Combined pulmonary fibrosis and emphysema (CPFE): does the type of emphysema predict the type of fibrosis?

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Purpose

Tobacco smoking has been historically considered an important contributor to respiratory diseases; it is the major etiological factor for the development of chronic obstructive pulmonary disease (COPD), lung cancer and adversely affects the control of asthma [1]. At the beginning of the previous decade a group of diverse interstitial lung diseases was emerged called smoking interstitial lung diseases (SRILDs) encompassing respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial lung disease (DIP), pulmonary Langerhans cell histiocytosis (PLCX) and pulmonary fibrosis [2]. In 2005 along with the publication of the seminal paper by Cottin V et al a new syndrome has emerged called combined pulmonary fibrosis and emphysema (CPFE) characterized by the coexistence of emphysema in the upper lobes and pulmonary fibrosis in the lower lobes [3]. The syndrome is associated with pseudonormalization of the pulmonary function tests (PFTs) and significant impairment of diffusion capacity (DLCO) [4]. It is also associated with pulmonary hypertension that predicts a dismal prognosis [5]. Moreover it has been reported that paraseptal emphysema is more common than the centrilobular type [6]. In addition to that, although in the earlier days CPFE was considered to be characterized by a UIP pattern of fibrosis on HRCT, there is a more recent concept claiming that CPFE is a heterogeneous disease both on pathology and HRCT characterized by different pattern of fibrotic disease [7]. The purpose of this study is to investigate whether the predominant type of emphysema can predict the HRCT pattern of fibrosis in CPFE.
Methods and Materials

Approval of Local Ethics Committee and the institutional review board of the Hospital was obtained for the retrospective analysis of the medical records and the HRCTs of the patients. Informed consent of the patients' was waived according to the greek legislation. Inclusion criteria included the presence of emphysema >3% (see HRCT scoring system below) and presence of pulmonary fibrosis in the lower lobes. Exclusion criteria included the presence of respiratory infection, connective tissue diseases, drug toxicity, pneumoconioses, extrinsic allergic alveolitis, sarcoidosis, histiocytosis, lymphangioleiomyomatosis and eosinophilic pneumonia. The HRCTs of the chest of forty-nine smokers with upper-lobe emphysema and lower-lobe pulmonary fibrosis were retrospectively evaluated. Patients were stratified into two groups according to predominant type of emphysema: centrilobular or paraseptal (Figure 1, 2). Then they were stratified in three different groups according to the predominant HRCT pattern of pulmonary fibrosis: definite UIP pattern, probable UIP pattern and NSIP pattern (Figure 3, 4). HRCTs were scored independently by two Radiologists using a modification of a semi-quantitative HRCT scoring system at 5 predetermined levels [8]: 1) origin of great vessels; 2) main carina; 3) pulmonary venous confluence; 4) halfway between the third and fifth section; 5) immediately above the right hemi-diaphragm. Discrepancies were resolved in consensus. The HRCT scoring system - at each one of the five levels - used a 0 to 3 point scale for the evaluation of the coarseness of fibrosis (Coarseness) and evaluated to the nearest 5% the following variables: extent of emphysema (emphysema), total extent of interstitial lung disease (TotExtILD), extent of reticular pattern non-otherwise specified (RetNOS), extent of ground glass opacity with traction bronchiectasis (extGGOBx), extent of pure ground glass opacity (GGO), extent of honeycombing (HC). The total coarseness score was the summed score for all five levels (range 0 to 15) and the global HRCT scores for each variable were computed as the mean of the scores. The following PFTs were also recorded from the medical files of the patients: FEV1, FEV1/FVC, PEF, MMEF 75-25, FVC, TLC, RV, RV/TLC, DLCOsb (diffusing lung capacity - single breath), DLCOva (diffusing lung capacity - alveolar volume). The mean pulmonary arterial pressure (mPAP) was recorded when available. HRCT mean scores were correlated with PFTs, DLCo and mPAP (Pearson, Spearman). HRCT scores were compared between the two groups regarding the predominant type of emphysema (Independent Samples T-Test) and amongst the three groups regarding the predominant HRCT pattern of fibrosis (One way Anova, regression analysis).
Fig. 1: Figure 1. HRCT at the level of the upper lobes shows paraseptal emphysema associated with subpleural reticular pattern and minimal ground glass opacity.

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Fig. 2: Figure 2. HRCT of the same patient as in Figure 1, at the level of the lower lobes reveals extensive coarse reticular pattern characterized by traction bronchiectasis associated with ground glass opacity. The HRCT pattern is consistent more with UIP.

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Fig. 3: Figure 3. HRCT at the level of the upper lobes shows extensive predominantly centrilobular emphysema.

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Fig. 4: Figure 4. HRCT of the same patient as in figure 3, at the level of the lower lobes shows subpleural fine fibrosis characterized mainly by ground glass opacity, reticular pattern non-otherwise specified and absence of honeycombing. The HRCT pattern is consistent more with NSIP.

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Results

Mean HRCT scores in paraseptal and CLE groups were accordingly: 9 and 4.9 (Coarseness), 6.55 and 23.66% (emphysema), 51.55 and 34.29% (Tot Ext ILD), 28.9 and 18.2% (RetNOS), 38.95 and 21.5% (extGGOBx), 12.8 and 25.4% (GGO), 17.9 and 1.5% (HC). Significant differences were found between the 2 groups regarding "emphysema" (p<0.000), "TotExtILD" (p<0.01), "extGGOBx" (p<0.016), "HC" (p<0.005) and "Coarseness" (p<0.000). FEV1/FVC (p<0.04), PEF (p<0.042) and MMEF\textsubscript{25-75} (p<0.042) were significantly lower in "CLE" group, while TLC was significantly lower in the "paraseptal emphysema" group (p<0.028). DLCo was lower (30.4 versus 41.4) and SPAP was higher (43.5 versus 34.2) in the "paraseptal emphysema" group. When comparing the three different HRCT patterns amongst them, one-way Anova showed that extent of emphysema was significantly higher in NSIP versus UIP pattern (p<0.003) and that total extent of interstitial lung disease (p<0.008), GGO with bronchiectasis (p<0.018), honeycombing (p<0.000) and Coarseness (p<0.018) were significantly higher in definite UIP versus NSIP Pattern. Crosstabs revealed that 15 out of the 18 "paraseptal emphysema" cases had a "definite UIP pattern" and 22 of the 26 "CLE" cases had an NSIP pattern.
Conclusion

Predominant type of CLE is more common in CPFE patients compared to "paraseptal emphysema" type. In CPFE, patients with a predominant type of CLE have higher extent of emphysema than patients with paraseptal type of emphysema. Panlobular emphysema is commonly seen in patients with advanced CLE.

Large emphysematous lesions even in the lower lobes surrounded by GGO may erroneously present as thick-walled cysts and be misinterpreted as "honeycombing" [9]. The high incidence of UIP-pattern of fibrosis in CPFE pts in previous reports may be attributed to the misinterpretation of "GGO-surrounded" emphysematous cysts as honeycombing [3].

In CPFE, a predominant "CLE type" is associated with more GGO and less coarse fibrosis and honeycombing- resembling an NSIP - pattern, while a predominant "paraseptal type" of emphysema is associated with more coarse fibrosis, reticulation and honeycombing, resembling a UIP - pattern. Therefore a predominant "CLE type" may be associated with a more reversible type of pulmonary fibrosis more likely to respond to smoking cessation and immunosuppressive therapy [8], while a predominant "paraseptal type" of emphysema may be associated with a more irreversible type of pulmonary fibrosis with a worse prognosis. Future studies are needed to confirm these findings.


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