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Editorial

Combined Pulmonary Fibrosis and Emphysema Syndrome: What is the Role of Airflow Limitation?

Síndrome Combinación Fibrosis Pulmonar y Enfisema. ¿Cuál es el papel de la limitación al flujo aéreo?

Idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD) are two diseases with very different clinical, radiological and functional characteristics. However, both share a common factor: smoking. Smoking is the main etiological factor in the development of COPD, while in IPF, without being the cause of the disease, it is one of the main risk factors.[1,2] Therefore, the overlap between the two conditions is not uncommon.

Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome in which radiological signs of emphysema (predominantly in the upper lobes) and pulmonary fibrosis coexist in the same individual on high-resolution computed tomography (HRCT). CPFE is an emerging disease and it seems to be associated with a different natural history and prognosis than IPF. Due to the growing interest in this syndrome, a paper has recently been published discussing the definition as well as the main unknowns surrounding CFPE.[3] One question is whether patients with CFPE and airflow limitation, one of the characteristic features of COPD, represent a different phenotype.

This is because patients with CFPE present with a characteristic respiratory pattern, with apparently normal or minimally altered dynamic and static lung volumes contrasting with severe compromise of carbon monoxide diffusion (DLCO) and arterial hypoxemia, which is exacerbated during exercise. In addition, in interstitial diseases, airway resistance is decreased due to the traction exerted by fibrous tissue in the airway. All this results in low dynamic compression during expiration and the forced expiratory volume in the first second (FEV_1) and therefore the FEV_1/FVC are elevated.

This could be one of the explanations why we found few studies of IPF and COPD in the literature. In the previously mentioned document, the definition of the CFPE clinical syndrome only includes subjects with mild airflow limitation, suggesting the possibility that patients with COPD and IPF form a different phenotype. At present, it is unknown whether the evolution or response to treatment in patients with CFPE is different depending on whether or not airflow limitation. It is uncertain whether both situations represent the same disease with a higher degree of severity or if, on the contrary, they are two different entities.

There are few studies in the literature that answer this question. Most studies only assess the presence of emphysema and not obstruction, considering the radiological findings of emphysema (quantified by TACAR $\geq$ 15%) and COPD to be the same. Kitaguchi et al. analyzed the difference between the combination of CFPE with and without obstruction using pulmonary function tests and radiology imaging. In the imaging findings, the degree of emphysema was significantly lower in the group without obstruction. On the contrary, the degree of fibrosis was higher in this group. Regarding pulmonary function, the percentage of carbon monoxide diffusion adjusted for alveolar volume (KCO) was significantly lower in the group with obstruction. We also found a significant correlation between KCO and the degree of emphysema on chest HRCT among all patients with CFPE regardless of whether or not obstruction was present.[4]

Regarding the characteristics of patients with COPD and IPF, data from studies show that they are older patients, predominantly male, with a high pack-year index and more frequently present respiratory symptoms than patients with IPF alone.[5] Zantah et al. retrospectively reviewed the clinical data of patients with COPD-IPF and IPF. Events of acute IPF exacerbation in both groups and COPD exacerbation in the COPD-IPF group were collected. The data extracted from this study is that COPD-IPF patients can suffer from both IPF and COPD exacerbation, but COPD exacerbations required less intensive treatment compared to patients with IPF exacerbation. These data suggest that the type of acute exacerbation (COPD exacerbation or IPF exacerbation) has important implications for the treatment and prognosis of patients with COPD-IPF.[6] Another conclusion was that the severity of IPF exacerbation was independent of whether the underlying disease was COPD-IPF or IPF. These data are different from other studies, which indicate that the number of deaths due to acute exacerbations of IPF was higher in the IPF alone group than in the COPD-IPF group (42.6% vs. 18.8%).[5]

Regarding prognosis, a study by Zhang et al. compared patients with COPD-IPF versus isolated IPF over a 60-month follow-up period. The calculation of the Composite Physiological Index (CPI) was performed. This index is based on the extent of lung disease on HRCT and pulmonary function tests and correlates more closely with mortality than either pulmonary function value in isolation. A total of 80 subjects with COPD-IPF and 99 subjects with IPF completed follow-up. The CPI index scores of COPD-IPF patients were significantly higher than those of IPF patients at all time points during the course of the disease. the score in the COPD-IPF group

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increased more rapidly compared to that in the IPF group during the 36 months of follow-up, suggesting a more quickly progressive clinical course of COPD-IPF compared to that of IPF.[7]

All these questions have clinical implications. The impact of inhaled bronchodilators and corticosteroids, which are the main treatment for COPD, in patients with CFPE, and especially depending on the presence or not of airflow limitation, is unknown. Therefore, it is necessary to advance in the clinical consensus on the diagnostic criteria for CFPE syndrome and its differentiation from COPD-IPF overlap. In addition, the understanding of the different prognostic factors, and especially airflow limitation, should be explored in further prospective cohort studies to develop effective therapeutic strategies.

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