Combined pulmonary fibrosis and emphysema: a commonly missed diagnosis

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Hong Kong Med J 2022;28:85.e1-3
https://doi.org/10.12809/hkmj219418

In September 2019, a 79-year-old man was referred to the medical out-patient clinic for assessment of chronic cough and exertional shortness of breath. He was an ex-smoker for more than 10 years and previously worked as a bird market hawker. He stopped working 6 months previously because of coughing. He had no history of chemical or occupational dust exposure and took no drugs associated with pulmonary fibrosis. He had a known history of previous pulmonary tuberculosis. The patient had no history of fever, rash, polyarthralgia or uveitis. He had no family history of autoimmune disease. Physical examination revealed no rash or joint pain and no ulcers. He had full proximal and distal muscle power and no features of autoimmune disorder.

Immunological tests revealed rheumatoid factor, <15.9 IU/mL (normal range <15.9IU/mL); anti-proteinase 3, 5.5 RU/mL (normal range <20 RU/mL); and anti-myeloperoxidase, 3.7 RU/mL (normal range <20 RU/mL). Immunological tests were positive for anti-neutrophil cytoplasmic antibodies, but negative for anti-nuclear antibodies, anti-ds DNA, and anti-extractable nuclear antigen. Echocardiogram was not performed.

Lung function testing performed in September 2019 revealed a forced expiratory volume in 1 second (FEV1) of 2.23 L (98% predicted), forced vital capacity (FVC) 3.01 L (95% predicted) and FEV1/FVC ratio 74.1% (above predicted). Results of lung function tests suggested that the shortness of breath was likely due to a combination of restrictive and obstructive lung defects (the former plays a dominant role). The patient subsequently underwent chest radiography and computed tomographic (CT) imaging.

Chest radiograph in 2020 (Fig 1a) showed coarsened bilateral lower lobe interstitial markings, raising a concern for a superimposed parenchyma process, such as pulmonary oedema or other chronic process such as fibrosis. Reviewing patient's previous chest radiograph in 2009 (Fig 1b), there was no bilateral lower lobe interstitial markings. This demonstrated that bilateral lower lobe interstitial markings in the 2020 chest radiograph were recent onset.

Computed tomography thorax (Fig 2) in 2020 showed centrilobular and paraseptal emphysematous change at bilateral upper zones. There was septal thickening with reticulations, honeycomb formation and mild traction bronchiectasis at basal regions. On the basis of these findings, a radiological diagnosis of pulmonary fibrosis with emphysema was made.

Pulmonary function testing on 17 January 2020 revealed severely diminished diffusing capacity for carbon monoxide (DLCO) of 35% (predicted: 19.1 mL/mmHg/min, best: 6.6 mL/mmHg/min) and carbon monoxide diffusion coefficient of 41% (predicted: 4.29 mL/mHg/min/L, best: 1.74 mL/mHg/min/L). Results of testing demonstrated no airflow obstruction or significant post-bronchodilator response. The patient's DLCO and carbon monoxide diffusion coefficient were low, indicating impaired diffusion due to underlying pulmonary fibrosis. Based on his DLCO <80% predicted and FEV1 >80% predicted, cardiopulmonary exercise testing was proposed to determine any need for lung resection.

Radiological and clinical significance of combined pulmonary fibrosis and emphysema

Characteristic radiological findings of combined pulmonary fibrosis and emphysema (CPFE) syndrome include upper-lobe emphysema and lower-lobe interstitial fibrotic changes. The emphysema in CPFE includes bullous, paraseptal, and centrilobular changes and is typically distributed in the upper lobes. Fibrotic changes are not typical in emphysema and should prompt further aetiological investigation. Honeycombing refers to CT-detected clustered thick-wall cystic air spaces (3 to 10 mm in diameter, but occasionally as large as 25 mm) that are usually subpleural, peripheral and basal in distribution. Honeycombing indicates interstitial fibrosis. In our patient, bilateral basal honeycombing on CT confirmed end-stage fibrosis as the cause of increased interstitial markings seen on chest radiography.

The coexistence of pulmonary fibrosis and emphysema was first noted in 1990 but was not considered a distinct entity until further characterisation 15 years later. There has been increasing recognition that these two processes may coexist in some patients, and this overlapping disorder has often been termed combined emphysema and fibrosis or CPFE. In general, patients with CPFE have preserved FEV1 and FVC, but the

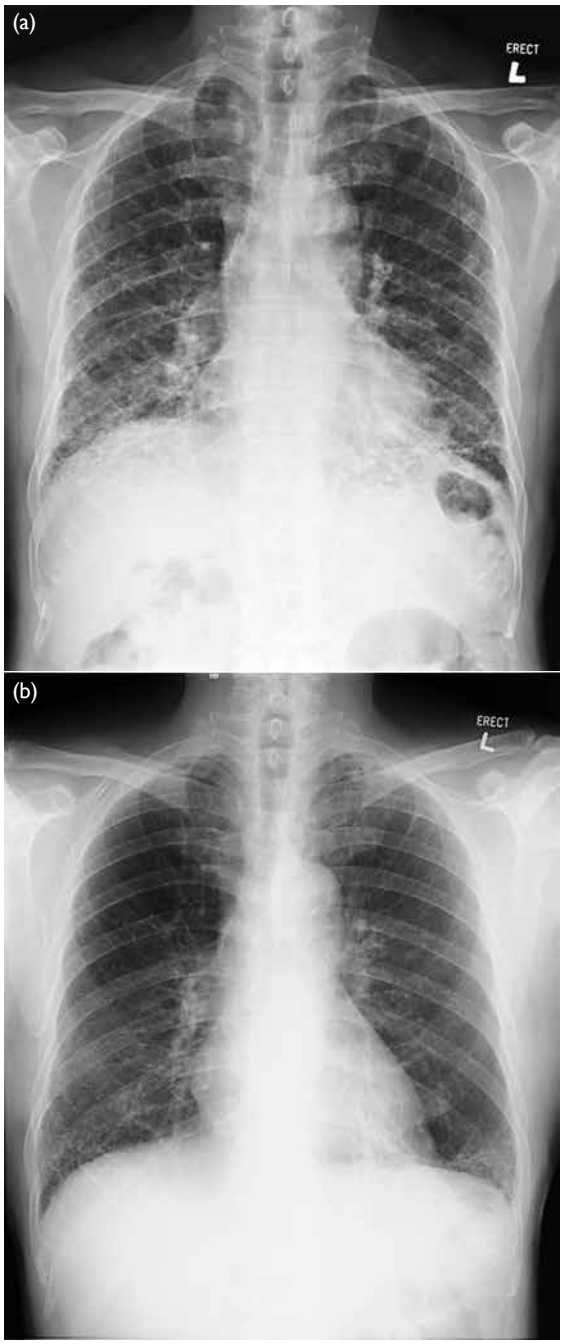

FIG 1. (a) Chest radiograph 2020. Chest radiograph in 2020 showing decreased upper lung markings, typical of the architectural destruction caused by emphysema. There are coarsened bilateral lower lobe interstitial markings. This raises a concern for a superimposed parenchyma process, such as pulmonary oedema or other chronic process such as fibrosis. The patient subsequently underwent high-resolution computed tomography thorax to determine the cause of increased basal interstitial markings. (b) Chest radiograph 2009. Previous chest radiograph in 2009 of the same patient showing preserved lung volume and no bilateral lower lobe interstitial markings. There is mild left apical fibrosis, possibly due to previous tuberculosis. This demonstrated that bilateral lower lobe interstitial markings in the 2020 chest radiograph were of recent onset

diffusion capacity of the lung for carbon monoxide is severely diminished.[1]

Typically, CPFE is more common in men, current or former smokers.[2] Some classic features of CPFE include the following:

- More rapid lung function decline than in patients with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF) alone. In CPFE, due to coexisting fibrosis and emphysema, the restrictive component (fibrosis) can counterbalance the obstructive component (emphysema), resulting in a near normal FEV1/FVC ratio. Nonetheless an isolated severe impaired DLCO on pulmonary function testing offers an important clue to a diagnosis of CPFE.[2]
- Increased risk of primary lung malignancy. Lung cancer significantly affects prognosis as lung function may not support surgery or chemotherapy.[3]
- In a retrospective study of 61 patients with CPFE, about half of all patients (47%) had concomitant pulmonary hypertension, with a poor prognosis. Survival was 87.5% after 2 years and 54.6% after 5 years. Median survival was 6.1 years.[4]
- A complication of CPFE is acute exacerbation (AE-CPFE) that can be attributed to the emphysematous component (AE-CPFE, COPD type) or fibrotic component of CPFE (AE-CPFE, IPF-type) Treatment depends on the predominant underlying type of exacerbation. The prognosis is worse with the above complications.

Management of combined pulmonary fibrosis and emphysema

The mainstay of treatment for patients with CPFE is supportive care. Smoking cessation is definitely indicated for both components of CPFE. Supplemental oxygen therapy may be beneficial, also COPD treatments such as bronchodilators and inhaled steroids. Case reports of patients with CPFE reveal that lung volume reduction (LVR) may be beneficial in cases of advanced emphysema, even without plethysmographic evidence of severe hyperinflation.[5] Treatment with antifibrotic drugs, such as pirfenidone and nintedanib, may be effective in CPFE but further trials are awaited.[2] There is evidence that nintedanib can decrease the annual rate of decline in FVC in patients with other (non-usual interstitial pneumonia-like) fibrotic patterns as well as those with IPF. Currently, to the best of our knowledge these are not yet available for CPFE.2 Further investigation is needed into future use of antifibrotic drugs for CPFE. Ultimately, lung transplantation is the only cure.

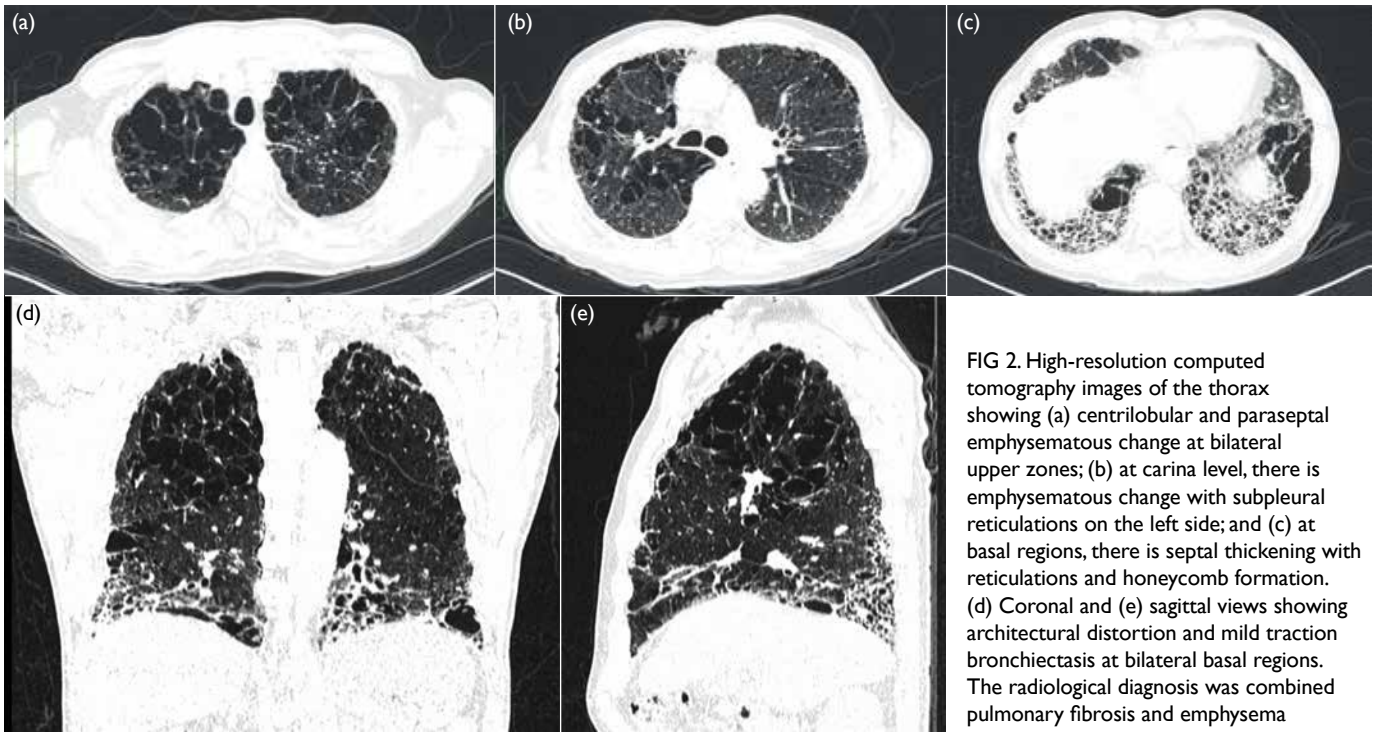

FIG 2. High-resolution computed tomography images of the thorax showing (a) centrilobular and paraseptal emphysematous change at bilateral upper zones; (b) at carina level, there is emphysematous change with subpleural reticulations on the left side; and (c) at basal regions, there is septal thickening with reticulations and honeycomb formation. (d) Coronal and (e) sagittal views showing architectural distortion and mild traction bronchiectasis at bilateral basal regions. The radiological diagnosis was combined pulmonary fibrosis and emphysema

Author contributions

All authors contributed to the concept, acquisition and interpretation of data, drafting of the manuscript, and revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors declare no conflicts of interest related to the work in this manuscript.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures, and verbal consent for the publication of this study.

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