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Original Research Article

Combined Pulmonary Fibrosis and Emphysema (CPFE): A distinct Clinico-Radiological entity

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Abstract: Combined pulmonary fibrosis and emphysema (CPFE) is a common yet under diagnosed entity with imaging findings of both pulmonary emphysema and fibrosis.Many have challenged the definition of CPFE and there still exists a lot ofcontroversy over various aspects of this syndrome. Initially considered to represent a chance coexistence of two separateentities, CPFE is now being increasingly recognized as a distinct syndrome. The recognition of this syndromeis important, as it is associated with a worse prognosis when compared to pulmonary emphysema or fibrosis alone. Its diagnosis is mainly based on HRCT findings and is clinically characterized by relatively preserved spirometric values with disproportionate impairment of gas exchange. Since radiology plays a key role in making this diagnosis, it is important for radiologists to be familiar with the existence and appearance of this syndrome. We review this unique clinic-radiological entity with special emphasis on its CT appearances.
Keywords: Combined pulmonary fibrosis and emphysema (CPFE), Radiology, Imaging, HRCT.

INTRODUCTION

Pulmonary emphysema and idiopathic pulmonary fibrosis (IPF) are two distinct clinic-pathological entities that are well recognized in practice. These twohave been regarded as separate entities with different clinical and radiological features and prognosis. Whereas emphysema belongs to the spectrum of obstructive airway diseases, IPF is a restrictive pulmonary disease. In recent yearsthere has been an increasing recognition of both emphysema and pulmonary fibrosis coexistingin a number of individuals. Thishas resulted in a lot of speculation regarding the existence of a distinct entity called 'Combined pulmonary fibrosis and emphysema (CPFE). While many believe that it is merely a chance occurrence of emphysema and fibrosis in the same patient, others argue that their coexistence has common etiological factors. A large group now considers it as a part of the spectrum of smoking-related lung diseases [1].

In 2005, Cottin *et al* [2] for the first time defined a syndrome termed 'combined pulmonary fibrosis and emphysema' (CPFE), which was characterized by history of heavy smoking, exercise hypoxemia, upper lobe emphysema and lower lobe fibrosis. It is now well recognized that CPFE is a distinct clinico-radiological entitywith typical features of exertional dyspnea, upper-lobe emphysema and lower-lobe fibrosis, preserved lung volume and severely diminished capacity of gas exchange [3]. This subgroup of patients has a poorer prognosis when compared with patients with emphysema or fibrosis alone. Complications like pulmonary arterial hypertension, acute lung injury and lung cancer are also more commonin this category of patients[3]. Management of patients with CPFE is difficult with poor results of medical therapy [4].

Identification of this subgroup of patients is important because of the distinct history and natural course of this disease [2]. Imaging plays an important role in establishing the diagnosis of CPFE along with clinical assessment and pulmonary function tests. High-resolution CT (HRCT) scanning has enhanced the detection of the simultaneous occurrence of emphysema and pulmonary fibrosis and is very useful in establishing the diagnosis of CPFE andthe various

complications associated with it [5].

MATERIAL AND METHODS

The present study is an observational study based on review of imaging features in patients with CPFE. All cases diagnosed as having CPFE in the last one year, based on clinical and radiological features were selected from our database and their HRCT chest images were retrospectively reviewed for pattern analysis and imaging findings. All these cases were referred for imaging to the Department of Radiology from clinical departments of the hospital.

RESULTS

A total of ten cases diagnosed as having combined pulmonary fibrosis and emphysema (CPFE) based on clinical presentation, pulmonary function tests and HRCT findings were shortlisted for review. Of the ten cases nine were males and only one female with ages ranging from 30 to 75 years. Eight out of the nine male patients were smokers or gave history of smoking in the past. One male and one female patients had scleroderma along with lung disease. One of the cases gave past history of pulmonary tuberculosis for which he was treated.

All patients presented with history of chronic intermittent dry cough and progressive shortness of breath. One case presented with recurrent pneumothorax and another case on follow up developed lung malignancy which was confirmed at histopathology as adenocarcinoma.

HRCT images were reviewed in all cases and it was observed that all cases had components of emphysema as well as fibrosis in varying proportions and this also reflected their clinical presentation. Both centrilobular and paraseptal emphysema was seen to exist either alone or together in all the patients. Fibrosis showed a typical subpleural distribution and lower lobe predominance in all cases. One striking imaging feature in most cases (8 out of 10 cases) was the presence of ground glass attenuation, which was most often observed in the lower lobes. Additional features noted in our cases with CPFE included presence ofbronchiolectasis (3 cases), honeycombing (3 cases), subcentimeter sized mediastinal lymph nodes (7 cases) and enlarged main pulmonary artery (8 cases) suggestive of pulmonary arterial hypertension. Coexisting old treated Koch's lesions were observed in one case and spontaneouspneumothorax in another case. One case of CPFE after a year of follow up developed lung malignancy which was confirmed by CT guided biopsy as adenocarcinoma.

DISCUSSION

The prevalence of emphysema is reported about 21.5 per 1,000 in the general population while that of IPF is much lowervarying from 14 to 42.7 cases per 100,000 [6]. The prevalence of CPFE is not exactly known butis reported in about 8% to 51% of patients with IPF patients [7, 8] and 4 to 8% of patients with emphysema on HRCT [9]. This wide variation in the detection of CPFE in the two groups on HRCT can also be attributed to the fact that a lesser number of emphysema cases are evaluated by HRCT when compared to IPF [4].

Patients with CPFE are usually older maleswith history of heavy smoking. Smoking has therefore been considered as the predominant risk factor for CPFE [1]. Eight out of our ten cases were smokers. Other environmental exposures like asbestos and mineral dusts as a potential trigger of lung injury in the CPFE syndrome has also been suggested [3]. A potential genetic susceptibility is also likely, as it explains why all smokers do not develop CPFE [1, 10]. Some authors have reported cases of CPFE in the absence of smoking and in the context of connective tissue diseases (CTD) like rheumatoid arthritis and systemic sclerosis. This category of patients with CTD-associated CPFE are more likely to be women, significantly younger and with less severe outcomes than their idiopathic CPFE counterparts [11]. Two of our cases with CPFE had scleroderma and of these, one was a young female patient.

The pathogenesis of CPFE is poorly understood but existing knowledge suggests that it may involve a variety of unknown cytokines and signaling pathways leading to overexpression of inflammatory mediators likePDGF, TNF-α and TGF-β. Pulmonary inflammation in CPFE is found to be similar to IPF and it is even suggested that progression of "fibrosis' component plays an important role in disease worsening in CPFE [4].

Clinical Presentation

Progressive shortness of breath especially on exertion is the most common and classical symptom in patients with CPFE. Other signs and symptoms such as cough, wheeze, perioral cyanosis, clubbing and asthenia may also be seen in some patients. On physical examination, patients with CPFE usually have inspiratory dry crackles or typical 'velcro sounds' on chest auscultation [4]. All of our patients presented with chronic intermittent cough and progressive shortness of breath and were found to have basal crepitations on auscultation.

Pulmonary function tests

Patients with CPFE have characteristic pulmonary function tests (PFT) that are different from pure emphysema or IPF. PFT reveal relatively normal lung volumes contrasted by a severely reduced diffusion capacity. The preserved lung volumes may be

attributed to the hyperinflation associated with emphysema and the reduced diffusing capacity may be due to composite effect of emphysema and pulmonary fibrosis on the gas exchange [3].

Imaging features of CPFE

Chest Radiographs

Chest radiographs are a standard part of the initial workup of subjects with COPD and IPF. They are inexpensive and readily available with minimal radiation exposure when compared to HRCT. However, chest radiographs are neither sensitivenor specific in diagnosing CPFE due to obvious reasons. The presence of increased lung volume due to emphysema is usually masked by the decrease in lung volume secondary to the concomitant pulmonaryfibrosis resulting in near normal lung volumes [12]. Some features that may provide a clue to the presence of CPFE are increased lucency of upper lung fields along with increasedreticular markings in the lower lobes.

All of our patients had undergone chest radiography and as expected the findings on chest radiographs were subtle and the extent of fibrosis or emphysema could not be assessed on radiographs alone. One case presented with spontaneous pneumothorax large enough to be detected on chest radiograph.

HRCT chest

The role of HRCT in the diagnosis and characterization of both pulmonary emphysema and fibrosis is well established and fairly accurate. It is therefore reasonable to assume that HRCT is equally accurate in establishing the diagnosis of CPFE [12]. Before we discuss the salient imaging features of CPFE on HRCT it is important to briefly review the existing imaging knowledge of various pathologic processes and their classical HRCT appearance.

Emphysema is defined as enlargement of air spaces distal to the terminal bronchioles due to the destruction of their walls. On high-resolution computed tomography (HRCT) emphysema is seen as areas of abnormal low attenuation with paucity of lung vasculature in contrast to the normal surrounding lung parenchyma.

There are three subtypes of emphysema namely centrilobular/centriacinar, panlobular/panacinar and paraseptal. Centriacinar emphysema is seen on HRCT images as focal lucency centered in the middle of the secondary pulmonary lobule, surrounding the centrilobular artery without any definable walls. This type of emphysema is typically seen in cigarette smokers andhas upper lobe predominance. Panacinar emphysemais seen as widespread abnormal low attenuation areas marginated by the interlobular septa and also centered on the centrilobular artery. It however, maintains the polyhedral shape of the secondary pulmonary lobule and predominates in the lower lobes. Paraseptal emphysema involves the distal aspect of the secondary pulmonary lobule and therefore has a subpleural distribution.It has an elongated shape with perceivable thin walls, which generally correspond to the interlobular septa. Paraseptal emphysema predominates in the upper lobe and is identified as a single row of subpleural cysts or bullae. This is incontrast to ‘honeycombing’seen in pulmonary fibrosisin whichthere are more than a single row of subpleural cysts as well as other associated findings of fibrosis like architectural distortion and traction bronchiectasis.

HRCT not only helps to assess the subtypes of emphysemaand its distribution of emphysema as apical, basal or diffuse, it also allows quantitative assessment of the severity of pulmonary emphysema by using various subjective and objective methods [12].

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown etiology, occurring primarily in older adults, characterized by progressive worsening of dyspnea and lung function and associated with a poor prognosis. It is the most common interstitial lung disease with a characteristic histologic pattern of UIP andis typically seen on HRCT as reticulation with honeycombing and/or traction bronchiolectasispredominantly in the lower lobes in subpleural distribution [4].

Smoking induced lung diseases interstitial fibrosis or SRIF is a term used to describe chronic unclassified interstitial fibrosis that can develop in smokers [13]. It is associated with enlarged airspaces of emphysema as well as respiratory bronchiolitis (RB). In addition, the fibrosis affects predominantly the subpleural parenchyma and often has a centrilobular distribution when present in deeper parenchyma [13]. It is essential to differentiate SRIF from other fibrotic interstitial lung diseases especially UIP and NSIP [4].

The classic description of CPFE includes features of centrilobular and/or paraseptal emphysema in the upper lobes and pulmonary fibrosis (mainly IPF/UIP) in the lower lobes [2] [Fig 1] Although most cases of CPFE depict the common fibrotic pattern of UIP, sometimes non-specific interstitial pneumonia (NSIP), smoking-related ILD even other unclassified fibrotic lung diseases are also observed [2] [Fig 2].

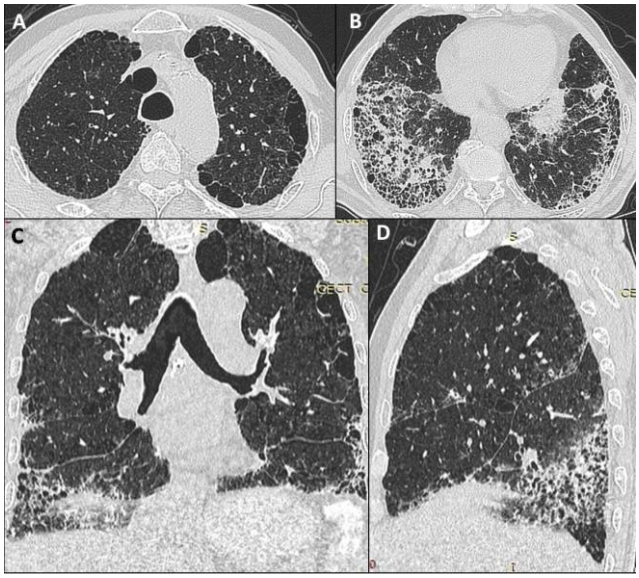

Fig 1 (A-B). Axial, (C) coronal and (D) sagittal CT images in a case of CPFE with paraseptal emphysema in both upper lobes and basal subpleural interstitial fibrosis with honeycombing (UIP pattern) resulting in volume loss of lower lobes – features classical of CPFE

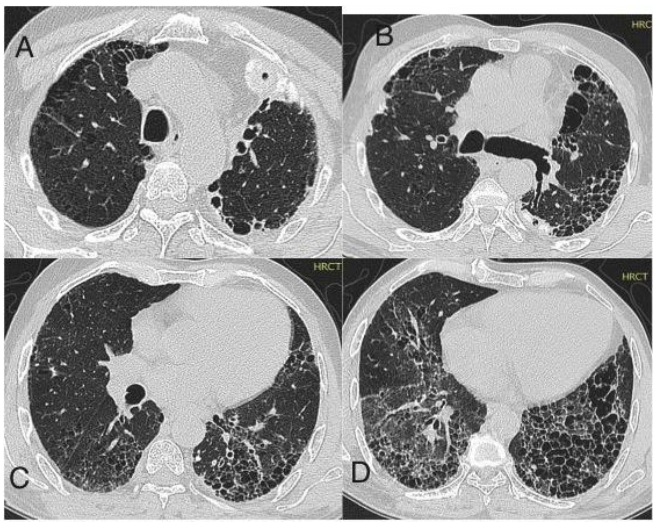

Fig 2 (A-D) Axial HRCT images of a 66 year old chronic smoker with CPFE. Note centrilobular and paraseptal emphysema in upper lobes with interstitial thickening and extensive macrocystic honeycombing and ground glass attenuation in lower lobes.

Cottin *et al* [2] were the first to describethe radiologic criteria for diagnosis of CFPE. According to them, firstly, the presence of emphysema on HRCT, defined as welldemarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a verythin (<1mm) wall or no wall, and/or multiple bullae(>1 cm) with upper zone predominance, and secondly, the presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT, defined as reticular opacitieswith peripheral and basal predominance, honeycombing, architectural distortion, and/or traction bronchiectasis orbronchiolectasis; focal ground-glass opacities and/or areas of alveolar condensation may be associated but should not beprominent.

The distribution of emphysema and fibrosis in patients with CPFE varies from patient to patient. Brillet *et al* [14] identified three HRCT patterns in patients withCFPE: (1) progressive transition with diffuse emphysema (centrilobular and/or bullous) and a zone of transition between bullae and honeycombing; (2) paraseptal emphysema with predominant subpleural bullae of enlarging size at the bases; (3) separate processes with independent areas of fibrosis and emphysema.

Differences also exist in the types of emphysema between CPFE and COAD groups of patients. Emphysema secondary to smoking is typically

centrilobular as seen in patients with COAD. Paraseptal emphysema is much more common in CPFE than in COAD and is considered a typical feature of CPFE [15, 16]. Fibrosis with UIP pattern is the most common feature of CPFE, but sometimes non-specific interstitial pneumonia (NSIP), smoking-related ILD even other unclassifiable fibrotic lung diseases are also observed in this group of patients [4, 17]. The spectrum of findings at HRCT in our cases is illustrated in the figures [Fig 1-4].

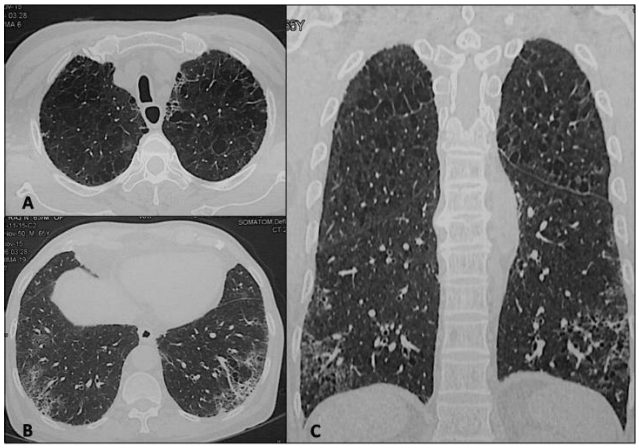

Fig 3. (A&B) Axial HRCT images in a case of CPFE showing extensive centrilobular emphysema in upper lobes with subpleural interstitial fibrosis and early honeycombing in bilateral basal lung parenchyma(C) Coronal CT image depicting the same findings suggestive of CPFE

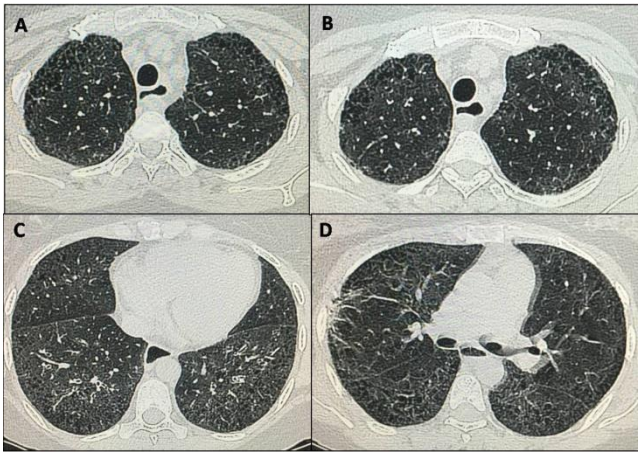

Fig 4 (A&C). Axial CT images showing centrilobular and paraseptal emphysema along with extensive ground glass attenuation and interlobular septal thickening (NSIP pattern) coexisting in a case of scleroderma showing mild progression of fibrosis over two years (B&D). Also note the presence of air filled dilated esophagus

Differentiating emphysema from pulmonary fibrosis may sometimes be complex and difficult on imaging. Thickened walls of emphysematous lesions may be mistaken for honeycombing and vice versa. Also the temporal association of emphysema and fibrosis may vary from patient to patient, with one pathology developing years after the other. Hence patients with suspected CPFE should be followed up on a regular basis [4].

It has also been noted that the proportion of emphysema and fibrosis varies in different patients with CPFE. Therefore it is reasonable to assume that different mechanisms may be involved in the development of clinical phenotypes of CPFE, which might be either "emphysema-dominant"or "fibrosis-dominant" based on the more prominent component [4].

Quantitative assessment of emphysema and fibrosis using 'Emphysema index' and 'Fibrosis score' based on CT calculations has been widely used to assess the severity of individual disease conditions in patients with COAD or ILD. Disease severity grading in CPFE using these quantitative CT methods may prove to be a very useful prognostic tool.CT quantitative methods thus need to be explored and established by larger studies [5].

A unique radiological and pathological entity described in patients with CPFE is the presence of

'Thick-walled cystic lesions (TWCL) [11]. Both radiological and pathological presence of TWCL has been reported in a large number of CPFE patients, but not in any patient with IPF or emphysema alone. Enlargement of these thick walled cystic lesions is probably an indicator of deterioration of interstitial pneumonia [18].

Presence of ground glass attenuation of lung parenchyma is also a common feature of CPFE.This being unique to CPFE and not seen in pure emphysema or IPF cases supports the possible smoking-related etiology of CPFE similar to desquamative interstitial pneumonia [3].

The presence of ground glass densities in the lung parenchyma was a frequent observation in our patients and all of these cases were also smokers [Fig 1-3].

Complications of CPFE

Pulmonary arterial hypertension (PAH)

PAH is associated with a poor prognosis in CPFE. CT of these patients may demonstrate enlarged central pulmonary arteries, right ventricularhypertrophy, right ventricular and right atrial enlargement, dilated bronchial arteries, and a mosaicpattern of lung attenuation due to variable lung perfusion [3]. PAH was observed in 8 of our cases as evidenced by enlarged main pulmonary artery on HRCT images.

Lung cancer

Emphysema and IPF have long been regarded as independent risk factors for development of lung cancer. The incidence of lung cancer is reported as 6.8-10.8% in COAD patients and 4-31.3% in IPF patients [18]. CPFE, which is associated with smoking and has features of both IPF and emphysema definitely has a much higher risk of lung cancer [Fig 5]. The same observation has been reported in many studies with the prevalence of lung cancerbeing as high as (35.8-46.8%) in patients with CPFE [4]. Squamous cell carcinoma has been reported to be the most common histologic type amongst the cancers in CPFE. This may be related to a heavy smoking history in most CPFE patients [19, 20]. One of our patients on follow up developed adenocarcinoma of the lung that was proven by CT guided biopsy.

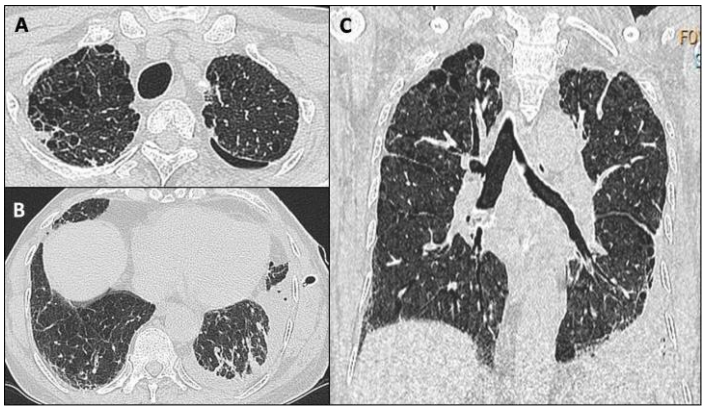

Fig 5. (A-C) Axial and coronal HRCT images showing centrilobular as well as paraseptal emphysema in upper lobes with basal subpleural fibrosis and evidence of hydropneumothorax on the left side

The location of lung cancer is also different in patients with CPFE, IPF and emphysema.Lung cancer of CPFE and IPF group has been reported to predominantly locate in the subpleural area while that of emphysema group occurs usually in the upper lung [19, 20]. Patients with CPFE and lung cancer have a much poorer prognosis than those with emphysema or IPF alone [18].

Spontaneous pneumothorax

Although not reported as a specific complication of CPFE, spontaneous pneumothorax may be seen in these patients as a complication of underlying paraseptal emphysema or subpleural honeycombing. One of our cases with CPFE presented with spontaneous pneumothorax that required tube drainage [Fig 6].

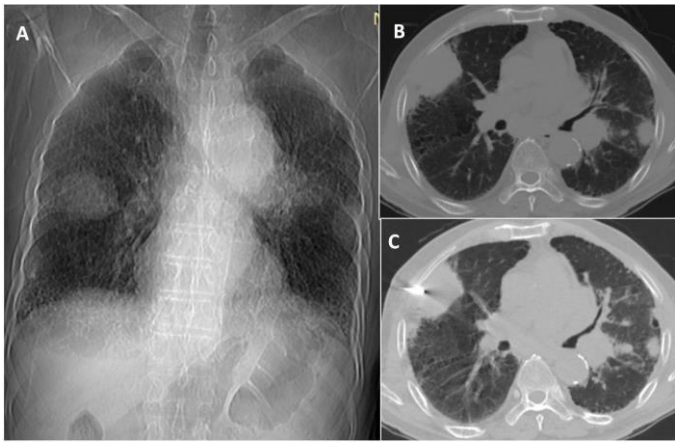

Fig 6 (A).Scanogram and (B) axial CT chest image in a case of CPFE showing a large peripheral mass lesion in the right lung with multiple nodular lesions in the left lung parenchyma. (C) CT guided biopsy from the right lung mass confirmed the presence of adenocarcinoma

Acute lung injury

CPFE may increase the risk of acute lung injury following surgical lung resection or chemotherapy. Therefore, it is important to assess the cardiopulmonary function in these patients thoroughly by clinico-radiological examination in order to evaluate the surgical tolerance, chemotherapy and radiation related complications in this special group of patients [3, 4].

Management and prognosis of CPFE

This subgroup of patients is difficult to treat as they show a suboptimal response to medical therapy.Treatment of CPFE is based on systemic corticosteroids, inhaled bronchodilators, immunomodulator drugs and oxygen therapy for hypoxemia [3]. Overall, the CPFE syndrome has a poor prognosis with a 5-year survival of 35-80% [2, 15]. The median survival of CPFE patients reportedin various studies ranges from 2.1 to 8.5 years [4]. The major causes of death in CPFE are chronic respiratory failure, acute exacerbation, PAH and lung cancer [3].

CONCLUSION

Combined pulmonary fibrosis and emphysema is an important yet under-diagnosedsyndrome that has unique clinical and radiologic findings. In this study, we have shared our observations and experience in cases of CPFE highlighting the various imaging findings of this entity as seen on HRCT scans.Since imaging playsan important role in the diagnosis and management of this condition, it is important for radiologists to be familiar with the existence and appearance of this syndrome.This will facilitate early and accurate diagnosis and in turn contribute to better patient management.

REFERENCES

1. Portillo K, Morera J; Combined pulmonary fibrosis and emphysema syndrome: a new phenotype within the spectrum of smoking-related interstitial lung disease. Pulmonary medicine, 2012; 2012.
2. Cottin V, Nunes H, Brillet PY; Combined pulmonary fibrosis and emphysema: a distinct underrecognized entity.Eur Respir J., 2005; 26:586-93.
3. Matthew D; Jankowich, Sharon I. S. Rounds. Combined pulmonary fibrosis and emphysema syndrome: A review. Chest, 2012; 141: 222-31.
4. Lin H, Jiang S; Combined pulmonary fibrosis and emphysema (CPFE): an entity different from emphysema or pulmonary fibrosis alone. Journal of thoracic disease, 2015; 7(4):767-79.
5. Choi SH, Lee HY, Lee KS, Chung MP, Kwon OJ, Han J, Kim N, Seo JB; The value of CT for disease detection and prognosis determination in combined pulmonary fibrosis and emphysema (CPFE). PloS one, 2014; 9(9):e107476.
6. Papiris SA, Triantafillidou C, Manali ED, Kolilekas L, Baou K, Kagouridis K, Bouros D; Combined pulmonary fibrosis and emphysema. Expert review of respiratory medicine, 2014; 9.
7. Ye Q, Huang K, Ding Y, Lou B, Hou Z, Dai H, Wang C; Cigarette smoking contributes to idiopathic pulmonary fibrosis associated with emphysema. Chinese medical journal, 2013; 127(3):469-74.
8. Ryerson CJ, Hartman T, Elicker BM, Ley B, Lee JS, Abbritti M; Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest, 2013; 44: 234-40.
9. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T; Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med., 2011; 364: 897-906.
10. Cottin V, Reix P, Khouatra C, Thivolet-Béjui F, Feldmann D, Cordier JF; Combined pulmonary fibrosis and emphysema syndrome associated with

familial SFTPC mutation. Thorax, 2011; 66: 918-19.
11. Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, Revel D, Valeyre D, Cordier JF; Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis & Rheumatism, 2011; 63(1):295-304.
12. Oliva IB, Cortopassi F, Rochester CL, Rubinowitz AN; Combined pulmonary fibrosis and emphysema syndrome: a radiological perspective. Monaldi Arch Chest Dis., 2011; 75: 220-34.
13. Katzenstein AL; Smoking related interstitial fibrosis (SRIF): pathologic findings and distinction from other chronic fibrosing lung diseases. Postgrad Med J., 2014; 90:597-602.
14. Brillet PY, Cottin V, Letoumelin P, Landino F, Brauner MW, Valeyre D, Cordier JF, Nunes H; Combined apical emphysema and basal fibrosis syndrome [emphysema/fibrosis syndrome]: CT imaging features and pulmonary function tests [in French]. Clinical Imaging, 2009; 33(4):332.
15. Cottin V; The impact of emphysema in pulmonary fibrosis. Eur Respir Rev., 2013; 22:153-7.
16. Kitaguchi Y, Fujimoto K, Hanaoka M, Kawakami S, Honda T, Kubo K; clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology, 2010; 15: 265-71.
17. Jankowich MD, Polsky M, Klein M, Rounds S; Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration, 2008; 75: 411-17.
18. Inomata M, Ikushima S, Awano N, Kondoh K, Satake K, Masuo M, Kusunoki Y, Moriya A, Kamiya H, Ando T, Yanagawa N; An autopsy study of combined pulmonary fibrosis and emphysema: correlations among clinical, radiological, and pathological features. BMC pulmonary medicine, 2014; 14(1):1.
19. Kwak N, Park CM, Lee J, Park YS, Lee SM, Yim JJ, Yoo CG, Kim YW, Han SK, Lee CH; Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. Respiratory medicine, 2014; 108(3):524-30.
20. Usui K, Tanai C, Tanaka Y, Noda H, Ishihara T; The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology, 2011; 16: 326-31.