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Combined pulmonary fibrosis and emphysema: case report and literature review

Abstract

We describe the case of a 61-year-old male patient, in which the search for the cause of chronic respiratory failure, severe pulmonary hypertension and secondary erythrocytosis resulted in a diagnosis of combined pulmonary fibrosis and emphysema (CPFE). This is a unique, recently characterised syndrome with upper-lobe emphysema and pulmonary fibrosis of the lower lungs. The cause is unknown, but one of the main risk factor remains smoking. The patient was a heavy smoker (over 40 pack-years). He complained of dyspnoea on exertion and cough. Physical examination revealed basal crackles and cyanosis. The patient had severe reduction in diffusing capacity, out of proportion to his lung volumes (DLCO 27% of predicted value, FEV1 2.95 l (100%), FVC 4.41 l (118%), FEV1/FVC (66%). The blood gas showed hypoxemia (pO₂ 37 mm Hg), hypocapnia and respiratory alkalosis. Diagnosis was based on chest computer tomography, which revealed upper lobe emphysema and lower lobe ground glass changes and honeycombing. Severe pulmonary hypertension (SPAP 80 mm Hg) was confirmed by echocardiography and right cardiac catheterisation. The patient received long-term oxygen therapy, inhaled corticosteroid and Ca-blocker.

Key words: combined pulmonary fibrosis and emphysema, pulmonary hypertension, chronic respiratory failure

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Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a seldom described disease. Until the last decade of the twentieth century, the possibility of a combination of pulmonary fibrosis and emphysema was thought to be only accidental coexistence [1, 2]. Only in the last few years has CPFE been treated as a distinct disease. The sources of information about it are mainly case reports [3–6].

In 2005 Cottin et al. [5] published retrospective analysis of cases in which the clinical presentation of CPFE has been described. Since then, the name CPFE has been used.

The syndrome consists of emphysema of the upper zones and fibrosis of the lower zones in chest

computer tomography, severe hypoxemia with slightly reduced lung volumes, often accompanied by pulmonary hypertension and a poor prognosis [5, 6].

Most sufferers from CPFE are men aged about 65. (Cottin et al. described 61 patients, only one of whom is female) [5]. Patients are usually heavy smokers, very often with more than 40 pack-years smoking history [6].

Patients complain mainly of dyspnea and cough. Physical examination reveals basal crackles (in 87% of cases) and wheezing (13% of cases). In some cases finger clubbing was found (43%) [5].

Pulmonary function tests are usually normal; or mild obstruction or restriction is observed. Very typical of this disease is a severe decrease in diffusion capacity with normal or mild reduced lung vo-

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lumes. Blood gases often reveal hypoxemic respiratory failure [3–6].

When the diagnosis is made, 47% of patients have been found to have pulmonary hypertension, but the incidence of pulmonary hypertension increases during the development of the disease [3, 5, 6].

The diagnosis first of all is based on the radiological findings in computed tomography, which show the coexistence of emphysema of the upper zones and fibrosis of the lower zones including ground glass opacities, honeycombing and traction bronchiectases [3–6].

We describe below the case, in which looking for the reasons for chronic hypoxemia, secondary erythrocytosis and pulmonary hypertension has led to the identification of CPFE.

Case report

The 61-year-old male patient, a car mechanic and former smoker (40 pack-years, he stopped smoking six years previously) complained of dyspnea on exertion. The dyspnea was first noticed five years ago, but increased significantly in the last six months before hospitalisation in the Department of Pulmonology and Lung Cancer of the Medical University in Wrocław. Moreover he complained of a productive cough and has hypertension and gout.

The patient has been hospitalised more than once in his home city, where polycythemia (Hb 20.4 g/dl), hypoxemic respiratory failure (saturation 75–81%) and pulmonary hypertension have been recognised. He had three bloodlettings. In trepanobiopsy, hematological changes have not been revealed and serum erythropoietin level has been normal (25.1 mU/ml). There was a suspicion of pulmonary embolism, but based on angio-CT, doppler ultrasonography and D-dimer levels, this suspicion has been excluded.

Because of snoring, obesity, chronic hypoxemia, secondary erythrocytemia and pulmonary hypertension, the symptoms which could suggest sleep apnoea syndrome, the patient was referred to the Department of Pulmonology and Lung Cancer of the Medical University in Wrocław to perform polysomnography.

The patient was in median-worse condition. He was obese (BMI 34), auscultation of the lungs revealed bilateral basal crackles. Moreover, he had central cyanosis and varicose veins of the legs. The patient had mild daytime sleepiness (4 points in Epworth scale). In polysomnography we did not find respiratory disorders (RDI = 0/hour). We observed still decreased oxygen saturation of 80% both in the night and during the day. Blood gas examination revealed significant hypoxemia (pO₂



Figure 1. Chest X-ray — description in text

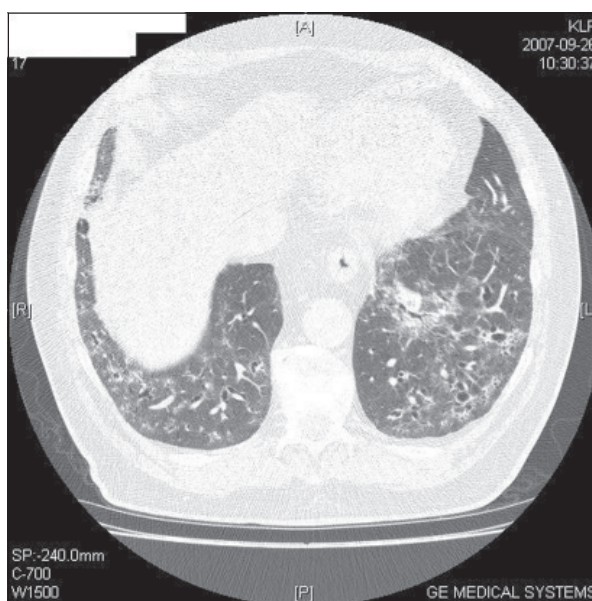


Figure 2. Chest computer tomography ground glass opacities and a little honeycombing in lower lobes

37.4 mm Hg) with hypocapnia (pCO₂ 30.9 mm Hg) and respiratory alkalosis (pH 7.46). During oxygen supplementation in the department we observed the increase of pO₂ to 51–55 mm Hg and the normalisation of other blood gas parameters. Pulmonary function tests revealed mild obstruction FEV₁/FVC 66%, FEV₁ 2.95 l (100% of predicted value), FVC 4.41 l (118% of predicted value) with negative bronchodilatory test (FEV₁ increase of 6%). We found severe reduction in diffusing capacity for carbon monoxide (2.36 mmol/min/kPa — 27% of predicted value).

A chest X-ray revealed infiltrative opacities of lower and median parts of lungs (Fig. 1)

Computed tomography showed in lower lobes ground glass opacities with traction bron-

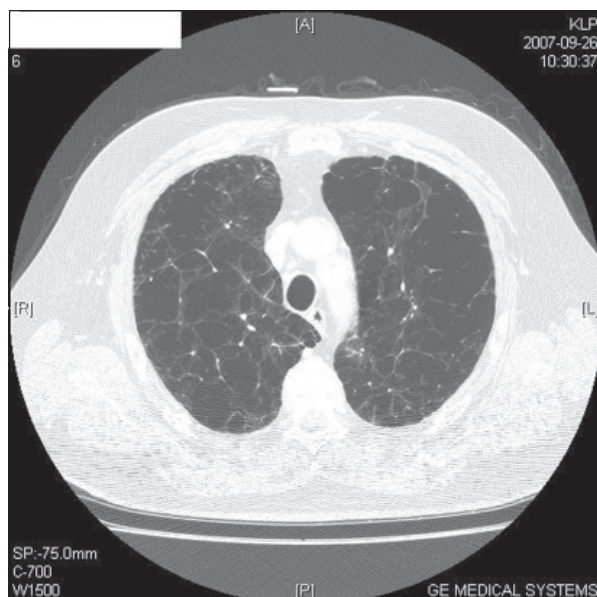


Figure 3. Chest computer tomography upper lobe emphysema

chiectases and small honeycombing areas (Fig. 2). In upper zones of the lungs, we observed giant bullous emphysema (Fig. 3). Echokardiography confirmed severe pulmonary hypertension (SPAP 80 mm Hg).

We tried to perform bronchofiberoscopy, but during the beginning of the examination we observed severe desaturations and for that reason the procedure was abandoned. In sputum we did not observe carcinomatous cells. We found in sputum bacteria and the patient received antibiotics. The pANCA and cANCA were not present as well as rheumatoid factor (RF) and anti-HIV antibodies.

Based on clinical presentation and radiological findings we recognised this was a case of combined pulmonary fibrosis and emphysema (CPFE). We decided on inhaled steroid therapy.

The patient was referred to the cardiological department, where the electrocardiography confirmed again severe pulmonary hypertension (systolic pressure in pulmonary artery Bernoulli 77 mm Hg) and revealed the dilatation of the right heart cavities with volume overload of the right ventricle and severe insufficient tricuspid valve. Hemodynamic tests and vasodilatation test were performed. They showed median pressure in pulmonary artery of 52 mm Hg and positive vasodilatation test — median pressure in pulmonary artery decreased to 40 mm Hg and cardiac output increased. Based on these findings, and remembering that the patient was in NYHA II, the cardiologists decided on Ca-blocker treatment in increasing doses.

Discussion

CPFE is a little-known disease. In Polish literature we did not find the description of a case report of it. Some of the researchers, including initially the authors of this case report, doubted whether CPFE is really a new and distinct disease or rather whether it is an accidental coexistence of a few clinical features. But all the presented case reports and research in larger groups of patients indicate many typical features of this disease [1–6].

Computed tomography of the chest is the most important part of CPFE diagnosis, but we have to realise that the interpretation of radiological findings can be very difficult. Cottin et al. decided to show the same CT to two independent experts, who did not know of the clinical presentations of the patients [5].

In the differential diagnosis we have to consider many interstitial diseases, in which the emphysema as well as fibrosis occur.

First to be considered is idiopathic pulmonary fibrosis (IPF), which is the clinical presentation of usual interstitial pneumonia (UIP). Some researchers even suggest that CPFE should be treated as a form of UIP [7]. In IPF there are marked changes to the basal parts of the lungs. Intralobular and intraalveolar septal thickening have been observed, which create a picture of reticular changes. Sometimes the ground glass opacities could be revealed, but they never dominate in IPF. Many authors think that the ground glass opacities indicate the active process, which is potentially reversible by the treatment [8, 9].

During the development of the disease more honeycombing and traction bronchiectases have been described. Very typical is decrease of lung volumes and high position of the diaphragm. Sometimes, along with with reticular changes and honeycombing occur giant cysts and emphysematous bullae. In these cases, lung volume can be normal or even increased [9].

In stage IV of sarcoidosis, the stage of advanced fibrosis, the honeycombing and traction bronchiectases have been observed. The zones of lungs not affected by fibrosis can be hyperinflated and the giant emphysematous bullae have been often recognised, but in sarcoidosis radiological changes localise mainly in the upper and median zones of the lungs [9].

Most cases describe ground glass opacities in lower zones, with only small honeycombing areas. Other authors describe in lower zones ground glass opacities as well as honeycombing and traction bronchiectases, with all these changes usually happening at the same time [3–6]. Cottin et al.

described honeycombing in 95% of patients, ground glass opacities in 66%, and reticular changes in 87%. These authors indicated that ground glass opacities were much more frequent in CPFE than in IPF [6]. Jankowich et al. in two patients (from 10 described) observed only ground glass opacities in lower zones of the lungs [4].

To the diseases with predominance of ground glass opacities in CT belong extrinsic allergic alveolitis, lipoproteinosis, acute interstitial pneumonia, desquamative interstitial pneumonia, hemosiderosis and alveolar haemorrhages. Especially difficult is differential diagnosis with extrinsic allergic alveolitis, because emphysema has been described in this disease in about 50% of cases [9].

Moreover, the correct identification of CPFE can be more complicated, because the typical radiological changes (emphysema and fibrosis) do not appear in the same time. Cottin et al. described only in 50% of cases the occurrence of emphysema and fibrosis at the same time, but in 25% of cases emphysema appeared five years before the fibrosis. Much rarer is the other sequence of radiological changes [5].

The time from the first symptoms to diagnosis is usually long, (median two to three years), but in some cases it has been as long as 19 years [5].

Because of the condition of the patient, in the described case we did not perform the bronchoscopy, did not make histopathological examination and did not decide for open lung biopsy. In cases known from the literature the UIP has been the most commonly described histopathological type, but DIP (desquamative interstitial pneumonia) or OP (organising pneumonia) have been observed too [4–6].

Pulmonary hypertension (PH) is one of the leading symptoms of CPFE and at the same time an unfavourable prognostic factor in this disease [3, 5, 6].

The problem of PH is very well known in interstitial lung diseases [10, 11]. PH has been recognised in 25% of patients with advanced lung diseases and in 28% of patients with advanced sarcoidosis. According to the actual classification from III World Symposium on Pulmonary Arterial Hypertension in 2003 in Venice, PH in interstitial lung diseases belongs in most cases to the group 3.2, only in sarcoidosis and other rare diseases (such as histiocytosis or lymphangiomyomatosis) does PH belong to group 5 [10]. In CPFE, pulmonary hypertension occurs in almost half of patients, a larger percentage than in IPF or in chronic obstructive pulmonary disease [5].

The observations of PH made in IPF are similar to those in CPFE. In both diseases, it has been shown that PH occurs in patients with severe re-

duction in diffusing capacity (DLCO) and in patients who need oxygen supplementation [5, 11]. In IPF, PH appears twice as frequently in patients with DLCO < 30% (in 56.4% cases) but only in 28.6% of patients with DLCO > 30%. Nathan et al. revealed the very interesting correlation that PH occurs more often in patients with FVC > 70% than in patients with FVC < 40% (trend) [12]. In most interstitial diseases, as well as in CPFE, PH is an unfavourable prognostic factor [10, 11]. In IPF, 5-years survival is 62.2% in patients without PH, and 16.7% with PH [13]. Moreover in scleroderma it has been shown that there is a correlation between PH and age, with every decade of life increasing the risk of PH [14].

Pulmonary hypertension can also appear in sleep apnoea syndrome, especially if the patient also has COPD [15]. Moreover, secondary polycythemia can also be a symptom of sleep apnoea syndrome. In these cases a lot of apneas with severe desaturation have been observed during sleep. Chronic alveolar hypoventilation has been observed even during the day [16]. So in the described case, the coexistence of obesity, pulmonary hypertension, secondary polycythemia and snoring explained the suspicion of sleep apnoea syndrome.

Recognising CPFE can be more complicated, because in some patients immunological abnormalities have been revealed which could suggest another disease. Moreover, the true incidence of these immunological abnormalities is unknown. Antinuclear antibodies were present in 17 out of 44 patients tested (39%), circulating immune complexes were found in six out of 20 patients tested, and antineutrophil antibodies in four out of 35 patients tested [5]. In the described case we did not find any immunological abnormalities.

The causal treatment is not known. Following experiences in steroidal treatment of IPF, some authors have tried to use inhaled as well oral steroids in CPFE therapy. Cottin et al. described oral prednisone treatment 0.5 mg/kg per day in 30 patients (50%). In this group 13 patients also received another immunosuppressant, and 14 patients used inhaled steroids. Improvement after treatment was found in only five of the patients. 49% of the patients received long-term oxygen therapy. In a few cases, lung transplantation has been performed [3, 5].

The prognosis in CPFE remains unfavourable, with median survival from diagnosis little more than three years.

The reasons for and pathogenesis of CPFE are unclear. All authors agree on a correlation between CPFE and smoking [3, 4, 5, 17]. Some researchers suggest that environmental exposure,

especially to agrochemical compounds combined with smoking, could lead to development of CPFE [17]. However, experimental research on animals has provided interesting information about the potential pathogenesis of this disease. Lundblad et al. revealed that in transgenic mo-uses with TNF- α (tumor necrosis factor) overexpression developed in lung fibrosis and emphysema at the same time [18], which suggests that TNF- α could play an important role in CPFE's pathomechanism.

The aim of this work was to draw attention to the coexistence of pulmonary fibrosis and emphysema as potential reasons for chronic respiratory failure, pulmonary hypertension and secondary polycythemia, and to show the problems associated with CPFE diagnosis and treatment.

References

1. Wiggins J., Strickland B., Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. *Respir. Med.* 1990; 84: 365–369.
2. Lim T.K. Respiratory failure from combined emphysema and pulmonary fibrosis. *Singapore Med. J.* 1993; 34: 169–171.
3. Grubstein A., Bendayan D., Schactman I., Cohen M., Shitrit D., Kramer M.R. 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: 948–954.
4. Jankowich M.D., Polsky M., Klein M., Rounds S. Heterogeneity in combined pulmonary fibrosis and emphysema. *Respiration* 2008; 75: 411–417.
5. Cottin V., Nunes H., Brillet P.-Y. et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur. Respir. J.* 2005; 26: 586–593.
6. Cottin V., Brillet P.Y., Nunes H. et al. Combined pulmonary fibrosis and emphysema. *Presse Med.* 2007; 36: 936–944.
7. Rogliani P., Mura M., Mattia P. et al. HRCT and histopathological evaluation of fibrosis and tissue destruction in IPF associated with pulmonary emphysema. *Respir. Med.* 2008; 22 [epub ahead of print].
8. Wesołowski S., Oniszh K., Kuś J. Znaczenie kliniczne typu zmian w obrazie tomografii komputerowej wysokiej rozdzielczości u chorych na samoistne włóknienie płuc. *Pneumonol. Alergol. Pol.* 2000; 68: 434–440.
9. Bestry I., Oniszh K., Pawlicka L., Dobkowski P. Rola metod obrazowych w diagnostyce śródmiąższowych chorób płuc. W: Rowińska-Zakrzewska E., Wiatr E., Pirożyński M. (eds). *Choroby śródmiąższowe płuc. α -medica press* 2001; 24–67.
10. Lewczuk J. Nadciśnienie płucne w śródmiąższowych chorobach płuc. *Pneumonol. Alergol. Pol.* 2007; 75: 153–157.
11. Lettieri C.J., Nathan S.D., Barnett S.D., Ahmad S., Shorr A.F. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006; 129: 746–752.
12. Nathan S.D., Shlobin O.A., Ahmad S., Urbanek S., Barnett S.D. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 657–663.
13. Hamada K., Nagai S., Tanaka S. et al. Significance of pulmonary arterial pressure and diffusion capacity of the lungs as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; 131: 650–656.
14. Schachna L., Wigley F.M., Chang B., White B., Wise R.A., Gelber A.C. Age and risk of pulmonary arterial hypertension in scleroderma. *Chest* 2003; 124: 2098–2104.
15. Weizenblum E., Chaouat A., Kessler R., Canuet M. Overlap syndrome: obstructive sleep apnea syndrome in patients with chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2008; 15: 237–241.
16. Brzecka A. Przyczyny wtórnej erytrocytozy u chorych z zespołem obturacyjnego bezdechu śródsewnego. *Adv. Clin. Exp. Med.* 2001; 10: 133–138.
17. Daniil Z., Koutsokera A., Gourgoulianis K. Combined pulmonary fibrosis and emphysema in patients exposed to agrochemical compounds. *Eur. Respir. J.* 2006; 27: 434.
18. Lundblad L.K., Thompson-Figueroa J., Leclair T. et al. Tumor necrosis factor-alpha overexpression in lung disease: a single cause behind a complex phenotype. *Am. J. Respir. Crit. Care Med.* 2005; 171: 1363–1370.