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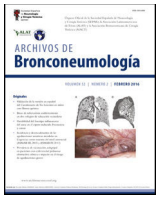

Editorial

Controversies in Fibrosis and Emphysema

Controversias en la fibrosis y el enfisema

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The clinical entity of combined pulmonary fibrosis and emphysema (CPFE) is characterized by the admixture of fibrosis and emphysema on high resolution computed tomography (HRCT). It can be observed in the context of idiopathic interstitial pneumonias such as idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) and in interstitial lung diseases associated with connective tissue disorders (CTD-ILDs) such as rheumatoid arthritis (RA) and systemic sclerosis (SSc).[1–3] It is still unclear whether this entity represents a distinct syndrome, a specific subtype of fibrosis, or a coincidental co-existence of two processes.

In contrast to isolated pulmonary fibrosis and emphysema, no specific pathogenic pathways which could lead to different treatment approach for CPFE have yet been identified. However, common pathogenetic pathways, such as increase in oxidative stress, accelerated lung aging associated with genetic abnormalities (for example, mutations in the telomerase genes), and increased neutrophil elastases are involved in both disorders.[4] Historically, the presence of radiologic emphysema was associated with smoking. Interestingly, in smokers with IPF, NSIP, rheumatoid and pulmonary scleroderma, the development of emphysema was associated with a lower pack-year smoking history than in smokers without fibrosis.[1–3] This could be viewed as indirect evidence of an interaction between fibrosis and smoking in the development of emphysema in this subgroup of patients. More intriguingly, in a large cohort of 333 patients with pulmonary scleroderma, 15/41 patients with CPFE were non-smokers, raising the possibility of an autoimmune origin of emphysema in this subgroup.[3] Obviously, in the absence of a control cohort, these results should be interpreted with caution, and need to be confirmed at the cellular and biological level.

CPFE poses significant difficulties in the diagnosis of the radiologic pattern of pulmonary fibrosis. It is generally accepted that in ILDs, diagnosis means prognosis. In clinical practice, the main concern is to distinguish IPF, the most common and severe form of ILD, from other fibrotic lung disease such as NSIP, some subtypes of chronic hypersensitivity pneumonitis, and unclassifiable ILD, which generally have a better prognosis. In CPFE, it is often difficult to distinguish between honeycombing cysts, the main characteristic of usual interstitial pneumonia (UIP) which is the radiologic counterpart of IPF, and pseudocysts due to admixture of emphysema and fibrosis. This difficulty was underlined in a recent study in the diagnosis of UIP among thoracic radiologists with special interest in ILDs.[5] Quantification of the extent of both processes is also problematic. Some experts have suggested using density masking, but the main constraint in this case is that areas of low density could correspond to either emphysema, or honeycombing, or traction bronchiectasis. The likely contamination of CPFE cohorts with entities like NSIP, and the difficulty in including patients with the same extent of emphysema and fibrosis has led to conflicting results regarding the prognostic significance of CPFE.[6–8] Mejia et al. reported an interesting finding, namely, that worse prognosis in CPFE was due to the high prevalence of pulmonary hypertension (PH).[6] Although this could facilitate early diagnosis of PH, it is clinically irrelevant because no effective treatment is available for PH associated with IPF or CPFE. In scleroderma lung, which exhibits different clinical behavior from IPF, the presence of trivial emphysema did not influence the prevalence of PH on echocardiography at presentation compared to patients with isolated fibrosis.[3] After adjustment for the extent of fibrosis on HRCT, emphysema was associated with an additional average reduction of 24.1% from baseline DLco levels and a 34.8% increase in the FVC/DLco ratio, but there was no overall significant effect on forced vital capacity (FVC) levels. These effects did not differ between smokers and nonsmokers, and on multivariate analysis pulmonary function tests were not influenced by either smoking status or total pack-years after adjusting for the extent of pulmonary fibrosis or the presence of emphysema. The FVC/DLco ratio is used in SSc as a marker of PH, and a value greater than 1.6 calls for an echocardiogram. However, this study showed that in the presence of emphysema, the ratio is not a reliable marker for echocardiographic features of PH.[3]

The coexistence of emphysema and fibrosis has a significant attenuating effect on serial FVC decline, with major implications for routine IPF monitoring and the use of serial FVC as a primary endpoint in IPF treatment trials. In a well-defined pharmaceutical IPF cohort, patients with IPF and concurrent emphysema had a

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significantly slower rate of decline of FVC than patients with IPF only when the extent of emphysema on HRCT was greater than 15%.[9] It should also be stressed that the coexistence of emphysema with IPF leads to spurious preservation of FVC, which has implications in the approval of antifibrotic drugs in countries where an upper limit for FVC is used to assess eligibility for treatment. There is still insufficient evidence to support the use of the composite physiolocic index (cpi), which takes into account the presence of emphysema, as an end-point in these patients. Baseline cpi correlates with the extent of IPF disease on CT and is superior to individual lung function variables in predicting survival in patients with concomitant radiologic emphysema, whereas in IPF patients without emphysema, baseline cpi has the same predictive value as baseline DLco.[10]

In the context of CTD-ILDs, the impact of concurrent emphysema on serial changes in FVC, which is also used as the primary end-point in clinical trials in SSc-ILD,[11] has not yet been studied. Recently though, it was observed that the presence of limited emphysema had no effect on baseline FVC after adjustment for the extent of ILD.[3]

In conclusion, the coexistence of emphysema with fibrosis remains controversial. This entity is not characterized by the activation of any particular pathways that can lead to the development of disease-specific treatment. In the case of IPF, the presence of emphysema causes difficulties in monitoring the behavior of the disease and the response to treatment due to the attenuating effect on serial FVC decline. Moreover, the preservation of FVC precludes the use of antifibrotic drugs in countries where an upper limit of FVC is used. These important observations must be taken into account by expert groups involved in establishing the most appropriate management strategy for this subgroup of patients.

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