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Review Article

Combined Pulmonary Fibrosis and Emphysema

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ABSTRACT

The combination of pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome, in which an upper lobe emphysema and lower lobe fibrosis coexist in a single patient. These patients have a characteristic lung function profile, with apparently normal or minimally altered dynamic and static lung volumes, contrasting with a significant reduction of carbon monoxide transfer (DLco), and hypoxemia, which worsens with exercise. Pulmonary hypertension is highly prevalent and is the principal negative prognostic factor for this condition. High resolution computed axial tomography (HRCT) is the main tool to confirm the diagnosis. Cigarette smoking has been proposed as the main factor in its etiology; however, neither pathogenic mechanisms nor the sequence of events involved in this syndrome has been clarified yet. Experimental studies in animal models are providing information on the involvement of some inflammatory mediators in the pathogenesis. There is currently no consensus on the therapeutic approach to be followed in these patients, since the studies published to date on this subject are limited to well-characterized series of cases. Therefore, it is a pathology with many unknowns yet to be resolved and highly likely to be underdiagnosed, unless its functional clinical characteristics are taken into account.

Combinación de fibrosis pulmonar y enfisema

Palabras clave:
Enfisema
Fibrosis pulmonar
Difusión del monóxido de carbono
Hipertensión pulmonar
Tabaquismo

RESUMEN

La combinación de fibrosis pulmonar y enfisema (CFPE) es un síndrome definido recientemente, en el cual coexisten en un mismo individuo enfisema en lóbulos superiores y fibrosis en lóbulos inferiores. Estos pacientes presentan un perfil funcional respiratorio característico, con volúmenes pulmonares dinámicos y estáticos aparentemente normales o mínimamente alterados que contrastan con una grave alteración de la difusión del monóxido de carbono (DLCO) e hipoxemia arterial, la cual empeora durante el esfuerzo. La prevalencia de hipertensión pulmonar es elevada y representa la principal condición que determina el pronóstico. La tomografía axial computarizada de alta resolución (TCAR) constituye la herramienta primordial para confirmar su diagnóstico. Se ha postulado al humo del tabaco como el principal agente etiológico; sin embargo, ni los mecanismos fisiopatológicos ni la secuencia de eventos involucrados en este síndrome han sido aún dilucidados. Estudios experimentales en modelos animales están proporcionando información sobre la participación de algunos mediadores inflamatorios en su patogenia. Actualmente, no existe un consenso sobre la actitud terapéutica que seguir en estos pacientes, puesto que lo publicado hasta la fecha sobre esta entidad se limita a series de casos bien caracterizadas. Es, por tanto, una patología con múltiples incógnitas todavía por resolver y con alta probabilidad de ser infradiagnosticada si no se tienen en cuenta sus particularidades clínico-funcionales.

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Introduction

Pulmonary emphysema and idiopathic interstitial lung diseases including idiopathic pulmonary fibrosis (IPF) are entities defined by different clinical, functional, radiological and pathological criteria.[1] IPF is the most common idiopathic interstitial lung diseases, with a worse prognosis and higher mortality, and a mean survival time of 3 years from the time of diagnosis.[2] Its pathologic-anatomical substrate is usual interstitial pneumonia (UIP) and it is characterized by breathing difficulties and a reduction in the carbon monoxide diffusion capacity (DLCO). Emphysema is defined as an enlargement of the air spaces distal to the terminal bronchioles due to the destruction of the tissues forming their walls.[3] Emphysema is present in chronic obstructive pulmonary disease (COPD), and can cause an obstructive pattern caused as the air flow becomes restricted due to the different structural changes occurring in the lung.[4-6]

The combination of both processes, seemingly so unalike in daily clinical practice, was first described over 30 years ago by Auerbach[7] in a pathological anatomical study of 1824 autopsy lungs. Even then, Auerbach suggested that smoking was in some way responsible for the coexistence of these processes, basing his suggestions on studies involving animal models exposed to tobacco smoke.[8,9] In the early nineties, with the addition of computerized axial tomography (CAT) to the arsenal of diagnostic tests for respiratory diseases, Wiggins et al[10] found a correlation between functional and radiologic findings in 8 subjects with a history of smoking who had severe dyspnea, but whose spirometry tests revealed no signs of obstruction, and who had normal static lung volumes, and significantly reduced DLCO. CT scans showed these patients had areas of upper-lobe-predominant emphysema, and lesions compatible with fibrosis in both lung bases. Since then, several series, most with a retrospective methodology, have been published in the literature.[1,10-22] Among these, the most important study is that by Cottin et al,[1] who characterized the disease as a well-defined clinical entity named "combined pulmonary fibrosis and emphysema" (CPFE).

Epidemiology and Clinical Characteristics

The prevalence of CPFE is not known, although it has been estimated to represent between 5% and 10% of cases of diffuse interstitial lung disease.[23] Most of the cohorts studied have been men, but the reasons for this remain unclear.[15,16] It is generally present in people over 65 years of age who are active smokers or heavy ex-smokers (over 40 pack-years). Exposure to agricultural compounds is another epidemiological data collected by some series.[1,21-24]

From a clinical perspective, dyspnea on exertion (functional class iii or iv of the New York Heart Association) is the most common symptom among patients. Physical examination usually reveals clubbing of the fingers or toes and Velcro crackles at the lung bases. Although less common, other signs and symptoms reported are dry or productive cough, wheezing, peribuccal cyanosis, and asthenia.[1,14,22,23]

Pulmonary hypertension is a common and important complication in the natural history of this syndrome,[1,15,23,25] as it is associated with a worse clinical course and lower survival rates, about which more details are given below. Furthermore, several authors have reported a significant prevalence of arteriosclerosis and bronchogenic carcinoma in these patients.[12,21,23] Although the co-existence of these diseases in CPFE may be directly associated with smoking, a common etiopathogenetic factor, there are studies suggesting the prevalence of lung cancer may vary depending on the ethnic group analyzed, with higher prevalence in Japanese series.[21] Therefore, studies with large patient samples are needed to confirm this.

Pathogenesis

Despite the lack of knowledge regarding the physiopathologic substrate of CPFE, we can suppose that it entails a complex, interwoven process involving different types of cells, common pathogenic pathways, and mediators with an inflammatory and/or fibrogenic capacity. This process finally leads to the destruction of the lung parenchyma and the aberrant remodelling characteristic of fibrosis. Furthermore, these cell mediators interact with environmental factors which could act as modifiers of the disease in the presence of a permissive genotype. The main etiopathogenic mechanisms described in relation to this syndrome will be looked at below.

Etiology

Cigarette smoking has been suggested as the main etiologic factor, as a history of smoking is a constant factor in all the cohorts reported.[10-23] Tobacco smoke, a complex mix of over 4000 chemical substances, has been associated with a wide range of diseases, with emphysema and lung disorders most commonly attributed to smoking.[26] For example, kaolinite or aluminium silicate is an inorganic industrial material found in tobacco smoke and which has been isolated in alveolar macrophages of smoker patients with lung emphysema and respiratory bronchiolitis with diffuse interstitial lung disease (RB/DILD).[27] It has been hypothesized that macrophage accumulation after chronic inhalation of this mineral triggers the series of physiopathological phenomena that, in the end, lead to respiratory bronchiolitis and emphysema.[28]

Although the etiology of IPF is unknown, it is thought to be a consequence of the interaction of environmental factors in individuals with a genetic predisposition, with increasing recognition of its association with smoking. This also has a proven detrimental effect on its prognosis.[29,30] In this context, Katzenstein et al[31] reported an unexpectedly high frequency of fibrosis in pieces of lung tissue removed from smokers who were candidates for tumor surgery. These patients showed no clinical evidence of interstitial lung disease. It should be pointed out that smoking has also been associated with a restrictive spirometric pattern in many epidemiological studies,[32] which supports the hypothesis that smoking can produce different types of effects on the lung parenchyma, as evidenced in different phenotypic expressions.[31]

The table shows the main studies relating exposure to tobacco smoke to IPF.

The high prevalence of vasculopathy and pulmonary hypertension described in patients with CPFE can also be attributed to smoking, a recognized risk factor in the development of blood vessel disorders. Exposure to tobacco smoke produces endothelial dysfunction in coronary and systemic arteries. The exposure of endothelial cells of the pulmonary arteries to tobacco smoke extract has been shown to cause an irreversible inhibition of endothelial nitric oxide synthase (eNOS) activity due to a reduction in its protein content and

Table
Case-control studies on environmental exposure and idiopathic pulmonary fibrosis. Odds ratio for exposure to tobacco

Author/year of publication	Cases/controls	Odds ratio (95% CI)
Scott J, et al *(BMJ 1990)*	40/140	1.11 (0.13-1.40)
Iwai K, et al *(Am J Respir Crit Care Med 1994)*	86/72	2.94 (1.37-6.3)
Hubbard R, et al *(Lancet 1996)*	218/569	1.57 (1.01-2.43)
Baumgartner KB, et al *(Am J Epidemiol 2000)*	248/491	1.60 (1.10-2.40)
Miyake Y, et al *(Ann Occup Hyg 2005)*	102/59	3.23 (1.01-10.84)
García-Sancho Figueroa MC, et al *(Respir Med 2010)*	97/560	[a]0.3 (0.1-0.8)
		[b]1.6 (1.006-2.5)

Abbreviation: CI, confidence interval. Modified from Taskar et al.[30]
[a] Active smoker.
[b] Ex-smoker.

messenger RNA. This inhibition of eNOS activity due to tobacco smoke may explain the decreased expression in pulmonary arteries seen in smokers and may predispose patients to greater changes in the pulmonary vessels.[33]

Oxidative Stress

Increases in oxidative and nitrosative stress have been postulated as mechanisms potentially involved in the development of CPFE; they increase inflammatory-cell (leukocyte) activation, which contributes to local and systemic increases in oxidant levels. The production of an excess of oxidants that are not neutralized by the body's antioxidant systems causes structural changes in epithelial, vascular and connective tissues.[31]

Metalloproteinases

Metalloproteinases (MMP) constitute a family of enzymes produced by alveolar epithelial cells, macrophages and neutrophils, which participate in emphysema development due to their significant proteolytic activity and collagen-degrading ability. The expression of MMP activity is modulated by several cytokines, including interleukin 13 (IL 13), which, in experimental models, is able to produce enlarged airway spaces, fibrosis, and inflammatory remodelling of the airways.[34] A recent study in a subgroup of CPFE patients reported an increase in the expression of some MMPs in the areas affected by a combination of emphysema and UIP, suggesting these proteins also have a role in extracellular matrix deposition and anomalous tissue remodelling – a characteristic of the process of fibrosis.[26]

Caveolin-1

Caveolae are invaginations of the cell membrane in various types of cells. They are rich in proteins, lipids and cholesterol and are formed and maintained by proteins called caveolins, with caveolin-1 being the most studied. This protein is a potent immunomodulator and it has been ascribed several functions, including signal transduction, the mediation of cell apoptosis, intracellular calcium and eNOS regulation, and the suppression of tumours.[35,36] Lung tissue expresses high levels of caveolins, and dysfunctions have been linked to pulmonary hypertension associated with COPD and emphysema, interstitial fibrosis and lung cancer. As a result, Caveolin-1 may be another important mediator in the etiology of CPFE, and it undoubtedly deserves to be the subject of further investigation.

Animal Models

Three studies using animal models have managed to reproduce the histopathological elements of CPFE. The first, performed by Hoyle et al,[37] showed that the overexpression of platelet-derived growth factor (PDGF) led to the enlargement of airway spaces, and inflammation and fibrosis in the lungs of transgenic mice. PDGF is a growth factor and has a pleiotropic effect on several lines of cells and is involved in both the pathogenesis of IPF and emphysema. This dual action may be due to its mitogenic activity on fibroblasts, its interaction with different inflammatory markers, and its probable capacity to induce a protease/antiprotease imbalance in the extracellular matrix, which would trigger the development of emphysema.

Overexpression of other mediators in the lungs, such as tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF–β), has also generated this complex phenotype of fibrosis and emphysema in research animals.[38,39] TNF-α is a multifunctional cytokine with some apparent profibrotic acitivity[40] and is considered an important mediator of various pulmonary and systemic symptoms in diverse respiratory diseases. Smoking causes this cytokine to be released into the lungs, both in humans and animal models, and high levels have been found in the sputum and peripheral blood of COPD patients.[41]

TGF-β is one of the most potent profibrogenic mediators known to play a role in the pathogenesis of IPF. The TGF-β_1 isoform induces the differentiation of fibroblasts into myofibroblasts, the transition of epithelial cells into fibroblasts, and the synthesis of molecules of the extracellular matrix, as well as promoting the apoptosis of alveolar epithelial cells.[40] Its role in the development of emphysema is less clear, although an increase in its expression in the bronchial epithelium and in the macrophages of the small airways has been observed in COPD patients.[42] In short, TGF-β is important during the transition from the immune inflammatory response to the tissue remodelling process.[43,44]

Diagnosis

Imaging Studies

A simple chest x-ray reveals an interstitial pattern or reticulonodular infiltrates in both lung bases and the subpleural region, and hyperlucency in the apices with a reduction in pulmonary vascular markings (Figure 1). However, the radiologic findings for CPFE may go unnoticed in a chest x-ray, so HRCT scanning is the reference technique for confirming diagnosis.[23,45] Images show the presence of emphysema predominantly in the upper lobes, represented by a well-defined hypodense area without visible walls, or with a very thin wall and/or multiple bullae. It co-exists with the radiological manifestations of diffuse lung diseases such as reticular opacities, traction bronchiectasis, septal thickening, ground glass opacity, and honeycombing in the lower lobes (Figure 2). Emphysema lesions correspond with centrilobular and paraseptal emphysema (subpleural bullae). Paraseptal emphysema has been described in 90% of cases, so some authors suggest it is a typical feature of CPFE.[1,23,46]

In some cases distinguishing images of emphysema from those of fibrosis is a complex task as a transition area can be observed between both regions, making it difficult to interpret them correctly.[46] The wealth of radiological semiology in these patients' HRCT scans correlates closely with histopathological data. UIP is the most common pattern, but lesions have also been reported which are compatible with non-usual interstitial pneumonia, and desquamative interstitial pneumonia,[16] this being a disease linked with smoking.

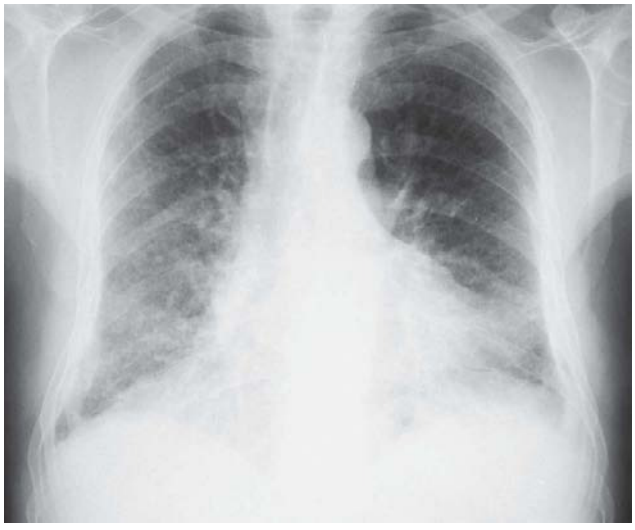

Figure 1. Chest x-ray of a patient diagnosed with combined pulmonary fibrosis and emphysema. A bilateral interstitial pattern can be seen, predominantly right-sided, with reticulonodular infiltrates in the lung bases and subpleural region, and a reduction of lung density in upper lung fields, mainly on the left.

Lung Function

The co-existence of emphysema and fibrosis leads to a characteristic functional profile which is in direct contrast to the degree of dyspnea suffered by these patients. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and total lung capacity (TLC) are usually within normal ranges or only slightly abnormal, unlike DLCO, which is significantly reduced. Hypoxemia is a common finding; it is generally moderate at rest and gets worse during exercise.[1,18,23] Overinflation and an increase in pulmonary compliance due to the loss of elasticity in the areas with emphysema probably compensate for the loss of volume caused by fibrosis.[17-19] In contrast, the overlapping of both pathologies could exert a negative synergic effect on gas exchange, resulting in a sharp decrease in DLCO. This particular functional disorder leads to at least 2 important clinical repercussions: first, the presence of normal lung volumes does not exclude the diagnosis of pulmonary fibrosis in this type of patients and, second, neither FVC nor TLC can be used as parameters to monitor the disease, as they do not reflect the degree of functional impairment. In this instance, DLCO is the variable which best correlates with the degree of parenchymal destruction. However, a low DLCO can also reflect disorders in the pulmonary vascular bed, specifically pulmonary hypertension (PH), as it is a highly prevalent condition in this entity.

Pulmonary Hypertension

PH is a common complication during the clinical course of CPFE, and is one of the main conditions influencing its evolution and prognosis.[23] A prevalence has been reported in these patients of between 47% and 90%, much higher than in COPD or IPF alone.[47] In most published series, the diagnosis of PH was established by a transthoracic echocardiogram, with a criterion of systolic pressure in the pulmonary artery $\geq$ 45 mm Hg. In the study by Cottin et al,[1] the presence of PH was an independent predictor of mortality, with a hazard ratio of 4.03 (P=.03). The 5-year probability of survival was 25% in patients with PH diagnosed by echocardiogram compared with 75% in those with no signs of PH at the time of diagnosis. The mean survival time in this series was 6.1 years, dropping to 3.9 years in those patients with associated PH.

On this note, Mejía et al[15] recently published a study in which different clinical, functional and prognostic variables were compared in a group of patients with CPFE and another with IPF with no evidence of emphysema. Using a logistic regression model, they showed that, together with the FVC, a SPPA $\geq$ 75 mm Hg was one of the main variables determining survival; this variable was lower in the group with CPFE. In these patients, the extent of the emphysema established by HRCT showed a positive correlation with SPPA.

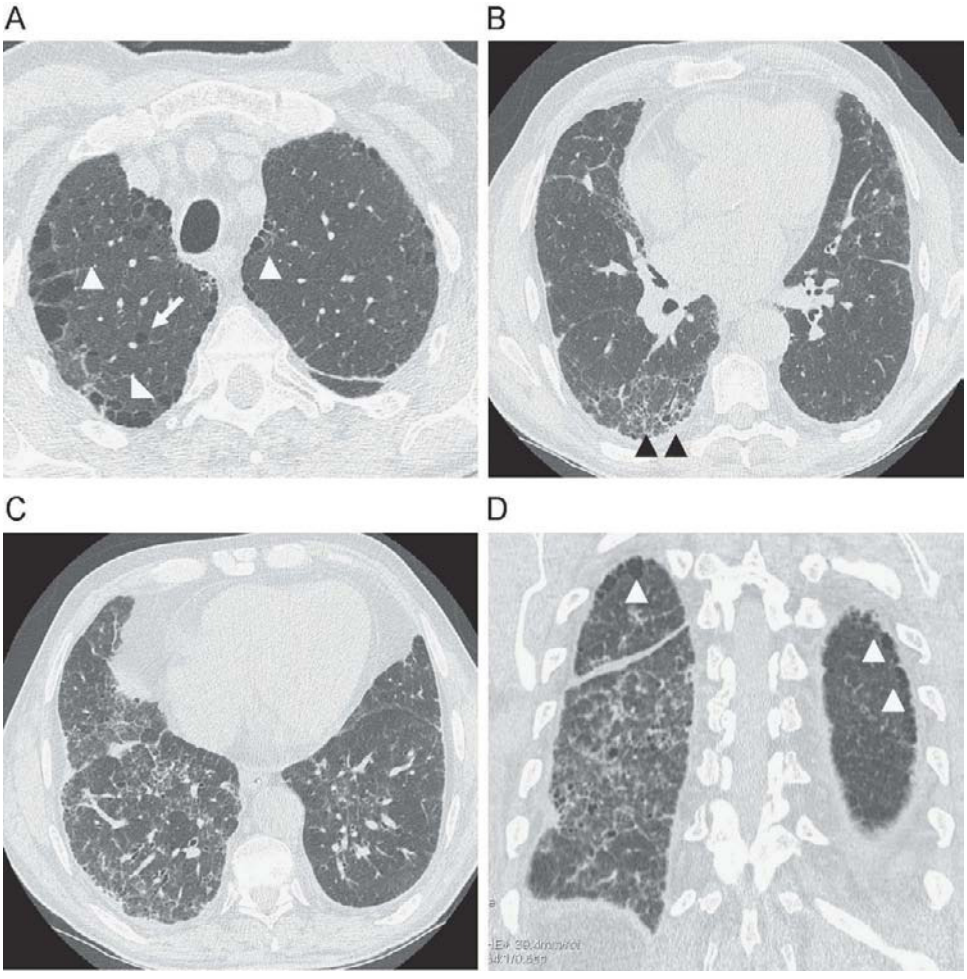

Figure 2. High resolution computerized tomography (HRCT) of the same patient. A) Presence of paraseptal emphysema and subpleural bullae (white arrowheads) and centrilobular emphysema (arrows) in both upper lobes. B) Reticular interstitial disease with intralobular thickening and images of subpleural honeycombing and traction bronchiectasis (black arrowheads) C) Reticular interstitial disease in middle and right lower lobes, with interlobular septal thickening, subpleural honeycombing and traction bronchiectasis. D) Coronal reconstruction in the posterior regions of both lungs: Bilateral paraseptal emphysema (white arrowheads) and reticular interstitial disease and honeycombing in right lower lobe.

The significant effect of pulmonary hemodynamics on mortality in this entity was shown in another study performed by Cottin's group[25] involving 40 patients with CPFE who had PH confirmed by right heart catheterization. The factors associated with a worse prognosis were: increased pulmonary vascular resistance, reduced cardiac index, a high heart rate and low DLCO. In this study, the diagnosis of PH was established at a mean of 16 months after the initial diagnosis of CPFE, and the estimated survival rate at 1 year in this cohort was 60%.

Therefore, routine screening of these patients for PH with Doppler echocardiography would be justified given its high prevalence and its important role in the prognosis. The presence of emphysema can make results difficult to interpret, so some authors propose assessing alternative diagnostic techniques such as magnetic resonance imaging (MRI). MRI flow mapping shows good correlations with hemodynamic parameters.[48,49] However, general access and use of this examination technique for this kind of patients is still very limited.

Treatment

The treatment options for CPFE are limited. Treatment with systemic corticosteroids and immunosuppressors, similar to that for treating IPF, has been used, but without clear, positive results in the published series. Complete cessation of smoking is a sensible measure that probably halts the progression of emphysema lesions. The possibility of using the specific therapy approved for treating pulmonary arterial hypertension (endothelin 1 receptor antagonists, prostanoids or phosphodiesterase type 5 inhibitors), as was trialed in COPD or IPF, has been considered by some authors. However, no studies have been published to date on this matter. It is important to point out that the presence of emphysema and disorders of the pulmonary vascular bed in these patients may be associated with an imbalance in the ventilation/perfusion ratio (V/Q), as hypoxic vasoconstriction is one of the main mechanisms to stop hypoxemia from worsening. These vasodilator drugs can worsen arterial oxygenation by inhibiting this mechanism. Thus, further studies with a suitable design are necessary to enable a detailed assessment to be made of the effect of these drugs on gas exchange.

Conclusions

Combined pulmonary fibrosis and emphysema reveals clinical, functional and radiological findings that are contradictory at first sight and can confuse doctors, leading to underdiagnosing. Associated PH is a common complication that it is important to identify, as it determines outcome. The overlapping of a wide variety of radiological and histopathologic lesions described in this article show tobacco to be the main agent involved, generating diverse parenchymal disorders with different phenotypic expressions. A better understanding of its physiopathology and the molecular mechanisms involved will make it possible to develop future therapeutic strategies. It should not be forgotten that the prevention and treatment of smoking would possibly have the biggest impact on the natural history of this disease.

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