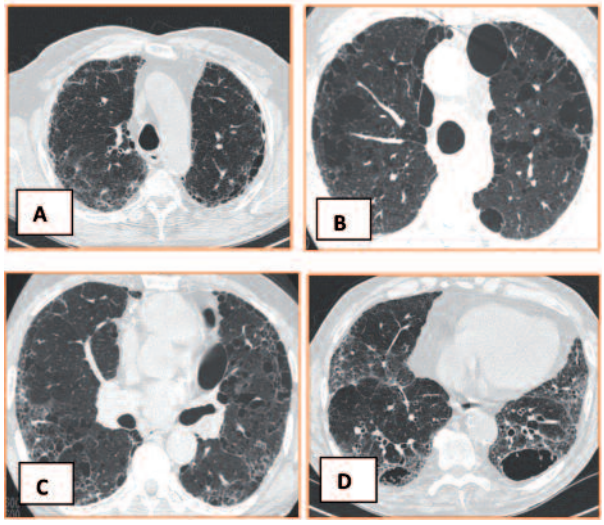

Fig. 5. Imaging patterns in CPFE differ from those in lone IPF. A, paraseptal is present in the upper zones, with mild interstitial changes; B, marked subpleural emphysema with mild ground glass opacity; C, admixture of reticulation and emphysema; D, fibrotic changes including reticulation and traction bronchiectasis, and thick walled large cysts of the lower zones of the lung

pattern that is unlike usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP). Instead, it is characterised by marked thickening of the alveolar septa and thick collagen bundles with a distinctive hyalinised quality (26).

CPFE is associated with a variety of comorbidities and complications (Figure 5). The risk of pulmonary hypertension is around six times higher in patients with comorbid emphysema and IPF versus IPF alone (27). Development of this complication is a critical determinant of prognosis; in one study of patients with CPFE, survival at 5 years was 25% in those with pulmonary hypertension at diagnosis versus 75% in those without (19).

By contrast, it has not been demonstrated that emphysema impacts survival in IPF; in one study with adjustment for the severity of fibrosis at imaging, there was no significant difference in survival between IPF patients with and without emphysema (20). Other studies have found conflicting results due to methodological issues.

CPFE is also associated with an increased risk of developing lung cancer. In a series of 47 patients with CPFE with lung cancer, all of whom were smokers, a pathological diagnosis of lung cancer was obtained in only 38 patients (81%) due to the underlying parenchymal lung disease. Overall, 20 patients could not receive standard-of-care treatment for lung cancer and median survival was just 7.6 months from cancer diagnosis (28).

There are currently no specific management recommendations for CPFE beyond smoking cessation and use of bronchodilators. Trials in patients with IPF use FVC as the primary endpoint, and are thus not relevant to CPFE. Specific assessment of pirfenidone and nintedanib in CPFE is urgently needed.

Conclusion

Patients with IPF should be carefully assessed for comorbidities, the most significant of which are cardiovascular disease and lung cancer. Both these comorbidities are associated with a significantly worse prognosis and are difficult to treat, with few established therapeutic options. Anticoagulation has been shown to increase mortality in patients with IPF. Meanwhile, in IPF patients with lung cancer, surgery, chemotherapy, and radiotherapy have all been linked with severe toxicity and especially acute exacerbations, which may be fatal. Emphysema is a less common comorbidity in IPF that is considered to represent a distinct clinical syndrome, known as CPFE. CPFE differs from IPF in several respects, including its strong male predominance, strong link with smoking, and very high prevalence of pulmonary hypertension. As with CVD and lung cancer, there are currently no specific management recommendations and assessment of pirfenidone and nintedanib in CPFE is urgently needed.

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