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## Severe pulmonary hypertension due to combined pulmonary fibrosis and emphysema: another cause of death among smokers

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### ABSTRACT

In 2005, the combined pulmonary fibrosis and emphysema (CPFE) was first defined as a distinct entity, which comprised centrilobular or paraseptal emphysema in the upper pulmonary lobes, and fibrosis in the lower lobes accompanied by reduced diffused capacity of the lungs for carbon monoxide (DLCO). Recently, the fibrosis associated with the connective tissue disease was also included in the diagnosis of CPFE, although the exposure to tobacco, coal, welding, agrochemical compounds, and tire manufacturing are the most frequent causative agents. This entity characteristically presents reduced DLCO with preserved lung volumes and severe pulmonary hypertension, which is not observed in emphysema and fibrosis alone. We present the case of a 63-year-old woman with a history of heavy tobacco smoking abuse, who developed progressive dyspnea, severe pulmonary hypertension, and *cor pulmonale* over a 2-year period. She attended the emergency facility several times complaining of worsening dyspnea that was treated as decompensate chronic obstructive pulmonary disease (COPD). The imaging examination showed paraseptal emphysema in the upper pulmonary lobes and fibrosis in the middle and lower lobes. The echo Doppler cardiogram revealed the dilation of the right cardiac chambers and pulmonary hypertension, which was confirmed by pulmonary trunk artery pressure measurement by catheterization. During this period, she was progressively restricted to the minimal activities of daily life and dependent on caregivers. She was brought to the hospital neurologically obtunded, presenting anasarca, and respiratory failure, which led her to death. The autopsy showed signs of pulmonary hypertension and findings of fibrosis and emphysema in the histological examination of the lungs. The authors highlight the importance of the recognition of this entity in case of COPD associated with severe pulmonary hypertension of unknown cause.

### Keywords

Pulmonary Emphysema; Pulmonary Fibrosis; Hypertension, Pulmonary; Pulmonary Heart Disease; Autopsy

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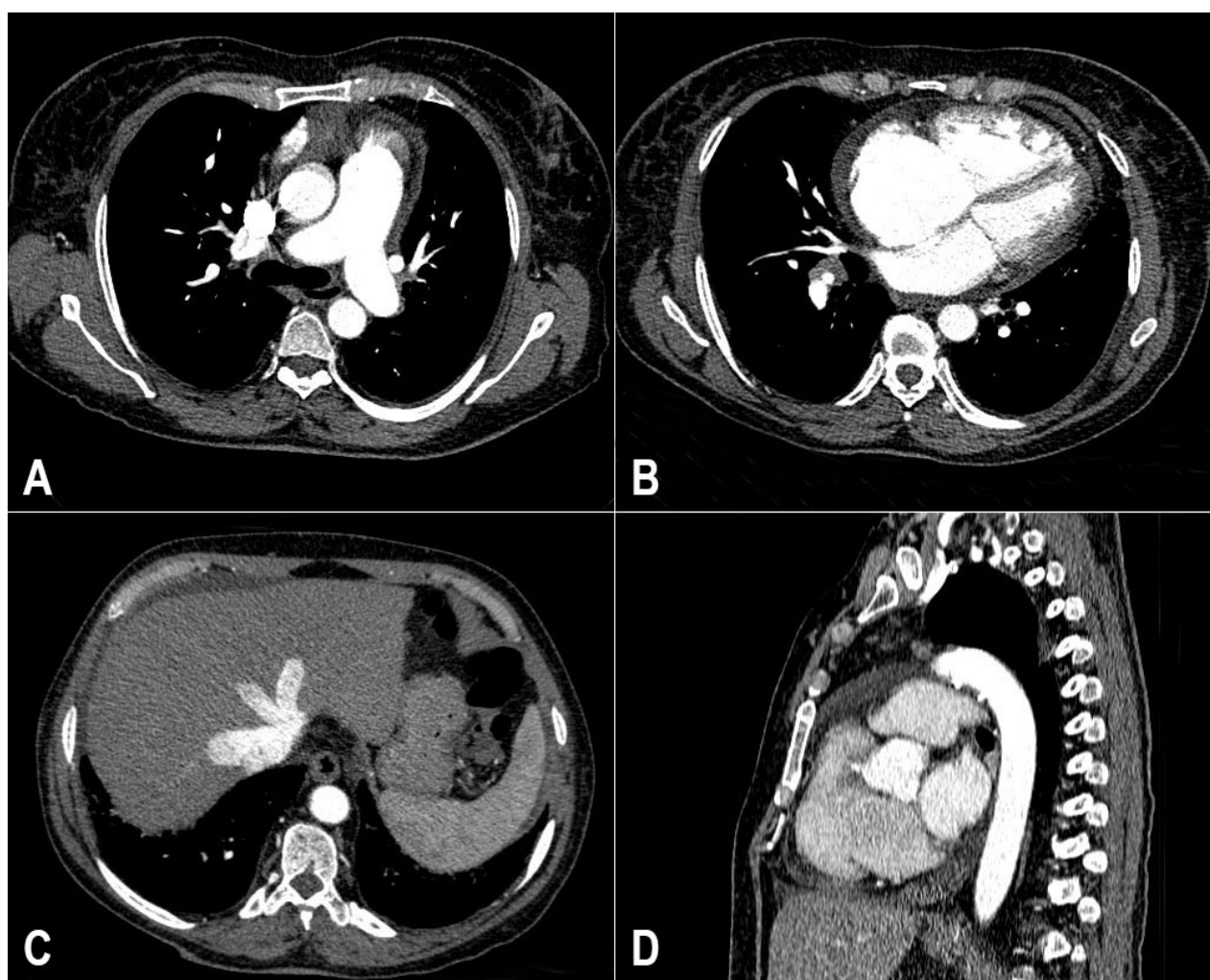
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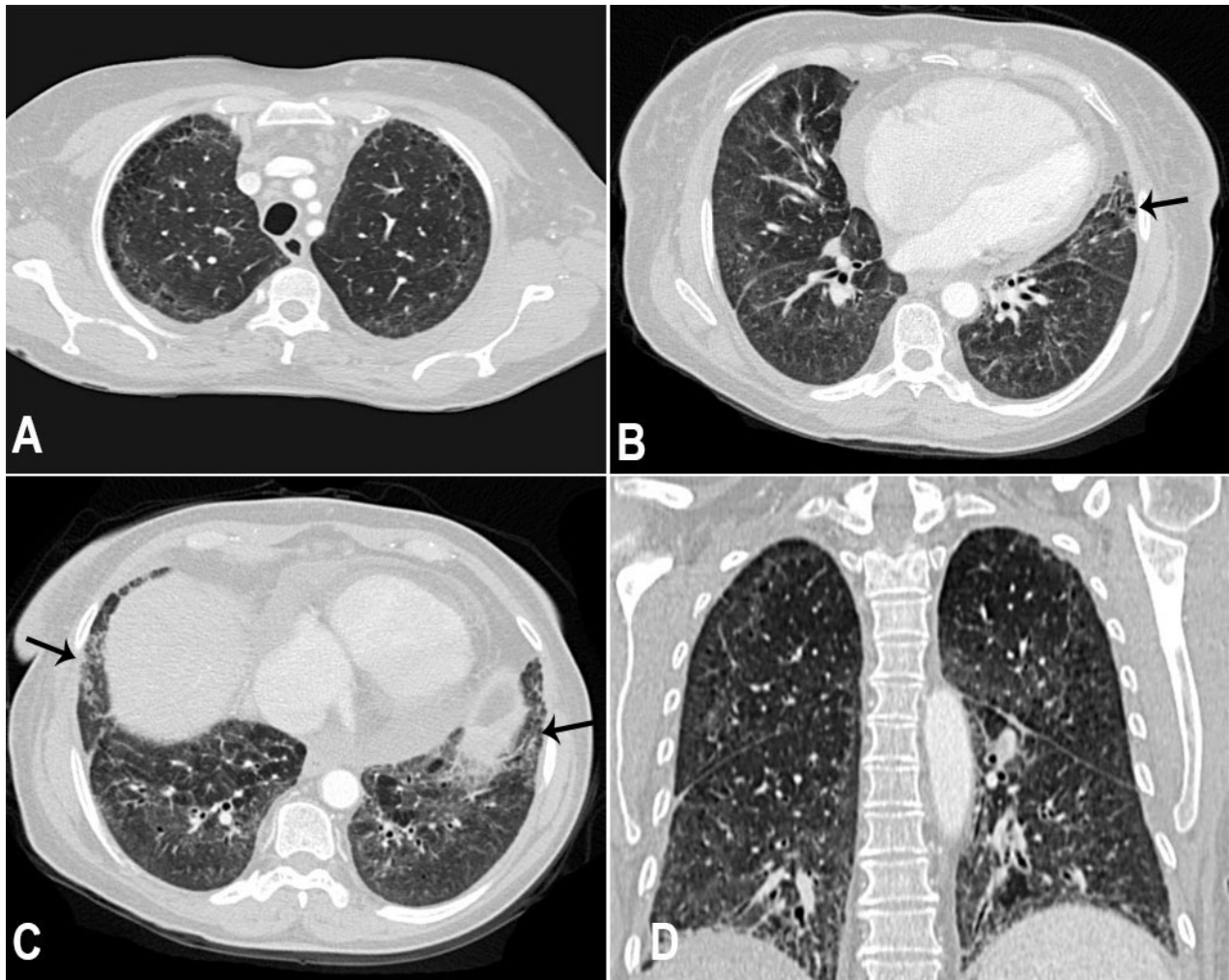
## CASE REPORT

A 63-year-old Caucasian woman sought the emergency department (ED) because of severe dyspnea during the last month, which had been worsening over the last 2 years. She was a heavy tobacco smoker (102 packs/year) since an early age and was irregularly following treatment for hypertension. In a 2-year period, she attended the ED five times complaining of dyspnea with the working diagnosis of decompensate chronic obstructive pulmonary disease (COPD) by respiratory infection. At her second emergency appointment, (specifically 18 months ago) she was submitted to a thoracic computed tomography (CT) that revealed signs of pulmonary hypertension characterized by the enlargement of the pulmonary trunk artery and its branches, dilation of the right

cardiac chambers, and moderate pericardial effusion (Figure 1). The analysis of the pulmonary window showed a disease characterized predominantly by ground glass opacity, eventually with subpleural sparing in the lung bases associated with some areas of thin reticulated and traction bronchiectasis. No honeycomb cysts were found. These imaging features were consistent with non-specific interstitial pneumonia (Figure 2). Emphysema, predominantly of the paraseptal subtype, was observed in the upper lobes. Additionally, there was a discrete atheromatosis of the aorta, which was negligible in the coronary territory, and a mild splenomegaly. The echo Doppler cardiogram showed a normal left ventricular systolic function, but an estimated pulmonary artery pressure of 100 mmHg, which was confirmed with the right cardiac catheterization and pressures



**Figure 1.** Chest CT mediastinal window, showing signs of pulmonary hypertension. **A** - Note the pulmonary trunk caliber is greater than the aorta; **B** - Dilation of the right cardiac chambers; **C** - Reflux of the contrast media into the dilated inferior vena cava and hepatic veins; **D** - Moderate pericardial effusion. **A**, **B**, and **C** = axial plane; **D** = sagittal plane.



**Figure 2.** Chest CT pulmonary window — fibroemphysema. **A** - Centrilobular and paraseptal emphysema in the upper lobes; **B**, **C** and **D** - Indication of fibrosing interstitial lung disease characterized by ground glass opacity, areas of thin reticulated and also traction bronchiectasis (arrow), predominantly in the subpleural regions of the lung bases. **A**, **B** and **C** = axial plane; **D** = coronal plane.

measurement. The stool examination (three samples) and rectal biopsy were negative for *Schistosoma mansoni*'s eggs; the pulmonary angiogram failed to demonstrate pulmonary thromboembolism; and laboratory work-up for connective diseases were all negative. Blood gas analysis showed severe hypoxemia without hypercapnia.

The patient was prescribed oxygen supplementation. In the following 18-month period, she developed several respiratory failure exacerbations concomitantly with progressive hypercapnia and bicarbonate retention. Clinically she developed worsening signs of heart failure and anasarca. The plain thoracic radiography showed an enlarged cardiac silhouette with a predominance of the right cardiac chambers. She became progressively restricted to bed and dependent on a caregiver for the essential activities

of the daily living. She was brought to the ED for the sixth time after being rescued in bed with cyanosis and presenting altered mental status.

The physical examination revealed an ill-looking patient, drowsy, disoriented, cyanotic, icteric, and afebrile. Vital signs were characterized by blood pressure of 110/70 mmHg, pulse of 84 beats per minute, pulse oximetry of 79% with 3 L/min oxygen supplementation, and capillary glucose of 88 mg/dL. Lower limbs presented symmetric edema with skin hyperemia in the left leg, and the jugular veins were distended in the neck's upright position. Heart auscultation revealed a systolic murmur in the tricuspid area, and crackles were detected in the lower left lung base. A large ascites was present hampering the viscera examination. The laboratory work-up showed normal hemoglobin determination, mild



leukocytosis without shift to the left, thrombocytopenia, prolonged prothrombin time, slight renal dysfunction, hyponatremia, hyperbilirubinemia at the expense of indirect bilirubin, and elevated C-reactive protein.

Blood (four samples) and urine cultures were negative. The abdominal ultrasound revealed an average dimension and echotexture of the liver; and dilation of the portal vein (16 mm), inferior vena cava, and suprahepatic veins. The spleen was slightly enlarged, and a huge ascites was present. The echo-Doppler cardiogram showed severe dilation of the right cardiac chambers despite normal right ventricle function, and a reduced volume of the left ventricle. The tricuspid valve had a dilated annulus with severe reflux. The estimated systolic pulmonary artery pressure (at this time) was 76 mmHg plus the central venous pressure; the inferior vena cava measured 26 mm, and the respiratory variation diameter was less than 50%. A non-restrictive pericardial effusion was present. The electrocardiogram showed a sinus rhythm, diffuse low-voltage complexes, and the QRS axis was anteriorly deviated.

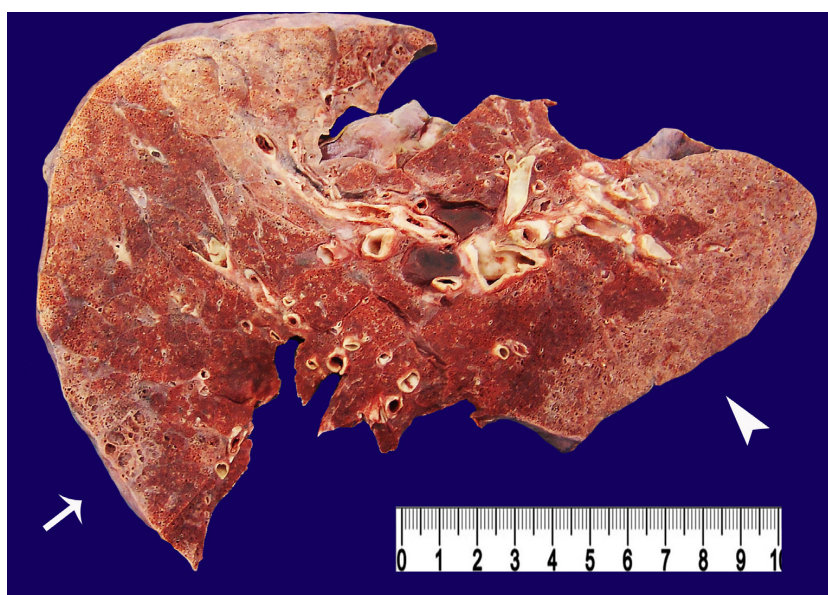
The patient was treated with diuretics as well as antibiotic and non-invasive respiratory support. The heart failure, attributed to the pulmonary hypertension, did not improve with conventional therapeutic measures. The outcome was unfavorable with progressive neurological deterioration, acute renal failure, worsening thrombocytopenia, and

enlargement of the prothrombin time. She died on day 7 of hospitalization in severe anasarca and due to respiratory failure. With the family's informed consent an autopsy was performed.

## AUTOPSY FINDINGS

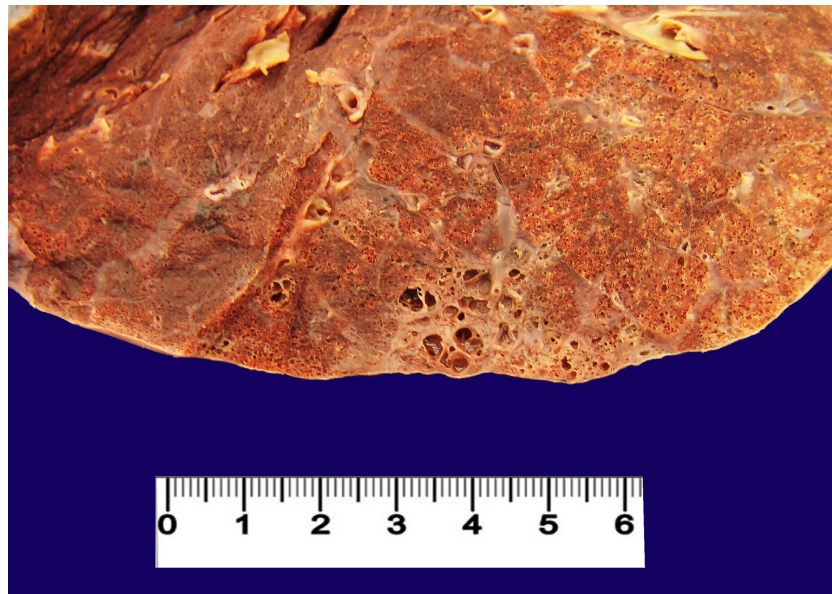
The autopsy confirmed the general signs of anasarca and right cardiac failure secondary to chronic lung disease. Ascites was most remarkable (8 L), and pericardial (20 mL) and pleural effusions (200 mL each side) were present.

The lungs were congested and boggy (right and left lungs weighed 601 g and 400 g, respectively) with partial atelectasis. The pleural surfaces showed mild fibrin deposition in the upper left lobe and anthracosis. The upper lobes showed foci of emphysema and multiple grayish and fibrotic areas, which became more evident after formalin fixation (Figures 3 and 4). Histology confirmed the areas of emphysema and fibrosis in the upper lobes (Figure 5A), and a diffuse interstitial homogeneous fibrosis in the upper and lower lobes (Figure 5B and 5C). Interstitial lymphomononuclear inflammatory infiltrate was mild (Figure 5D). No fibroblastic foci or honeycombing was detected. Some larger pulmonary artery branches were torturous with intimal fibrosis and fibromuscular hyperplasia. Some arteriolar branches were markedly thickened (Figure 6A and 6B). A few microscopic thrombi

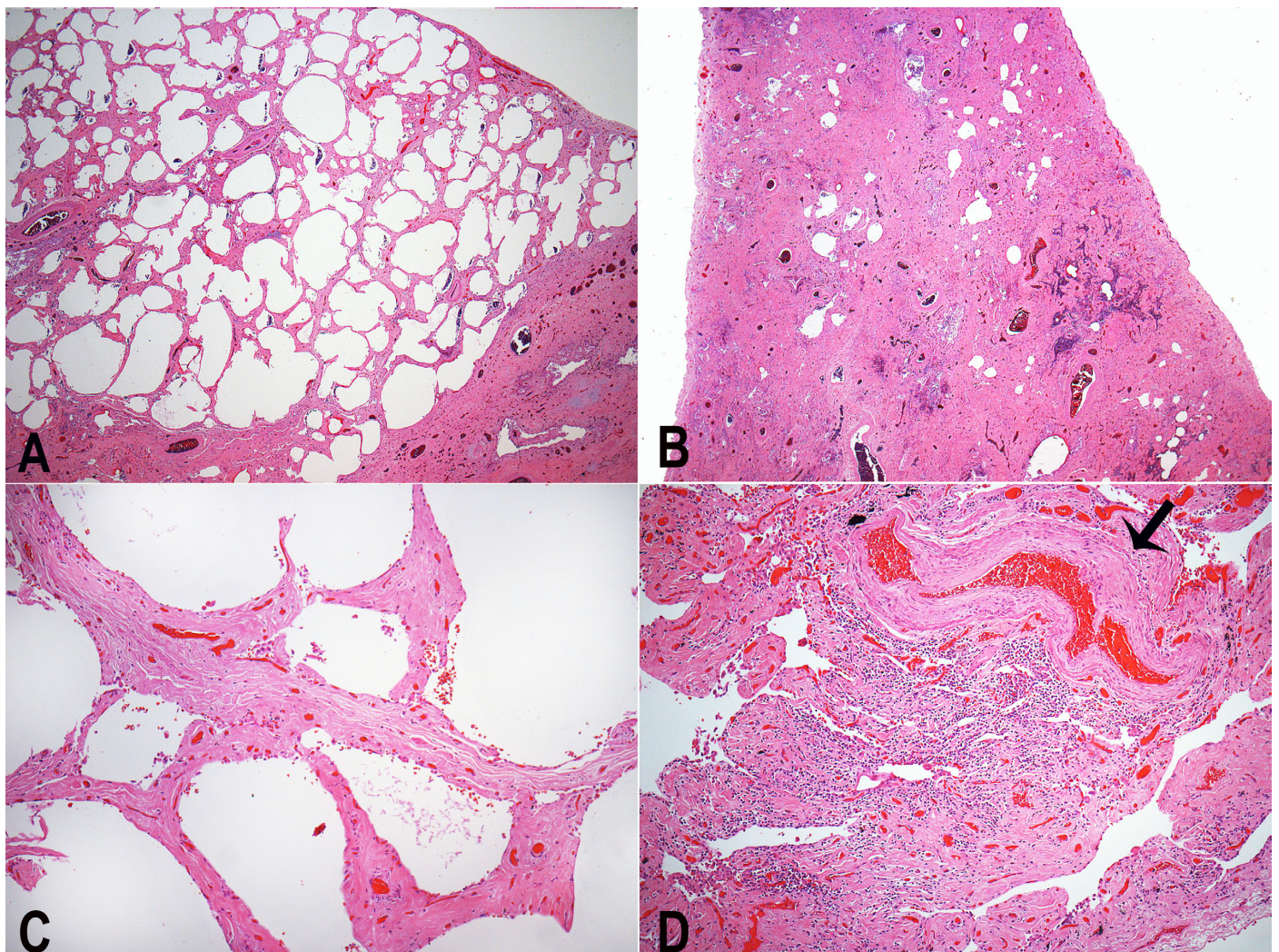


**Figure 3.** Gross findings of lung pathology. Section of right lung showing areas of emphysema (arrow) and fibrosis (arrowhead).





**Figure 4.** Gross findings of lung pathology. Detail of emphysematous areas.



**Figure 5.** Photomicrography of the lung. In **A** - Subpleural emphysema with airspace enlargement and fibrosis (panoramic view H&E 12.5X); **B** - Diffuse fibrosis with few alveolar spaces (H&E 12.5X); **C** - The alveolar septa are remarkably fibrotic (area of predominant peripheral fibrosis) (H&E 200X); **D** - Other areas showed fibrosis and mild lymphomononuclear inflammatory infiltrate. A tortuous and thickened pulmonary artery branch is seen (arrow) (H&E 200x).



were detected along with areas of alveolar edema, hemorrhage, and hemosiderin laden macrophages (Figure 6C and 6D). These findings were consistent with previous reports of combined pulmonary fibrosis and emphysema (CPFE) with signs of focal thrombosis, and acute and previous hemorrhage.

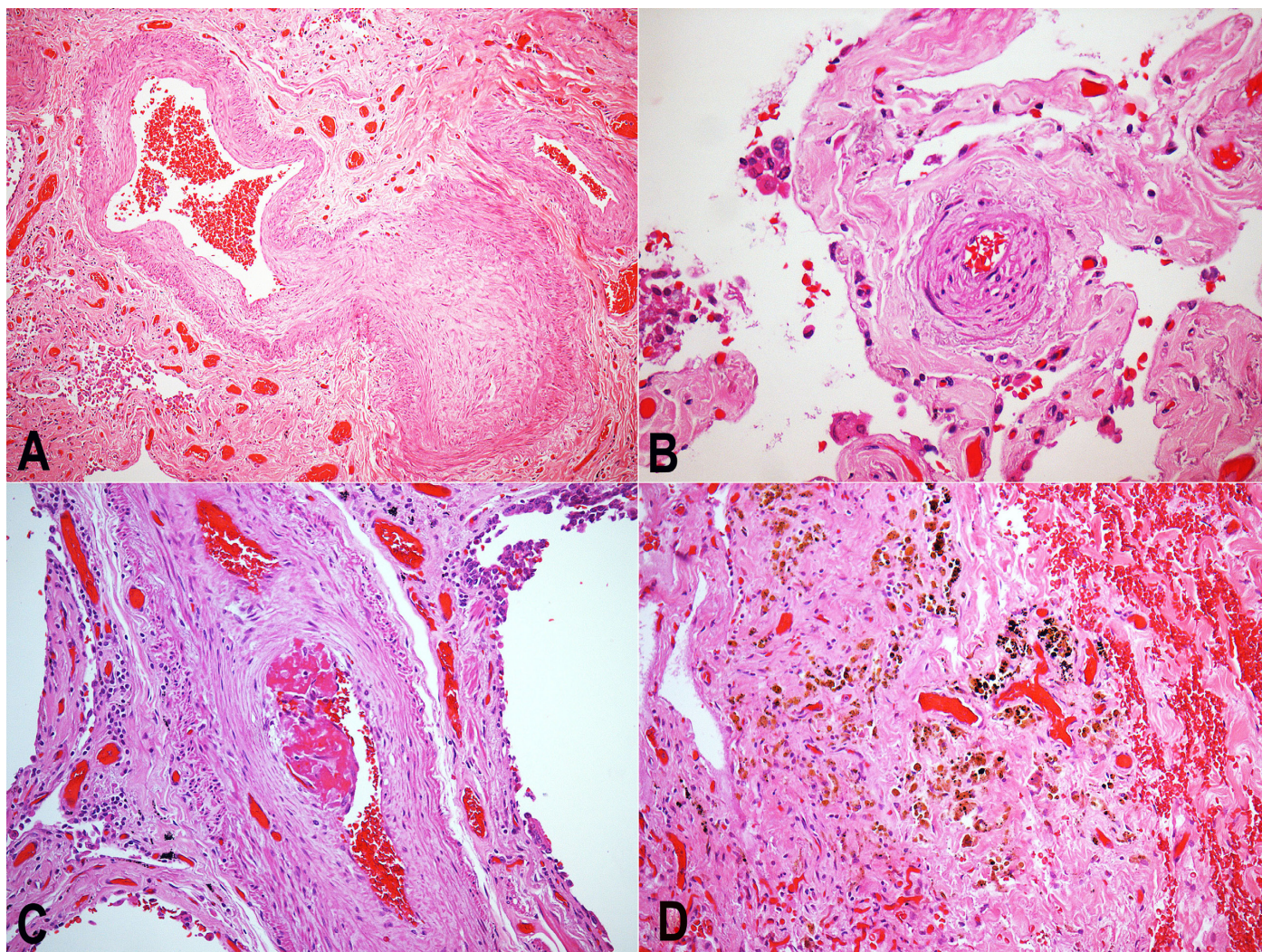
The heart was enlarged (500 g [mean reference value mRV; 262g]) mostly due to enlarged right chambers. The right atrium showed whitish pericardial plaques due to non-specific fibrosis and chronic pericardial effusion. No atherosclerosis was detected in the pulmonary artery. The aorta and coronaries showed non-complicated atherosclerosis.

The liver showed signs of chronic passive congestion with dilated veins, a nutmeg appearance at gross examination, centrilobular congestion, and

necrosis. Chronic centrilobular, sinusoidal, and septal fibrosis was already present. Chronic congestive splenomegaly (293g, [mRV 112g]) was also detected at autopsy. Finally, signs of ischemia and necrosis related to systemic hypoxia and shock were detected in the brain, kidneys, and pancreas. The cause of death was interpreted as final complications of *cor pulmonale* related to pulmonary fibrosis and emphysema, with microscopic signs of lung thrombosis and hemorrhage.

## DISCUSSION

The CPFE has become a topic of great debate since its first description by Cottin et al.,<sup>1</sup> in 2005, as a distinct clinicopathologic entity, with unique



**Figure 6.** Photomicrography of the pulmonary vascular pathology. **A** - Tortuous branch of pulmonary artery with intimal fibrosis (H&E 100X); **B** - Small artery with marked fibromuscular hyperplasia (H&E 400X); **C** - Focal pulmonary artery branch thrombosis (H&E 200X); **D** - Areas of fibrosis and hemosiderin deposition (left) and focal interstitial hemorrhage (right) (H&E 400X).



clinical features, radiologic patterns, and prognosis. By definition, the diagnosis of emphysema has historically excluded the presence of fibrosis.<sup>2</sup> In 1974, Auerbach et al.<sup>3</sup> described both injuries in an autopsy for the first time. In 1990, Wiggins et al.<sup>4</sup> reported a series of cases of fibrosing alveolitis simultaneously to emphysema, by CT. He also characterized reduced diffused lung capacity for carbon monoxide (DLCO) and preserved lung volumes in these patients.

The first description by Cottin et al.<sup>1</sup> comprised an entity combining centrilobular or paraseptal emphysema in the upper lobes accompanied by pulmonary fibrosis in the lower lobes. Initially, patients with interstitial lung diseases (ILD), other than idiopathic pulmonary fibrosis, were excluded from the description. More recently, there have been reports of CPFE associated with other ILD, including ILD associated with connective tissue diseases (CTD).<sup>5-7</sup>

The prevalence of CPFE is not yet precisely known, ranging from 8% to 51% in patients with idiopathic pulmonary fibrosis (IPF).<sup>8,9</sup> On the other hand, pulmonary fibrosis occurs in 4.4–8% of patients with emphysema.<sup>10-12</sup> The prevalence of emphysema in the general population is of 21.5 cases per 1,000, while that of IPF is about 14–42.7 cases per 100,000.<sup>13</sup>

Patients with CPFE are mostly older males, with a mean age of 65 years. Cigarette smoking history (usually heavy smoking) is found in the vast majority of patients.<sup>14-16</sup> Whether the male predominance is caused by greater exposure to tobacco or if gender is an independent risk factor for CPFE, is still uncertain.

There is a great debate whether CPFE is an altogether distinct entity or merely a simultaneous occurrence of emphysema and fibrosis in the same lung, as both injuries have a great causal relation with smoking. It is hypothesized that the resulting damage is determined by a genetic susceptibility and an environmental trigger, possibly mediated by oxidative stress.<sup>13,17</sup> This oxidative stress causes cellular injury and apoptosis—leading to emphysema<sup>18</sup>—or cellular injury, activation of fibroblasts and myofibroblasts, and extracellular matrix deposition, resulting in pulmonary fibrosis.<sup>19</sup> The resulting phenotype, then, would depend on the balance between apoptosis, proteolysis, and fibrosis.

Tobacco, via oxidative stress, is capable of regulating genes associated with inflammatory

response, and genes that codify cytokines, chemokines, and adhesion molecules, mostly through transcription factors such as NF- $\kappa$ B and activator protein-1. These genes are transcribed chiefly by the histone acetylation, which is intensified by the reduction of histone deacetylase function caused by tobacco smoking.<sup>20</sup> Some associated inflammation mediators are platelet-derived growth factor (PDGF),<sup>21</sup> tumor necrosis factor alpha (TNF- $\alpha$ ), transforming growth factor beta (TGF- $\beta$ ),<sup>22,23</sup> and chemokine ligands 5 (CXCL5) and 8 (CXCL8).<sup>24</sup> The latter two are chemokines related to neutrophilic infiltration, which contribute to both emphysema and fibrosis.

CPFE is also caused by occupational exposure, mostly coal<sup>25</sup> and welding,<sup>26</sup> but also agrochemical compounds<sup>27</sup> and tire manufacturing.<sup>28</sup>

A group of patients developed CPFE secondary to CTD, which is more frequently related to rheumatoid arthritis and systemic sclerosis,<sup>7</sup> that still maintain associations with smoking. This particular type of CPFE is more commonly found among younger women, with milder pulmonary hypertension, minor impairment of the DLCO, and a less severe prognosis.

The pathological pattern of fibrosis is greatly varied. There have been descriptions of interstitial pneumonia,<sup>1</sup> airspace enlargement with fibrosis,<sup>29</sup> non-specific interstitial pneumonia,<sup>1</sup> respiratory bronchiolitis-associated ILD with alveolar septal fibrosis,<sup>30</sup> desquamative interstitial pneumonia with extensive fibrosis,<sup>31</sup> and unclassified smoking-related interstitial fibrosis.<sup>32</sup> Our patient's pulmonary pathological findings were briefly characterized by emphysema in the upper lobes and diffuse fibrosis in the entire lungs, accompanied by marked vascular changes consistent with pulmonary hypertension.

Studies have been showing differential patterns of genetic expression in CPFE. Genes associated with the immune system are mostly expressed in areas of fibrosis, whilst genes related to cellular division, membrane biology, and vascular biology characterize the expression in emphysema.<sup>33</sup>

Some reports of CPFE in non-smokers shine a light on possible pathways of genetic expression. A young non-smoking woman with CPFE was shown to carry a mutation in the surfactant protein C gene.<sup>34</sup> A young non-smoking man had CPFE possibly because of a mutation in the ABCA3 gene.<sup>35</sup> Both genes are



associated with surfactant homeostasis and lung epithelial type II cells injury and death.

Another factor implicated in the pathogenesis of CPFE is accelerated ageing due to telomere shortening. Mutation of telomerase genes—namely, hTERT and hTR—have been reported in familial cases of CPFE. Telomerases are enzymes responsible for adding repeat sequences to telomeres. A shortening of telomeres possibly lowers the threshold of damage caused by tobacco smoking or other environmental triggers associated with CPFE.<sup>36-38</sup>

The preeminent symptoms in patients with CPFE, similarly to COPD and IPF, are cough and dyspnea. Among these three entities, COPD usually presents with a productive cough early on,<sup>39</sup> while CPFE and IPF feature mainly progressive dyspnea, and cough with sputum may only appear in the later stages of the disease.<sup>40</sup> Another key characteristic of CPFE is the exertion dyspnea. Other possible manifestations are wheezing, oral cyanosis, and asthenia. On auscultation, typically, “Velcro crackles” are frequently heard. Finger clubbing is also prevalent.<sup>41</sup>

Pulmonary arterial hypertension is severe and is a predictor of poor prognosis.<sup>41</sup> Its prevalence ranges from 47% to 90%.<sup>42-44</sup> Five-year survival is as low as 25%.<sup>42</sup> An interesting correlation exists between the degree of emphysema on high-resolution computed tomography (HRCT) and systolic pressure in the pulmonary artery.<sup>45</sup> The gold standard method for the diagnosis of pulmonary hypertension remains right ventricle catheterization; however, transthoracic echocardiogram may be used as a screening tool.

Our patient had dyspnea as the pre-eminent symptom, which is characteristically progressive in nature. She had considerable exposure to tobacco during her lifetime. *Cor pulmonale* signs were evident, with lower limbs edema and congestive hepatopathy. This patient had an estimated pulmonary artery pressure of 100 mmHg, which explains the right-sided heart failure. The autopsy findings confirmed the typical findings of the pulmonary hypertension.

Characteristically, chest x-rays of CPFE patients are non-specific and not very useful for diagnosis or follow-up. The most common findings are reticulation in the bilateral lower lung fields and hyperlucency in the lung apices, corresponding to emphysematous areas.<sup>46</sup> The diagnosis of CPFE is based on HRCT imaging, which

shows bilateral emphysema (mainly in the upper zones of the lungs) and fibrosis (mostly in the lower zones), with a progressive transition between emphysema and fibrosis.<sup>1,47</sup> The air-space lesions include centrilobular, paraseptal emphysema, and bullae.<sup>48</sup> In COPD, the most common pattern is centrilobular, while in CPFE patients paraseptal emphysema is more common and is supposed to be distinctive of this syndrome.<sup>17,49</sup> Regarding the fibrotic pattern, the usual interstitial pneumonia (UIP) is most commonly detected; however, studies have shown that the imaging findings are heterogeneous.<sup>50</sup> There are reports of CPFE patients with HRCT showing patterns of non-specific interstitial pneumonia (NSIP), airspace enlargement with fibrosis (AEF), respiratory bronchiolitis-associated ILD (RB-ILD) with alveolar septal fibrosis, desquamative interstitial pneumonia with extensive fibrosis, and unclassifiable smoking-related interstitial fibrosis.<sup>50</sup>

The AEF pattern stands out as a distinct feature of CPFE.<sup>14,49</sup> This pattern consists of thick-walled large cysts in the lower zones of the lung where reticulation is present. It is always associated with emphysema, and represents the development of pulmonary fibrosis in the setting of an emphysematous lung, with enlargement of the cysts due to retraction forces.<sup>51</sup>

Besides specific lung tissue findings, other CT findings for CPFE are those associated with pulmonary hypertension (a common finding in CPFE patients).<sup>45</sup> CT scans may show dilatation of the central pulmonary arteries, enlargement of the right heart, and reduction of the peripheral branches of the pulmonary parenchyma.<sup>51</sup>

In our case, the CT findings showed major signs of pulmonary hypertension, such as pulmonary trunk caliber greater than the aorta, dilation of the right cardiac chambers, reflux of the contrast media into the dilated inferior vena cava and hepatic veins, and the presence of moderate pericardial effusion. The findings in lung parenchyma are also typical, showing paraseptal emphysema in the upper lobes, fibrosing ILD characterized by ground glass opacity (which were represented by fibrosis in the histological examination), thin reticulated and traction bronchiectasis, predominantly in the subpleural regions of the lung bases (a pattern associated with NSIP). In this case, the fibrosis findings are more remarkable than its emphysematous counterpart; however, both were present.

Pulmonary function tests in CPFE patients are characterized by normal or near-normal spirometric values and static lung volumes, and a significant reduction of DLCO.<sup>1,52</sup> This is explained by the cohabitation of the two types of lesions present in CPFE: emphysema and fibrosis. While emphysema causes hyperinflation, obstruction of airways, and greater lung compliance, fibrosis causes restrictive effects, traction to support the small airways and prevent them from collapsing, and a decrease in lung compliance.<sup>46</sup> Therefore, CPFE patients have shown a faster decrease in forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) than patients with IPF only, and a higher decrease in vital capacity (VC) and FVC compared to patients with COPD alone.<sup>53,54</sup>

The reduction in DLCO is explained by the reduced vascular surface area and pulmonary capillary blood volume, which is caused by fibrotic and emphysematous lesions, in combination with alveolar membrane thickening, which is caused by fibrotic lesions.<sup>47</sup> There also seems to be a correlation between the different patterns on HRCT, and specific changes on pulmonary function tests.<sup>53</sup> Although a single pulmonary function test does not seem to be accurate in defining the prognosis for CPFE patients, follow-up with annual testing appears to be useful in evaluating disease progression, by analyzing FEV1 values.<sup>53</sup> Unfortunately, our patient was not tested for pulmonary function because of non-compliance with a regular medical follow-up.

As far as we know at the date of this article, no particular recommendation is available regarding the management of patients with CPFE. It is accepted that measures for smoking cessation should be taken,<sup>55</sup> and oxygen therapy for patients with respiratory failure is also accepted.<sup>56,57</sup> Vaccination for influenza viruses and *Streptococcus pneumoniae* might be also recommended.<sup>13</sup> Bronchodilators might be prescribed in patients with a positive response to these drugs in pulmonary function tests.<sup>41</sup> Recently discovered treatments for idiopathic pulmonary fibrosis, such as pirfenidone and nintedanib, might be beneficial for CPFE patients as well;<sup>58</sup> however, further studies with CPFE patients need to be carried out to define the response to this particular population.<sup>59</sup> In severe cases of the disease, patients should be considered for lung transplantation.<sup>50</sup>

Median survival for CPFE patients has been reported to be between 2.1 and 8.5 years. Five-year survival ranges between 38% and 55%.<sup>1</sup> Progressive lung function tests can be used to define the prognosis in CPFE patients.<sup>53</sup> In IPF patients, the annual rate of decline in FVC and DLCO are shown to be independent predictors of survival, while in patients with the diagnosis of CPFE the survival is strongly related to the decline in FEV1.<sup>53</sup>

Clinical factors for the worst prognosis in CPFE patients include active smoking, finger clubbing, and the development of pulmonary hypertension and lung cancer.<sup>15,60,61</sup> Radiological examination factors take into account both the fibrotic and the emphysematous lesions. The extent of the fibrosis in the lungs seems to be strongly related to survival as well as the pattern of emphysema.<sup>15,62</sup> Centrilobular or mixed emphysema had a better survival rate compared to patients with only IPF, and compared to CPFE patients with minor emphysema or advanced paraseptal emphysema.<sup>62</sup> The reason for these findings remains unknown, but they might suggest that the extent of the fibrosis is the most important factor in prognosis, while emphysema seems to only influence the survival rate in cases of very extensive lesions.<sup>59</sup>

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