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Combined pulmonary fibrosis and emphysema in alpha-1-antitrypsin deficiency

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Combined pulmonary fibrosis and emphysema (CPFE) is characterized by severe dyspnea at exertion, distinct physiology with preserved static and dynamic lung volumes contrasting with significantly altered gas exchange capacity, and a combination of upper lobe emphysema and features of pulmonary fibrosis predominating in the lower lobes on chest CT [1]. A variety of patterns have been described both at chest imaging and histopathology, including usual interstitial pneumonia (UIP), non-specific idiopathic pneumonia, desquamative interstitial pneumonia, and more recently smoking related interstitial fibrosis [2]. Prognosis is dismal in progressive forms, with a median survival of 3 to 5 years. Mortality is mostly driven by the development of precapillary pulmonary hypertension, acute exacerbation of fibrosis, and lung cancer [1].

Very few genetic variants have been associated with CPFE. Herein we report on a case of CPFE in the context of alpha-1-antitrypsin (A1AT) deficiency (AATD) with progressive course leading to death.

Observation

A 62-year-old female, who had smoked less than 5 pack-years until the age of 30 years, was diagnosed with liver cirrhosis, which was then related to AATD, with a low serum level of A1AT (0.23 g/L), and a PiZZ protease inhibitor phenotype. She had progressive shortness of breath over the past few months as well. Pulmonary investigations at that time demonstrated predominantly paraseptal emphysema in the upper lobes at chest CT. Pulmonary function tests were normal. Therefore, augmentation therapy was not introduced and the patient followed a watchful waiting strategy.

Six years later, the patient (now aged 68) was admitted for progressive chronic dyspnea limiting daily activities. Lung examination found basal “Velcro” crackles. The chest CT now demonstrated bilateral fibrotic changes, with basal and subpleural predominance, consisting of reticulations, traction bronchiectasis, and honeycombing. Paraseptal emphysema in the upper lobes was unchanged. Forced vital capacity (FVC) was 2.52L (111% of predicted value), forced expiratory volume in one second was 2.11L (112% of predicted), and the diffusion capacity of the lungs for carbon monoxide was 42% of predicted. Autoimmune studies were negative. With these findings, the diagnosis of CPFE was established, in this case corresponding to idiopathic pulmonary fibrosis (IPF) combined with predominantly paraseptal emphysema. The stage of cirrhosis was Child-Pugh A, allowing initiation of antifibrotic therapy with nintedanib, later switched to pirfenidone due to disease progression.

Nevertheless, lung fibrosis inexorably progressed with an average decline of FVC of 270 mL/year. The patient died from chronic respiratory failure 5 years following CPFE diagnosis.

Because she had a sister with pulmonary fibrosis, genetic tests were performed. No mutation was found in the telomerase-related genes (*TERT*, *TERC*, *RTEL1*, *DKC1*, *PARN*, *TINF2*) and a panel of other genes associated with pulmonary fibrosis. Homozygous mutation p.E366K was found in the *SERPINA1* gene coding for A1AT.

Discussion

The current case is the first reported association of CPFE syndrome and AATD. Despite the wealth of reports on genetic predisposition to pulmonary fibrosis, large cohorts of patients with AATD, and series of patients with CPFE, the association between AATD and pulmonary fibrosis seems very rare. In the seminal description of CPFE as a syndrome, the level of A1AT was low (0.19 g/L) in only one of 65 patients with CPFE, who was PiZZ homozygous, and another patient with a PiMZ phenotype had a normal serum level of A1AT (1.6 g/L). Among homozygous twin sisters with a PiZZ phenotype, one had liver cirrhosis and the other developed IPF [3]. A cluster of both familial pulmonary fibrosis and AATD (with PiSZ or PiMZ phenotypes in several family members yet normal serum levels of A1AT) was reported in one family, including one individual who had IPF, and one who had both IPF and liver cirrhosis [4]. Another patient had liver cirrhose due to AATD and IPF but no emphysema [5]. A highly significant increase in the frequency of PiMZ phenotype was also found among patients with pulmonary fibrosis, both with and without rheumatoid arthritis [6].

Our case presented a radiologic UIP pattern, combined with upper lobe paraseptal emphysema and without characteristic panlobular emphysema as commonly observed in AATD. In addition, large cysts with thickened walls were present in lung bases, suggesting association with smoking-related interstitial fibrosis [2]. The lung function profile at baseline was characteristic of the CPFE syndrome and supported the diagnosis [1]. However, the outcome was characterised by progressive restrictive lung physiology and eventually death despite treatment, in a timeframe consistent with IPF. Antifibrotic therapy could be prescribed as the stage of liver cirrhosis was Chid-Pugh A.

The pathophysiology of CPFE has not been fully elucidated. Tobacco smoking is by far the most common etiology. Other risk factors such as increasing age, male sex, and environmental or occupational exposures are shared with IPF. CPFE occurs also in non-smoker subjects with connective tissue diseases and hypersensitivity pneumonitis. CPFE has

been reported in association with gene variants implicated in pulmonary fibrosis, including mutations in telomerase-related genes [7] and genes coding for surfactant proteins [8]. However, less attention has been paid to potential genetic components generally associated with an increased risk of emphysema. AATD is a genetic disorder with more than 100 genetic variants described, and an estimated prevalence of 23 per 100,000 persons [9]. The estimated prevalence of IPF in France is 8.2 per 100,000 persons [10]. It is noteworthy that mostly familial forms of IPF [3, 4] or CPFE (the present case) have been reported in combination with AATD. Indeed, our patient had a family history of pulmonary fibrosis, although no genetic variant could be identified in the proband.

What caused the coexistence of AATD and CPFE in our patient is unknown. The two conditions may well be associated by chance, with two genetic disorders clustered in the same family, as previously reported for AATD and IPF [4]. The patient was a smoker, which is a risk factor shared by emphysema and pulmonary fibrosis. It remains to be elucidated whether AATD might *predispose to*, or *protect from* pulmonary fibrosis. Although emphysema and fibrosis have distinct pathophysiology [11], experimental data in pallid mice that are deficient in serum alpha-1-proteinase inhibitor, suggested that both may coexist after exposure to bleomycin and may be potentiated by AATD, potentially through neutrophil elastase [12]. Indeed, AATD increases sensitivity to oxidative stress and inflammatory mediators within the lung, and might conceivably predispose to a pro-inflammatory and pro-fibrotic response to lung injury. If true, however, one would expect to encounter a sizable number of subjects with AATD-related emphysema also harboring pulmonary fibrosis. Conversely, administration of alpha-1-proteinase inhibitor (A1AT) to bleomycin-treated hamsters reduced experimental pulmonary fibrosis [13]. A1AT supplementation therapy was not prescribed in our patient because IPF predominated over emphysema; however, whether it might have had an impact on the course of IPF, if prescribed, is unknown.

Altogether, the current data mostly support the coincidental association of two genetic conditions predisposing to emphysema (AATD) and to pulmonary fibrosis. Whether AATD may alter the risk of pulmonary fibrosis in either way remains to be determined.

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Figure legends

Figure 1. Axial CT-scan of the lung in a patient with CPFE. A: limited paraseptal emphysema in the left upper lobe, associated with mild thickening of the cyst walls. B: usual interstitial pneumonia pattern in the lung bases, with honeycombing, subpleural reticular opacities and traction bronchiectasis in the lung bases. C: worsening of fibrotic features two years later than C; D: large cyst with thick walls in the right lower lobe, suggesting a pattern of smoking-related interstitial fibrosis.

