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IPF and CPFE — the two different entities or two different presentations of the same disease?

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Abstract

In this article the co-existence of pulmonary emphysema with lung fibrosis of typical pattern and distribution for usual interstitial pneumonia (UIP) was compared with idiopathic pulmonary fibrosis (IPF) alone. Author discusses the etiopathogenesis of these diseases, differences in signaling pathways and the role of senescent cells. Moreover, clinical course, pulmonary function tests as well as main complications are reviewed. However, the lack of well-established diagnostic criteria for CPFE along with mainly retrospective character of the studies make current knowledge about this entity rather deficient.

Key words: idiopathic pulmonary fibrosis, IPF, combined pulmonary fibrosis and emphysema, CPFE

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Introduction

At the first glimpse the two entities are very similar. Idiopathic pulmonary fibrosis (IPF) is a progressive disease with fibrosis of the lung alveoli and interstitium of unknown etiology, but poor prognosis (median survival 3–4 years). Combined pulmonary fibrosis and emphysema (CPFE) comprises, besides lung fibrosis, pulmonary emphysema with typical distribution. IPF as well as CPFE present with UIP (usual interstitial pneumonia) pattern of fibrosis: reticular opacities, honeycombing with or without traction bronchiectasis, localized in subpleural, bottom parts of the lungs in the lower lobes [1]. Besides fibrotic changes, cenrtilobular and/or paraseptal emphysema or bullous changes in the upper lobes are characteristic of CPFE. Emphysema can also be present in IPF patients as reticulation admixed emphysema and may mimic honeycombing [2, 3]. Of note, emphysema concomitant with interstitial lung disease is not only specific for IPF pattern [4].

CPFE is a quite new entity. In 1990 Wiggins *et al.* [5] for the first time described eight patients with cryptogenic fibrosing alveolitis with emphysema. Fifteen years later, in 2005, Cottin *et al.* [6] gave in clinical, pathophysiological and imaging terms — the comprehensive description of patients with CPFE. Thus, they proved that CPFE is a distinct entity, different from IPF as well as from emphysema, with distinct prognosis and typical comorbidities (i.e. pulmonary hypertension). Then they have also noticed that the disease affected almost exclusively older men, heavy smokers. Such a high men predominance — 100% in some studies, with the male/female ratio 9:1 in the others, while in IPF, this ratio is 2:1, could not be explained only by the greater exposure to cigarette smoke in men [7].

During the last decade, a great progress in diagnostic and therapeutic approach to patients with IPF has been made. Although the main risk factor for lung fibrosis and emphysema is cigarette smoke, the pathomechanism of these entities is quite different. According to the current view,

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persistent exposure to the detrimental environmental factors like cigarette smoke, air pollution, viral infection in susceptible individuals leads to dysregulated cross-talking between epithelial and mesenchymal cells [8–10]. Injured alveolar epithelial cells orchestrating with recruited inflammatory cells, proteinase-antiproteinase imbalance along with oxidative stress contribute to dysregulated epithelial-mesenchymal transition (EMT) [8–10]. Released by epithelial and other cells pro-fibrotic cytokines, mainly TGF-β, PDGF, connective tissue growth factor (CTGF) stimulate EMT, activate myofibroblasts, which acquire antiapoptotic and invasive properties [11–13]. In consequence, the histological hallmark of UIP — fibroblastic foci coexist with fibroblasts and myofibroblasts. These myofibroblasts with their contractile fibrils, mainly α-SMA (alpha smooth muscle actin), are presumably responsible for alveolar collapse and restrictive phenotype of patients with IPF [14].

In the last years, in both IPF and emphysema, accelerated senescence associated with decreased telomere length was found [15, 16]. About 10% of familial IPF patients harbored mutations affecting telomerase reverse transcriptase — TERT or telomerase RNA component — TERC [17]. According to this concept, senescent cells with increased β-galactosidase activity as well as P53, P21 and P16 proteins acquire antiapoptotic and secretory features [18, 19]. Such cells with senescence-associated secretory phenotype (SASP) produce broad repertoire of proinflammatory cytokines, chemokines, growth factors influencing neighboring tissues. Physiologically, the number of senescent cells increases with age [20]. However, in IPF, accelerated senescence of epithelial cells and fibroblasts with accumulation of these cells in the lungs was demonstrated [19, 21]. Furthermore, it was revealed that the process is mainly regulated by microRNA-34a [22]. Thus, SASP cells emerge as the main driver of fibroproliferative mechanism perpetuating abnormal epithelial-mesenchymal interactions. Moreover, in the murine model, senolytic intervention with disatinib and quercetin showed striking improvement in pulmonary and physiological functions [21]. If so, this model can change the existing paradigm of the fibroblast role: from aberrantly activated cells to cells with senescence phenotype.

Of note, according to this scenario, in COPD -emphysema, abnormal senescence is associated with mesenchymal cells insufficiency, leading to decrease of extracellular matrix and alveolar vanishing [23]. On molecular basis, in IPF, Wnt/β — catenin and Notch signaling pathways increase, which through the complex interactions enhance TGF-β concentration [24, 25]. Instead, in COPD -emphysema these pathways are significantly inhibited [23, 26]. So, contrary to IPF, decreased ECM components due to increased MMPs activity along with depressed fibroblasts function and their reduced response to TGF-β were reported [27]. It is intriguing that in dysregulated inflammatory and remodeling processes, similar factors can lead to different epithelial-mesenchymal responses, favoring either emphysema or fibrosis.

Comparing clinical course of IPF and CPFE, many studies indicated much worse prognosis of CPFE [7, 28]. Zhang *et al.* [28] studying the Chinese population, found a 5-yr survival rate in CPFE subjects at 43% with all-cause mortality rate at 56.6%, compared to IPF group with 65.7% and 34.4%, respectively. Also composite physiologic index (CPI) that represents a combination of pulmonary ventilation, diffusing capacity for carbon monoxide and chest HRCT score, increased more dramatically in CPFE patients at each point during 36 months of observation. Furthermore, pulmonary hypertension — a common complication in advanced CPFE, was found to be an additional predictor of poor prognosis [29].

However, there are also data indicating the same [30] or even longer survival in CPFE patients vs. IPF subjects [31]. In fact, some authors reported that median survival of CPFE patients with autoimmune markers like ANA, ANCA was 51 months, compared to 38 months in those with negative autoimmune profile ($p = 0.052$) [32]. As might be expected, patients with positive immunological markers expressed high level of CD 20+ cells in lung specimens, forming lymphoid follicles adjacent to fibroblast foci. However, these observations suggested rather ongoing autoimmune disease than CPFE. On the other hand, we cannot exclude the possibility that some patients with CPFE were included into the IPF group. Although the prevalence of CPFE in the general population is still unknown — about 8% to 53% of those with IPF after reevaluation were identified as CPFE patients [33, 34]. That is why the median survival in patients with CPFE is reported to cover a wide range: from 2.1 to 8.5 years. Moreover, the extent of emphysema on CT scans, by different researchers is defined as greater than 5%,10%, 15% or even bigger percentage of the lung volume. Taking into account that too small range of emphysema may exert discernible effect on the disease, the recently proposed equal to or more than 15% — seems to be commonly acceptable.

As the main risk factor for lung cancer (LC) development is cigarette smoke, and emphysema is additional independent risk factor [35], one might assume that the incidence of LC is higher in the CPFE group compared to the IPF one. Kwak *et al.* [36] for the first time analyzing retrospectively medical records of patients hospitalized in Seoul National University Hospital from 2000 to 2011, found similar risk of LC in CPFE patients and IPF subjects (HR 1.11, p = 0.845). However, LC risk in both groups was significantly higher than that in solely emphysema patients (HR 4.62, p = 0.005 for CPFE and 4.15, p = 0.046 for IPF). Like previously reported, cancer had mainly subpleural localization, in the lower lobes, while in patients with emphysema — in the upper lobes [36–38]. Furthermore, a 5-year survival rate did not differ between the CPFE and IPF group (22% and 22%, respectively) [39]. Similar results were reported by Sato *et al.* [40]. However, an extremely low 5-year survival rate in CPFE subjects comparing to the group with sole emphysema (18.7% and 67.1%, respectively) was also recorded [41]. Of note, CPFE patients significantly more frequently developed postoperative cardiopulmonary complications than those with IPF (40). Interestingly, according to scarce data, squamous cell cancer followed by adenocarcinoma were the most common types in the CPFE group [39, 40]. In the IPF group, that sequence may be reversed [39, 40, 42].

As there is no treatment capable of halting or reversing these diseases and even no commonly accepted therapeutic option is available for those with CPFE, the approach to subjects with IPF and CPFE is quite the same. Smoking cessation, oxygen supplementation, antifibrotic drugs like pirfeniden and nintedanib, along with bronchodilators in those with obstructive pattern are recommended. However, no efficacy of specific pulmonary hypertension therapy has been noticed. Like in patients with IPF, lung transplantation is the last option.

So, what is the role of emphysema in CPFE patients?

Due to emphysema, normal or nearly normal lung volume is preserved, because hyperinflation acts contrarily to fibrosis. However, already diffusing capacity of the lung for carbon monoxide is lower than that in IPF subjects. Also higher risk for the development of pulmonary hypertension, a strong predictor of mortality is observed [29]. But no additive impact of emphysema on lung cancer development in CPFE patients has been found [36]. Interestingly, a few months ago Jacob *et al.* [43], in a retrospective analysis reported that the presence and extent of emphysema had no prognostic impact on survival of patients with IPF after correction for baseline disease severity. Furthermore, only isolated emphysema distant from fibrosis was independently associated with lower DLCO but had no impact on the lung volume. Whereas emphysema admixed with fibrosis exercised no influence on DLCO but preserved forced vital capacity.

Looking at the conflicting results of different, often retrospective studies based on heterogeneous populations, along with the lack of precise CPFE definition as well as treatment consensus strategy, it is high time to shed more light on this young and still unrecognized disease.

So finally, looking at the data above, it seems that IPF and CPFE are rather two different entities.

Conflict of interest

The author declares no conflict of interest.

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