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Review Article

Combined pulmonary fibrosis and emphysema (CPFE)

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Abstract

Combined pulmonary fibrosis and emphysema (CPFE) is rare but increasingly recognized condition characterized by simultaneous coexistence of both upper lobe predominant emphysema and diffuse pulmonary fibrosis mainly in lower lobe. Patients with CPFE are usually heavy smokers or former smokers. HRCT has a pivotal role in diagnosis. Pulmonary function test showed relatively preserved lung volumes and reduced diffusing capacity of the lung for carbon monoxide (DLCO). Development of pulmonary hypertension (PH) is largely attributed to morbidity in patients with CPFE which is the principal prognostic factor for this condition. However more studies are needed to establish natural history of the disease & treatment option. In this review, we will discuss the current knowledge of the pathogenesis, clinical characteristics, treatment options and prognostic factors of CPFE.

Keywords: *Combined pulmonary fibrosis and emphysema (CPFE), pulmonary arterial hypertension (PAH), forced expiratory volume in 1 second (FEV1).*

Introduction:

Combined pulmonary fibrosis and emphysema (CPFE) is a radiologically defined syndrome characterized by simultaneous coexistence of both upper lobe emphysema and lower lobe pulmonary fibrosis.[1]With the advent of HRCT, the combination of these two conditions has been increasingly described and has been proven to be a prevalent and distinct entity rather than a rare coincidence. Initially the association of Interstitial Pulmonary Fibrosis (IPF) and emphysema was described by Wiggins et al in 1990.[2] But the term CPFE was first used in 2005 by Cottin et al who described a group of patients with CT findings of emphysema in the upper zones and interstitial lung disease (ILD) with pulmonary fibrosis in the lower lobes.[1] In 2005,Grubstein et al. reported an association of fibrosis with emphysema in eight patients, their clinical and functional findings being similar to those of the aforementioned study. The authors also found moderate to severe pulmonary arterial hypertension (PAH) and postulated that smoking is an important factor linking emphysema, pulmonary fibrosis, and pulmonary vascular disease.[3] When CPFE was first described, patients with ILDs other than interstitial pulmonary fibrosis(IPF) were excluded from the study.[1]Later on, CPFE was described in patients with other ILDs, such as connective tissue disease (CTD) associated ILD,[4-7]as well as in patients with microscopic polyangiitis[8]

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The fact that IPF has the worst prognosis in relation to other chronic lung fibrotic diseases, it is important to establish the interstitial lung disease that constitutes the fibrotic component of CPFE. Patients with CPFE are predominantly male, with a history of heavy tobacco exposure, and usually present with severe breathlessness and cough. Physical examination reveals "Velcro" crackles at the lung bases and digital clubbing.[1,9]Pulmonary hypertension is a hallmark of the syndrome and determines poor prognosis.[9]Studies have shown that patients with CPFE associated with CTDs (e.g. rheumatoid arthritis and systemic sclerosis) are significantly younger than their idiopathic CPFE counterparts, are predominantly female, and have less DLCO impairment.[4]

Pathogenesis:

The exact pathogenetic mechanisms that lead to the development of CPFE has yet to be elucidated. Smoking is believed to play a major role as almost all (about 98 %) of CPFE patients are current or former smokers .Tobacco smoke-induced oxidative and nitrative stress in the lungs may amplify inflammation due to reduced histone deacetylase activity that may contribute pathogenetically to both emphysema and fibrosis.[10]Smoking may also contribute to both emphysema and fibrosis by over expression of tumor necrosis factor-α and platelet-derived growth factor-β(PDGF-β).[11,12] Exposure to agrochemical substances has also been described as risk factor for CPFE.[13] Diaz CleLeon *et al*. demonstrated evidence of emphysema in 20% of telomerase mutation carriers with idiopathic pulmonary fibrosis(IPF).[14] Cottin *et al*. reported a dominant mutation 173T in the surfactant protein C gene in a patient with CPFE.[15]

Lung Function in CPFE :

In patients with CPFE, spirometry can be normal or show mild abnormalities. They typically present with preserved or slightly reduced lung volumes in relation to the extent of fibrotic changes in the lungs. Forced vital capacity (FVC), FEV_1 , and Total lung capacity(TLC) values usually within normal limits or slightly reduced. The ratio FEV1/FVC can be normal or reduced (<70 %)and is lower compared to patients

with IPF alone.[16]One possible explanation for normal or subnormal spirometry results despite severe impairment in DLCO is that hyperinflation and greater lung compliance as a result of loss of elasticity in the areas of emphysema can compensate for the losses in volume and lung compliance caused by fibrosis. Another plausible explanation is that fibrosis prevents the early small airway closure observed in patients with emphysema. However, both processes cause damage to the alveolar-capillary membrane resulting in a disproportionately reduced DLCO.[1,17-19] In patients with CPFE, arterial oxygen tension (PaO2) and arterial oxygen saturation (SaO2) at rest, and SaO2 and PaO2 at exercise are significantly decreased.[20,21] Hypercarbia is usually not observed.[1,22] Patients with fibrosis adopt a rapid/ shallow pattern of breathing which increases alveolar ventilation and thus reduces the levels of alveolar and blood pCO2. Exertional dyspnea is the most common presenting symptom in patients with CPFE. on examination, end-inspiratory fine 'velcro' crackles mainly in basal regions are the predominant findings and digital clubbing may also be seen in many of these patients.[22]

Imaging studies in CPFE:

The diagnosis of the CPFE syndrome is based on findings on High-Resolution Computed Tomography (HRCT) of the chest.[1] HRCT scans typically show centrilobular or paraseptal emphysema in the upper lobes, as well as reticular opacities, traction bronchiectasis, septal thickening, ground-glass opacities, and honeycombing in the lower lobes. (Figures 1). Although Usual Interstitial Pneumonia (UIP) is the most common CT pattern, some patients have ground-glass opacities that are more extensive than expected for a UIP pattern and are therefore suggestive of nonspecific interstitial pneumonia, Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD), and even Desquamative Interstitial Pneumonia (DIP).[1]

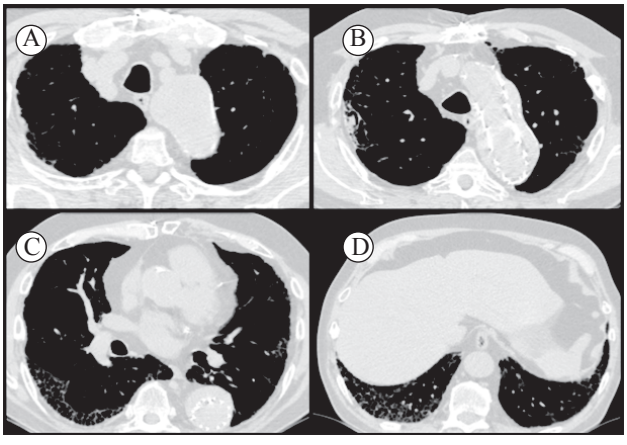

Figure 1 : shows CT scan of the chest of a 67-year-old female patient with combined pulmonary fibrosis and emphysema, showing centrilobular and paraseptal emphysema in the upper lobes (A and B), as well as ground-glass opacities, traction bronchiectasis, and honeycombing in the lower lobes (C and D). Note an aspergilloma in one of the paraseptal bullae in the right upper lobe (white arrow, in B)

Paraseptal emphysema seems to be more common in the CPFE population than in patients with COPD. In the study by Cottin et al. [1] it was observed in 93 % of patients and was suggested to be a hallmark of CPFE. The increased prevalence of paraseptal emphysema in CPFE was also observed in another study. Furthermore, the presence of paraseptal emphysema has been associated with a higher extent of fibrosis in comparison to centrilobular emphysema.[23]

The coexistence of emphysema and fibrosis makes the estimation of the extent of fibrosis really difficult. In the transition zone of the emphysematic to the fibrotic areas it is very tricky to make the appropriate distinction. Brillet et al. [24.] identified three HRCT patterns in 61 patients with CPFE: i) progressive transition (38%) with diffuse emphysema (centrilobular and/or bullous) and zone of transition between bullae and honeycombing, ii) paraseptal emphysema (21 %) with predominant subpleural bullae of enlarging size at the bases and iii) separate processes (23 %) with independent areas of fibrosis and emphysema.

CPFE and pulmonary hypertension (PH):

The prevalence of PAH is exceedingly high in patients with CPFE, and PAH correlates with worse survival.[1,24,25] The prevalence of PAH in CPFE patients varies from 47% to 90%, being considerably higher than that in patients with COPD or IPF alone.[26] Transthoracic echocardiography used to measure pulmonary artery pressure (Ppa) is an operator dependent imaging examination. Furthermore, the presence of emphysema can add further difficulties in the accurate estimation of right ventricular systolic pressure (RVSP). Right heart catheterization (RHC) remains the gold standard for the diagnosis of PAH. Cottin et al. retrospectively estimated the prevalence of PAH in 40 CPFE patients with RHC.[24] Out of them 27 patients (68 %), the mean Ppa was >35 mmHg.

The increased prevalence of PAH in CPFE is probably explained by the coexistence of emphysema and fibrosis. Both cause destruction of the pulmonary vasculature bed and of the lung parenchyma. The destruction of pulmonary vasculature reduces the total cross sectional area. Furthermore, as mentioned CPFE patients are usually hypoxemic due to V/Q mismatching caused by the coexisting emphysema and pulmonary fibrosis. The induced hypoxic pulmonary vasoconstriction is also an important cause of elevated pulmonary arterial pressure. If other pathogenic pathways are implicated, then the development of "out of proportion" PAH remains to be clarified. From a clinical point of view the physician should be vigilant in looking for underlying intermittent nocturnal and exercise induced intermittent hypoxia.[27-29]

Novel noninvasive methods for the diagnosis and quantification of PAH in CPFE patients have been proposed, including time-resolved Magnetic Resonance Angiography (MRA), which allows anatomic imaging of the pulmonary vasculature and evaluation of hemodynamic parameters. Using this technique, Sergiacomi et al. prospectively studied

18 CPFE patients using pulmonary arterial mean transit time and time to peak enhancement as surrogate parameters for hemodynamic data (mean pulmonary artery pressure and pulmonary vascular resistance), which were obtained through right heart catheterization performed three days before time-resolved MRA was performed. Pulmonary arterial mean transit time and time to peak enhancement showed good correlation with the invasive parameters.[30]

Patient Management & Prognosis :

Therapeutic options for patients with CPFE are limited. According to the most recent international guidelines, there are no data on which to make recommendations for treatment of emphysema in the setting of IPF.[31] Smoking cessation is an obvious objective. Oxygen therapy is appropriate for the management of hypoxemia. Inhaled bronchodilators are often prescribed. Currently, there are two approved drugs for the treatment of IPF, pirfenidone and nintedanib.[32] They slowed disease progression by reducing the annual rate of FVC decline independent of the presence of emphysema at baseline.[33] The main concern is not whether pirfenidone and nintedanib are efficacious in CPFE, but whether the rate of FVC decline underestimates their efficacy in this specific subpopulation.

The presence of emphysema and abnormal pulmonary pathology in patients with CPFE and pulmonary hypertension may be associated with an imbalance in the ventilation / perfusion ratio (V/Q), as hypoxic vasoconstriction is one of the main mechanisms to avoid worsening arterial oxygenation. Vasodilator drugs can worsen hypoxemia by inhibiting this mechanism.[34] Specific therapies approved for treating pulmonary arterial hypertension in appropriately designed trials are also necessary to study the effect of these drugs in CPFE patients.[35]

Patients with CPFE seem to be at greater risk for developing lung cancer. Thus, increased vigilance is required for early detection of such lesions. Management of lung cancer in CPFE patients should follow current guidelines.[36] Stem cell therapy is a promising approach for COPD and IPF. Conducting clinical trials of stem cell therapy in CPFE is an intriguing project that could shed further light in the areas of pathogenesis and treatment.[37]

In IPF patients the follow up and response to therapy are based on the measurement of FVC and DLCO. However, CPFE patients tend to exhibit a delay in the reduction of FVC and DLCO which reduces their utility as surrogate markers for disease progression[17, 38]. In addition, a decline in DLCO should be viewed cautiously, as it could be the result of development/progression of pulmonary hypertension which is commonly encountered in CPFE. The annual decrease of the ratio FEV1/ FVC in CPFE seems to be significantly higher compared to IPF.[17, 19]

In a study by Schimdt et al., mortality in CPFE patient was better predicted by the decline in FEV1, while changes in FVC, DLCO and Composite Physiological Index (CPI) were not predictive at 12 months follow-up and only FVC was predictive at 6 months[38]. The prognostic validity of FEV1 increased with increasing severity of emphysema in a dose-dependent fashion. On the other hand, FEV1 had no prognostic role in patients with IPF and with no emphysema.

Conclusion:

CPFE is a recently recognized entity with unique features. It is more frequent (30%) than previously believed and may have a worse prognosis than IPF alone, with PAH being the major determinant of morbidity and mortality. The rate of FEV1 decline is the strongest predictor of mortality.

It is obvious that many aspects of the CPFE syndrome still remain to be explored. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of CPFE, with or without PH, and also to delineate more precisely the boundaries between IPF and patients with CPFE syndrome. Further research is essential to understand etiology, pathophysiology, and management of this distinct clinical entity.

References:

1. CottinV, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, *et al*. Combined pulmonary fibrosis and emphysema: a distinct under recognized entity. Eur Respir J 2005;26:586-93.
2. WigginsJ, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema a: the value of high resolution computed tomography in assessment. RespirMed.1990;84(5):365-9.
3. GrubsteinA, BendayanD, SchactmanI, CohenM, ShitritD, KramerMR. Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. Respir Med. 2005;99(8):948-54.
4. CottinV, NunesH, MouthonL, GamondesD, LazorR, HachullaE, etal. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum.2011;63(1):295-304.
5. LubattiC, ZeniS, IngegnoliF. Combined pulmonary fibrosis and emphysema syndrome in systemic sclerosis. Int J Rheum Dis. 2012;15(5):122-3.
6. CottinV, FreymondN, CabaneJ, CordierJF. Combined pulmonary fibrosis and emphysema syndrome ina patient age 28years with severe systemic sclerosis. J Rheumatol. 2011;38(9):2082-3.
7. CottinV, CordierJF. Combined pulmonary fibrosis and emphysema in connective tissue disease. Curr Opin Pulm Med. 2012;18(5):418-27.
8. Tzouvelekis A, Zacharis G, Oikonomou A, Koulelidis A, Steiropoulos P, Froudarakis M, et al. Combined pulmonary fibrosis and emphysema associated with microscopic polyangiitis. EurRespir J. 2012;40(2):505-7.
9. KishabaT, ShimaokaY, Fukuyama H, YoshidaK, TanakaM, Yamashiro S, etal. A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema. BMJ Open.2012;15:2(3).
10. Barnes PJ , AdcockI M, Ito K. Histone acetylation and deacetylation : Importance in inflammatory lung diseases. EurRespirJ 2005;25:552-63.
11. LundbladLK, Thompson- FigueroaJ, LeclairT, SullivanMJ, PoynterME, IrvinCG, *etal*. Tumor necrosis factor-alpha over expression in lung disease :A single cause behind a complex phenotype. Am J Respir Crit Care Med 2005;171:1363-70.

12. HoyleGW, LiJ, FinkelsteinJB, EisenbergT, LiuJY, LaskyJA, *etal.* Emphysematous lesions, inflammation, and fibrosis in the lungs of transgenic mice over expressing platelet-derived growth factor. Am J Pathol 1999;154:1763-75.

13. DaniilZ, Koutsokera A, GourgoulianisK,. Combined pulmonary fibrosis and emphysema in patients exposed to agrochemical compounds. Eur Respir J 2006;27:434.

14. Diazde LeonA, CronkhiteJT, KatzensteinAL, GodwinJD, RaghuG, GlazerCS, *et al* .Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLoS One 2010;5:e10680.

15. CottinV, ReixP, KhouatraC, Thivolet-BéjuiF, FeldmannD, CordierJF. Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPC mutation. Thorax 2011;66:918-9.

16. Strickland NH, Hughes JM, Hart DA, et al. Cause of regional ventilation- perfusion mismatching in patients with idiopathic pulmonary fibrosis: a combined CT and scintigraphic study. Am J Roentgenol. 1993;161(4):719–25.

17. AkagiT, MatsumotoT, HaradaT, etal. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis.RespirMed.2009;103(8):1209–15.

18. Jankowich MD, Rounds S. Combined pulmonary fibrosis and emphysema alters physiology but has similar mortality to pulmonary fibrosis without emphysema. Lung.2010;188:365–73.

19. KimYJ, Shin SH, Park JW, Kyung SY,Kang SM,Lee SP, etal. Annual Change in Pulmonary Function and Clinical Characteristics of Combined Pulmonary Fibrosis and Emphysema and Idiopathic Pulmonary Fibrosis:Overa3-Year Follow-up. Tuberc Respir Dis.2014;77(1):18–23.

20. Oikonomou A, Mintzopoulou P, Tzouvelekis A, etal. Pulmonary fibrosis and emphysema: Is the emphysema type associated with the pattern of fibrosis? World JRadiol.2015;7(9):294–30

21. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis a population-based cohort study. Am J Respir Crit Care Med.2000;161(1):5

22. KitaguchiY, FujimotoK, Hanaoka M, KawakamiS, HondaT ,Kubo K. Clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology.2010;15(2):265–71

23. BrilletPY, CottinV. Letoumelin Petal., Combined apical emphysema and basal fibrosis syndrome (emphysema /fibrosis syndrome):CT imaging features and pulmonary function tests. JRadiol.2009;90 (1Pt1):43–51.

24. CottinV, Le PavecJ, PrévotG, MalH, HumbertM, SimonneauG, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. EurRespirJ.2010;35(1):105-11.

25. MejíaM, CarrilloG, Rojas-SerranoJ, EstradaA, SuárezT, Alonso D,et al. Idiopathic pulmonary fibrosis and emphysema :decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009;136(1):10-5.

26. Portillo CarrozK, Roldán Sánchez J, Morera PratJ. 18.Combined pulmonary fibrosis and emphysema [Article in Spanish].Arch Bronco neumol.2010;46(12):646-51

27. Corte TJ, WortSJ, GatzoulisMA, etal. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. Thorax.2009;64:883–8.

28. HamadaK, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis.Chest.2007;131:650–6.

29. LettieriCJ , Nathan SD, Barnett SD, etal. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest.2006;129:746–52.

30. Sergiacomi G, Bolacchi F, CadioliM, AngeliML, Fucci F, CruscoS, et al. Combined pulmonary fibrosis and emphysema: 3Dtime-resolved MR angiographic evaluation of pulmonary arterial mean transit time and time to peak enhancement. Radiology. 2010;254(2):601-8.

31. Raghu G, Collard HR, Egan JJ, etal .An official ATS/ERS/JRS/ ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. AmJ Respir Crit Care Med2011;183:788–824.

32. RicheldiL, duBoisRM ,Raghu G.etal; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis.NEnglJMed.2014;370:2071–82.

33. Pfeifer M et al. Effect of baseline emphysema on reduction in FVC decline within tedanib int heINPULSIStrials. Pneumologie.2015;69:P254.

34. Portillo K, MoreraJ. Combined pulmonary fibrosis and emphy sema syndrome: a new phenotype within the spectrum of smoking-related interstitial lung disease. Pulm Med 2012;2012:

35. CottinV. Treatment of pulmonary hypertension in interstitial lung disease: do not throw the baby with the bath water. Eur Respir J2013;41:781–783.

36. Detterbeck FC, Lewis SZ, Diekemper R, et al. Executive Summary: Diagnosis and management of lung cancer, 3rded: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5Suppl):7S–37S

37. TzilasV, BourosD et al. Prospective phase1open clinical trial to study the safety of adipose derived mesenchymal stem cells (ADMSCs) in COPD and combined pulmonary fibrosis and emphysema (CPFE).ERJ.2015, 46 (suppl59).

38. Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011;38(1):176–83.

33. KwakN, Park CM, LeeJ, etal. Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. RespirMed. 2014;108:524e30.

34. UsuiK,TanaiC,Tanaka Y,NodaH,Ishihara T.The prevalence of pulmonary fibrosis combined with emphyse main patients with lung cancer. Respirology. 2011;16:326–31.