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Original Article

Clinical features and prognosis differences of advanced pulmonary fibrosis and combined advanced pulmonary fibrosis and emphysema syndrome in the elderly

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Abstract: Objective: To investigate clinical features and prognosis differences of advanced pulmonary fibrosis (PF) and combined advanced pulmonary fibrosis and emphysema syndrome in the elderly. Methods: The clinical data of 80 cases of elderly patients with advanced pulmonary fibrosis admitted to our hospital from January 2009 to January 2015 were retrospectively analyzed. According to the condition of whether combined with emphysema syndrome, the patients were divided into combined pulmonary fibrosis and emphysema (CPFE) group (n=57) and PF group (n=23). Analysis of blood gas, pulmonary function examination, VEGF, TGF-β1 level, survival time and high-resolution CT scanning results of the two groups were statistically analyzed. Results: Compared with PF group, CPFR group has lower SaO2 (P=0.027), higher PA-aDO2 (P=0.003), higher FVC and TLC (P=0.003, P=0.014), lower FEV1/FVC (P=0.031), lower VEGF and TGF-β1 levels (P=0.013, P=0.009) as well as significantly shorter survival time (P=0.041) and lower incidence of reticular pattern (P=0.023). Conclusion: The clinical features of advanced pulmonary fibrosis are significantly different from those of combined advanced pulmonary fibrosis and emphysema syndrome in elderly patients. And the prognosis of the former is better than that of the latter.

Keywords: Elderly patients, pulmonary fibrosis, combined pulmonary fibrosis and emphysema syndrome, advanced stage, clinical features, prognosis

Introduction

Pulmonary fibrosis is a proliferation of pulmonary fibroblasts and large collections of extracellular matrix, accompanied with inflammatory injury and destruction of tissue structure [1]. Emphysema is an abnormality and a persistent cavity enlargement of the distal to the terminal bronchiole as well as a destruction of the alveolar wall with unapparent fibrosis [2]. In terms of pathological characteristics, the two diseases are very different. But as early as in 1985, there were clinical cases of patients with emphysema showed pulmonary fibrosis [3]. With the continuous development of the studies, pulmonary fibrosis combined with emphysema is regarded as an independent disease, named as combined pulmonary fibrosis and emphysema (CPFE) [4-6]. To improve the differential diagnosis and targeted treatment of CPFE, this study retrospectively analyzed the clinical data of 80 cases of elderly patients with advanced pulmonary fibrosis admitted to our hospital from January 2009 to January 2015. The clinical features and prognosis differences between elderly patients with advanced pulmonary fibrosis and with combined advanced pulmonary fibrosis and emphysema syndrome were compared and reported as follows.

Materials and methods

General information

The clinical data of 80 cases of elderly patients with advanced pulmonary fibrosis admitted to our hospital from January 2009 to January 2015 were retrospectively analyzed. Informed consents were signed by all patients and their families. This study was approved by the Ethics Committee of our hospital.

Inclusion criteria: All patients met the diagnostic criteria of elderly pulmonary fibrosis in the

Table 1. Comparison of the general data of the two groups

Group	Case	Gender		Age (year)	Course of disease (year)	Smoking history (year)	Mean follow-up period (month)
		Male	Female				
CPFE group	57	43 (75.44)	14 (24.56)	69.7±9.0	14.0±9.7	22.1±1.3	30±2.3
PF group	23	15 (65.22)	8 (34.78)	70.3±9.4	14.6±9.8	22.4±1.4	33±2.0
t/χ^2		2.71		1.886	1.638	1.533	-1.705
P		0.394		0.493	0.331	0.384	0.163

Table 2. Comparison of blood gas analysis of the two groups ($\bar{x}\pm s$)

Group	Case	SaO2 (%)	PaCO2 (mmHg)	PaO2 (mmHg)	PA-aDO2 (mmHg)
CPFE group	57	90.0±1.2	36.3±4.8	69.2±14.4	64.4±34.6
PF group	23	96.7±1.6	38.6±5.0	71.2±17.0	35.7±18.3
t		4.303	1.476	1.440	3.182
P		0.027	0.095	0.084	0.003

Table 3. Comparison of pulmonary function tests of the two groups ($\bar{x}\pm s$)

Group	Case	FEV1 (L)	FVC (L)	FEV1/FVC	TLC (L)
CPFE group	57	1.7±0.2	2.5±0.4	0.68±0.06	5.4±1.0
PF group	23	1.6±0.1	2.0±0.2	0.84±0.07	4.2±0.8
t		1.306	2.776	2.571	2.447
P		0.343	0.003	0.031	0.014

advanced stage [7]. The diagnostic criteria were as follows: in high-resolution CT film, the reticular pattern and the honeycomb lung were mainly showed both in peripheral and lower lung field; the structures of the lung tissue were damaged; traction bronchiectasis existed; a spot of ground-glass opacity and consolidation might exist in partial. All the patients were in the late stage, the stage showed collagenous fiber deposition in pulmonary interstitium.

Exclusion criteria: Patients with pneumoconiosis, non-extrinsic allergic alveolitis or other secondary diseases were excluded.

According to the condition of whether combined with emphysema syndrome or not, the patients were divided into two groups: combined pulmonary fibrosis and emphysema group (CPFE group, n=57) and pulmonary fibrosis group (PF group, n=23). The diagnostic criteria of emphysema: In high-resolution CT film, there was a clear low-density image; no wall or thin wall showed at the boundary; or bullae of lung were appeared; the upper lung field lesions were severe.

The treatment and hospitalization information

The two groups of patients were given conventional therapies, including oxygen therapy, anti-infection, anti-fibrosis as well as symptomatic and supportive treatments. The blood gas analysis, the arterial oxygen saturation (SaO2), arterial partial pressure of carbon dioxide (PaCO2), arterial partial pressure of oxygen (PaO2) and alveolar-arterial oxygen partial pressure difference (PA-aDO2) of the patients were recorded in detail. The occurrences of carbon dioxide retention and hypoxemia were observed. At the same time, the lung function was examined, and the data of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC value and total lung capacity (TLC) of the patients were recorded. The occurrences of ventilatory dysfunction and diffusion disorder were observed. In addition, the vascular endothelial growth factor (VEGF) and serum transforming growth factor-β1 (TGF-β1) of the two groups were measured by enzyme-linked immunosorbent assay.

Follow-up

The two groups of patients were followed up by outpatient service or telephone monthly. The survival time of the patients was recorded, and the last follow-up time was April 1st, 2017.

Statistical analysis

Statistical analysis was performed with software SPSS 20.0. The measurement data such as blood gas analyses,pulmonary function tests, VEGF and TGF-β1 levels, pulmonary fibrosis scores were expressed as mean ± standard deviation ($\bar{x}\pm s$), and the comparison between the two groups was conducted with the

Table 4. Comparison of the VEGF, TGF-β1 levels and survival time of the two groups ($\bar{x}$±s)

Group	Case	VEGF (pg/L)	TGF-β1 (pg/L)	Survival time (month)
CPFE group	57	465.8±33.7	158.3±23.6	18.0±3.1
PF group	23	527.7±41.5	183.4±27.1	23.0±3.8
t		2.365	2.360	4.541
P		0.013	0.009	0.041

Table 5. Comparison of the results of high-resolution CT of the two groups

Group	Case	Reticular pattern	Honeycombing shadow	Mediastinal lymphadenectasis	Bronchiectasis
CPFE group	57	8 (14.04)	24 (42.1)	14 (24.6)	9 (15.8)
PF group	23	17 (85.0)	9 (45.0)	5 (25.0)	5 (25.0)
χ^2		12.83	1.32	2.77	4.11
P		0.023	0.197	0.256	0.352

Student's t-test. Survival time was compared by nonparametric test. The count data including the incidence of reticular pattern, honeycombing shadow, mediastinal lymphadenectasis and the ratio of traction bronchiectasis of the two groups were expressed as rates (%). The comparison between the two groups was conducted by χ^2 test with the inspection standard of α=0.05.

Results

Comparison of the general data of the two groups

The general data between the two groups were not statistically significant (P>0.05, **Table 1**).

Comparison of blood gas analysis of the two groups

In CPFE group, the SaO2 was significantly lower than that in PF group (P<0.05), and the PA-aDO2 was evidently higher than that in the PF group (P<0.05), but the differences of PaCO2 and PaO2 between the two groups were not significant (P>0.05), see **Table 2**.

Comparison of pulmonary function of the two groups

Compared with PF group, the FVC and TLC of patients in CPFE group were significantly higher (P<0.05) and the FEV1/FVC was apparently lower (P<0.05), but the difference of FEV1 between the two groups were not significant (P>0.05), see **Table 3**.

Comparison of the VEGF, TGF-β1 levels and survival time of the two groups

The VEGF and TGF-β1 levels of CPFE group were significantly lower than those of PF group (P<0.05), and the survival time in CPFE group was evidently shorter than that in PF group (P<0.05), see **Table 4**.

Comparison of the results of high-resolution CT of the two groups

The patients in CPFE group showed significantly lower incidence of reticular pattern than patients in PF group (P<0.05), but the differences of the incidence of honeycombing shadow, mediastinal lymphadenectasis and traction bronchiectasis between the two groups were not significant (P>0.05), see **Table 5**.

Discussion

The results of this study showed that compared with PF group, CPFE group has lower SaO2 and FEV/FVC as well as higher PA-aDO2, FVC and TLC (all P<0.05). The differences were significant. The results illustrated that patients with CPFE had basic normal ventilation function, TLC etc. And the main pathogenesis of CPFE was that emphysema caused hyperinflation, while pulmonary fibrosis obstructed the ventilation, so the disorder was alleviated to some extent. In addition, fibrosis would cause traction of the bronchus, prevent the expiratory airway collapse caused by emphysema, maintain the tension of small airway to protect the FEV [8]. Less blood of pulmonary capillary and vascular bed thicker alveolar membrane were the major causes of severe damage of CPFE gas exchange [9]. In patients with CPFE syndrome, the decreased lung capacity caused by lung fibrosis and hyperinflation caused by emphysema cancelled each other out, but their effects on diffusion function would overlap. Thus, it

caused that patients had relatively normal lung volume but had significantly lower diffusion function. Therefore, in patients with CPFE, severe hypoxemia would occur both in the resting state and in the exercise state [10].

VEGF is also called angiotropin or vascular permeability factor, mainly in vascular endothelium. It can provide a good prerequisite for the proliferation of vascular endothelial cells, promote the increasing of permeability, prevent endothelial cell apoptosis, and induce the expression of survivin and antiapoptotic proteins [11, 12]. In idiopathic pulmonary fibrosis (IPF), TGF-β1 stimulated the proliferation of cells originated in mesenchyme, inhibited the proliferation of cells originated in epithelial cells and neuroectodermal cells [13, 14]. Meanwhile, TGF-β1 could also inhibit the colony of mouse hemopoietic precursor cells in long-term bone marrow cultures, the expression of megakaryocyte colony stimulating factor and IL-3 as well as the proliferation of T, B cells and mitogen [15, 16]. Compared with healthy people, IPF patients had significantly higher level of serum TGF-β1 [17]. The results of this study showed that the VEGF and TGF-β1 levels of patients in CPFE group were significantly lower than those in PF group ($P<0.05$). The reason might be that TGF-β1 provided a good prerequisite for high expression of extracellular matrix. At the same time, it inhibited the degradation of extracellular matrix, altered the cell morphology, and promoted the development of abnormal differentiation and proliferation. Animal experiments showed that local TGF-β1 injection could provide a good prerequisite for the formation of typical granulation tissue. Simultaneously, it also accelerated the healing speed of the wound [18, 19].

The main high-resolution CT manifestation of CPFE patients was reticular pattern and honeycombing shadow in double lower lobes. It could be seen that the bronchus was stretched and dilated, and the interlobular septum was thickened. These all reflected the interstitial fibrous changes. Honeycombing shadow was an extremely typical change of pulmonary fibrosis [11]. The results of this study showed that the incidence of reticular pattern in CPFE group was significantly lower than that in PF group ($P<0.05$). It illustrated that high-resolution CT could provide an effective basis for clinical identification and judgement. Patients with CPFE had significantly higher mortality. At the same time, compared with PF patients, patients in CPFE group had a poorer prognosis [20]. This study also found that the survival time of patients in CPFE group was significantly shorter than that in PF group.

There were also some shortcomings in this study. The quantity of patients in CPFE group was small, and bias may exist. The sample size should be increased in future studies to obtain more accurate results.

In conclusion, the clinical characteristics of advanced pulmonary fibrosis in the elderly were significantly different from those of combined pulmonary fibrosis and emphysema in the elderly. The prognosis of the former was better than that of the later. Thus, clinical attention is deserved.

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Disclosure of conflict of interest

None.

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References

[1] Luzina IG, Todd NW, Sundararajan S and Atamas SP. The cytokines of pulmonary fibrosis: much learned, much more to learn. Cytokine 2015; 74: 88-100.

[2] Come CE, Kramer MR, Dransfield MT, Abu-Hijleh M, Berkowitz D, Bezzi M, Bhatt SP, Boyd MB, Cases E, Chen AC, Cooper CB, Flandes J, Gildea T, Gotfried M, Hogarth DK, Kolandaivelu K, Leeds W, Liesching T, Marchetti N, Marquette C, Mularski RA, Pinto-Plata VM, Pritchett MA, Rafeq S, Rubio ER, Slebos DJ, Stratakos G, Sy A, Tsai LW, Wahidi M, Walsh J, Wells JM, Whitten PE, Yusen R, Zulueta JJ, Criner GJ and Washko GR. A randomised trial of lung sealant versus medical therapy for advanced emphysema. Eur Respir J 2015; 46: 651-662.

[3] Villarroel Saavedra JC, Orazi ML, Romanczuk M, Svetliza GN and Precerutti JA. [Emphysema and pulmonary fibrosis]. Medicina (B Aires) 2013; 73: 290-291.
[4] Xiao W. [Combined pulmonary fibrosis and emphysema]. Expert Review of Respiratory Medicine 2013; 36: 248-249.
[5] Alilovic M, Peros-Golubicic T, Tekavec Trkanjec J, Hecimovic A and Smojver-Jezek S. [Combined pulmonary fibrosis and emphysema syndrome]. Lijec Vjesn 2015; 137: 22-26.
[6] Cottin V, Le Pavec J, Prevot G, Mal H, Humbert M, Simonneau G and Cordier JF. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010; 35: 105-111.
[7] Kokuho N, Ishii T, Kamio K, Hayashi H, Kurahara M, Hattori K, Motegi T, Azuma A, Gemma A and Kida K. Diagnostic values for club cell secretory protein (CC16) in serum of patients of combined pulmonary fibrosis and emphysema. COPD 2015; 12: 347-354.
[8] Matsuoka S, Yamashiro T, Matsushita S, Kotoku A, Fujikawa A, Yagihashi K and Nakajima Y. Quantitative CT evaluation in patients with combined pulmonary fibrosis and emphysema: correlation with pulmonary function. Acad Radiol 2015; 22: 626-631.
[9] Cottin V and Cordier JF. Combined pulmonary fibrosis and emphysema in connective tissue disease. Curr Opin Pulm Med 2012; 18: 418-427.
[10] Ando K, Sekiya M, Tobino K and Takahashi K. Relationship between quantitative CT metrics and pulmonary function in combined pulmonary fibrosis and emphysema. Lung 2013; 191: 585.
[11] Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, Revel D, Valeyre D and Cordier JF. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum 2011; 63: 295-304.
[12] Venkatadri R, Iyer AK, Ramesh V, Wright C, Castro CA, Yakisich JS and Azad N. MnTBAP inhibits bleomycin-induced pulmonary fibrosis by regulating VEGF and Wnt signaling. J Cell Physiol 2017; 232: 506-516.
[13] Li FZ, Cai PC, Song LJ, Zhou LL, Zhang Q, Rao SS, Xia Y, Xiang F, Xin JB, Greer PA, Shi HZ, Su Y, Ma WL and Ye H. Crosstalk between calpain activation and TGF-beta1 augments collagen-I synthesis in pulmonary fibrosis. Biochim Biophys Acta 2015; 1852: 1796-1804.
[14] Liu Q, Chu H, Ma Y, Wu T, Qian F, Ren X, Tu W, Zhou X, Jin L, Wu W and Wang J. Salvianolic acid B attenuates experimental pulmonary fibrosis through inhibition of the TGF-beta signaling pathway. Sci Rep 2016; 6: 27610.
[15] Moore BB, Coffey MJ, Christensen P, Sitterding S, Ngan R, Wilke CA, McDonald R, Phare SM, Peters-Golden M, Paine R 3rd and Toews GB. GM-CSF regulates bleomycin-induced pulmonary fibrosis via a prostaglandin-dependent mechanism. J Immunol 2000; 165: 4032-4039.
[16] Piguet PF, Grau GE and de Kossodo S. Role of granulocyte-macrophage colony-stimulating factor in pulmonary fibrosis induced in mice by bleomycin. Exp Lung Res 1993; 19: 579-587.
[17] Lubatti C, Zeni S and Ingegnoli F. Combined pulmonary fibrosis and emphysema syndrome in systemic sclerosis. Int J Rheum Dis 2012; 15: e122-123.
[18] Lee YC, Hung MH, Liu LY, Chang KT, Chou TY, Wang YC, Wu YC, Lai CL, Tsai CC, Su KC and Perng DW. The roles of transforming growth factor-beta(1) and vascular endothelial growth factor in the tracheal granulation formation. Pulm Pharmacol Ther 2011; 24: 23-31.
[19] Zhou LU, Wei JG, Wang W and Cui GB. The role of the transforming growth Factor-β1 and the vascular endothelial growth factor in the angiogenesis of the bleomycin induced pulmonary injury. Journal of Practical Radiology 2003.
[20] Shekar M and Udnur HB. HRCT diagnosis of combined pulmonary fibrosis and emphysema in a patient of chronic obstructive pulmonary disease with pulmonary hypertension and clinical or radiograph suspicion of pulmonary fibrosis. 2016; 20150070.