Concomitant Systemic Sclerosis and Sarcoidosis with Combined Pulmonary Fibrosis and Emphysema

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Abstract

A 75-year-old woman was referred to our hospital with the chief symptom of dyspnea. Chest computed tomography revealed lymphadenopathy, emphysema, and honeycombing. Sarcoidosis was diagnosed due to an elevated serum ACE level and the findings of a lymph-node biopsy. Her smoking history, radiography findings, and impaired gas exchange indicated combined pulmonary fibrosis and emphysema (CPFE). Raynaud's phenomenon gradually appeared, and we also diagnosed her with systemic sclerosis (SSc). Right heart catheterization revealed pulmonary hypertension (PH). Smoking was assumed to be the chief cause, but SSc may also induce the development of CPFE. Severe PH induced by CPFE or SSc was present, but the influence of sarcoidosis also could not be ignored.

Key words: combined pulmonary fibrosis and emphysema, systemic sclerosis, sarcoidosis, pulmonary hypertension

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Introduction

Combined pulmonary fibrosis and emphysema (CPFE) typically occurs in male smokers in their 60's, and it is characterized by upper-lobe emphysema, lower-lobe fibrosis, and a severely impaired gas exchange, also frequently complicated by pulmonary hypertension (PH) (1). CPFE has been reported to be a smoking-induced chronic lung disease, but it occasionally appears as a connective tissue disease (CTD) (2).

Concomitant systemic sclerosis (SSc), sarcoidosis and CPFE presenting together is a rare occurrence; therefore, we herein report the case of a 75-year-old woman presenting with this condition and describe her clinical progression.

Case Report

A 75-year-old woman presented at a local clinic with dyspnea on physical exertion [British Medical Research Council (MRC) dyspnea scale grade 4] with a history of

two months. She was referred to our hospital because of dyspnea and mediastinal lymphadenopathy on chest computed tomography (CT).

She had previously suffered from hypothyroidism and dyslipidemia, and her only present medication was levothyroxine sodium tablets (50 µg/day). She was allergic to pyrine medicine. She did not drink alcohol, and had a smoking history of 11-pack-years. On examination, her vital signs and oxygen saturation were normal (SpO₂: 96% ambient air). There were fine crackles on the bilateral dorsal lower-lung fields. All other findings were normal. Laboratory tests revealed elevated levels of KL-6 and SP-D, and a mild elevation of ACE (Table).

A chest X-ray (Fig. 1) showed bilateral hilar lymphadenopathy, emphysema in the bilateral upper-lung fields, and a reticular shadow in the bilateral lower-lung fields. A chest CT scan (Fig. 2) demonstrated severe emphysema in the bilateral upper-lobes and honeycombing in the bilateral dorsal lower-lobes. A chest CT scan also exhibited severe bilateral hilar and mediastinal lymphadenopathy. Lung function testing revealed a vital capacity of 2.29 L (117.4%), forced ex-

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Table. Laboratory Findings at the First Visit.

Hematology			Coagulation		
WBC	7,400 (3,500-8,500)	/μL	PT	81.5 (70-130)	%
Neut	55.2 (35-75)	%	INR	1.07 (0.9-1.25)	
Lym	32 (18-50)	%	APTT	28.5 (25-40)	sec
Eos	6.6 (1-6)	%	Serology		
Mono	5.8 (2-10)	%	CRP	0.2 (0-0.3)	mg/dL
Baso	0.4 (0-1.5)	%	KL-6	2,113 (103-435)	U/mL
RBC	470 (375-500)	×104/μL	SP-D	326 (0-109.99)	ng/mL
Hb	13.4 (11.5-16.0)	g/dL	Antinuclear Ab	positive	(negative)
PLT	32.5 (13-37)	×104/μL	Anti-centromere Ab	positive	(negative)
Biochemistry			Anti-Scl70 Ab	negative	(negative)
TP	8.2 (6.7-8.3)	g/dL	Anti-RNP Ab	negative	(negative)
Alb	4 (3.9-4.9)	g/dL	Anti-SS-A Ab	negative	(negative)
AST	27 (8-30)	IU/L	Anti-SS-B Ab	negative	(negative)
ALT	13 (4-30)	IU/L	Anti-Sm Ab	negative	(negative)
LDH	242 (106-211)	IU/L	Tumor marker		
Glu	98 (70-109)	mg/dL	CEA	6.1 (0-5)	ng/mL
BUN	15.3 (8-20)	mg/dL	CYFRA	1.1 (0-3.5)	ng/mL
Cre	0.64 (0.2-0.8)	mg/dL	Pro-GRP	65 (0-69.99)	pg/mL
Na	141 (135-147)	mEq/L	sIL-2R antibody	592 (145-519)	U/mL
K	4.3 (3.6-5)	mEq/L	Arterial blood gas (ambient air)		
Cl	107 (98-108)	mEq/L	pH	7.439 (7.35-7.45)	
Ca	9.8 (8.7-11)	mg/dL	PaO2	65.9 (75-100)	mmHg
T-Bil	0.9 (0.2-1.3)	mg/dL	PaCO2	32.4 (35-45)	mmHg
TSH	4.67 (0.38-4.31)	μIU/mL	HCO3	21.5 (20-26)	mmol/L
FT4	10.4 (6.10-12.4)	μg/dL	B.E.	-2.7 (-3-+3)	mmol/L
FT3	1.03 (0.8-1.6)	ng/mL	Bronchoalveolar lavage fluid		
Immunology			Region	rt. B8	
IgG	1,962 (870-1,700)	mg/dL	Recovery rate	14	%
IgA	364 (110-410)	mg/dL	Number of cells	1.03×10 ⁶	/mL
IgM	136 (35-220)	mg/dL	Neut	1.3	%
ACE	22 (8.3-21.4)	U/L	Lym	2.3	%
			Eos	2	%
			Mono	0	%
			Baso	0	%
			Macro	94.4	%
			CD4/CD8	0.91 (0.4-2.3)

Figure 1. A chest radiograph showed bilateral hilar lymphadenopathy and emphysema in the upper-lung fields, and reticular shadowing in the bibasilar lung fields.

piratory volume in 1 second (FEV₁) of 1.62 L (113.3%), FEV₁/forced vital capacity of 73.6%, total lung capacity (TLC) of 4.41 L, residual volume (RV) of 2.15 L, RV/TLC of 48.8%, diffusing capacity of the lung for carbon monoxide (DLCO) of 4.68 mL/min/mmHg (46.6%) and DLCO/alveolar volume of 1.34 L (31.5%).

Due to the lymphadenopathy and the elevated serum ACE level, sarcoidosis was considered. Ga scintigraphy (Fig. 3) revealed a marked uptake at the hilar and mediastinal lymph nodes which supported the diagnosis of sarcoidosis. Bronchofiberscopy (BFS) was performed, but proved inconclusive. The bronchoalveolar lavage fluid (BALF) revealed a normal pattern and CD4/CD8 ratio (Table). After 7 months, her dyspnea gradually progressed, and Raynaud's phenomenon appeared. We suspected the existence of CTD, and both the antinuclear antibody (ANA) and anti-centromere antibody (ACA) levels were elevated (ANA:×1,280, ACA:×168). Anti-Scl-70 antibody was not present (Table). Concurrently, sclerodactyly also appeared.

She was diagnosed with SSs due to sclerodactyly, bibasilar pulmonary fibrosis, and a positive ACA test. The positive ACA, Raynaud's phenomenon, and limited skin change from the distal part of the arm to the elbow indicated a limited cutaneous SSs pattern. Echocardiography exhibited a normal left ventricular wall motion, but the pulmonary artery pressure was elevated (49.7 mmHg). Right heart catheterization was performed and revealed a high mean pulmonary artery pressure (PAP) at rest, pulmonary vascular resistance (PVR) (PAP: 39 mmHg, 601 dynes/sec/cm⁵), and a normal pulmonary capillary wedge pressure (11 mmHg) indicated PH.

Figure 2. A chest CT scan exhibited: (A) severe emphysema in both upper-lobes; (B) honeycombing in the bilateral dorsal lower-lobes. (C, D) Bilateral hilar and mediastinal lymphadenopathy were also seen, especially in the right pretracheal lymph node (40 mm) (arrow).

Figure 3. Ga scintigraphy revealed a marked uptake at the hilar and mediastinal lymph nodes. No other uptake was seen.

Home oxygen therapy was administrated for the dyspnea on physical exertion, and BFS was reperformed. A biopsy specimen from a subcarinal lymph node by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) revealed non-caseous epithelioid granuloma (Fig. 4). Because of the bilateral lymphadenopathy, Ga scintigraphy findings, and non-caseous epithelioid granuloma, the diagnostic criteria for sarcoidosis were met (3). One reason for the normal BALF findings might be due to an insufficient collection of BALF.

Bosentan hydrate and Tadalafil were administered, but

neither could be continued because of headache, fatigue, and dizziness. At present, we are administering sildenafil (40 mg/day) and observing the patient for any signs of progress. Neither corticosteroids nor immunosuppressive drugs were administered as they were deemed inappropriate given the presence of emphysema and honeycombing.

Discussion

We herein described the findings of an adult woman presenting with concomitant SSc and sarcoidosis with CPFE. Idiopathic CPFE is usually reported predominantly in men with a mean age of 65 years (1). The clinical characteristics of CPFE are: (A) coexistence of emphysema predominantly in the upper lungs and fibrosis predominantly in the lower lungs, exhibited in high-resolution CT (HRCT); (B) normal spirometric values and lung volumes despite extensive radiographic evidence of lung disease, as well as marked impairment in gas exchange; (C) often complicated with the presence of PH suggesting a poor prognosis; and (D) an increased risk of lung cancer (4). In this case, the patient was diagnosed with CPFE due to a significant impairment in gas exchange, a normal FVC and FEV₁ and the coexistence of emphysema and fibrosis in chest HRCT.

CPFE is reported to have a strong correlation with cigarette smoking, and most patients present with approximately 40-pack-year histories or more (1, 5). A retrospective study of 61 patients with CPFE revealed elevated ANA levels in a third of the patients, though none of them had overt CTD when diagnosed with CPFE (1). There are some other stud-

Figure 4. A biopsy specimen from the subcarinal lymph node by EBUS-TBNA revealed non-caseous epithelioid granuloma and the infiltration of lymphocytes.

ies which report that CTD patients, especially those with rheumatoid arthritis and SSc, sometimes have CPFE. Cottin reported four CPFE patients with CTD that were nonsmokers, including two with SSc (2). In addition, a young woman with CPFE, a nonsmoker, was reported to have a surfactant protein-C (CFTPC) mutation (6), therefore, CPFE may have an underlying genetic predisposition.

In this case, the emphysema predominantly in both upper lobes was most likely caused by smoking, and the bibasilar honeycombing was thought to be caused by SSc. However, she had a relatively light smoking history of only 11-pack-years. In addition, Cottin et al. reported 2 non-smoker cases of CPFE with SSc. Thus, we cannot ignore the influence of SSc in the development of CPFE.

Reports of coexisting SSc and sarcoidosis are rare (7, 8). Sarcoidosis has been occasionally described in association with rheumatoid arthritis (3.4%), Sjögren's syndrome (1.3%), and SSc (0.7%) (9). Sarcoidosis is a Th1-mediated disease, whereas Th2 is predominantly present in the early and active stages of SSc (10). The underlying cause for this coexistence is unknown, but this coexistence is thought to be rare. There may be a common genetic, environmental and/or pathogenetic mechanism that remains to be elucidated, and thus further research is needed.

The radiographic features of fibrosis in sarcoidosis are predominantly observed in the upper lung fields. Occasionally, fibrosis is seen in the lower lung fields (11), but CPFE with sarcoidosis has not yet been reported. We cannot rule out the possibility that sarcoidosis may be the cause of honeycombing in the lower lung fields, although we did not perform a transbronchial lung biopsy. Finally, based on the findings of this case, CPFE seems to have a strong correlation with smoking and SSc.

It is well known that SSc can induce PH, especially with CPFE or without any elevation in the anti-scl-70 antibody levels (12-14). PH is a strong prognostic factor for SSc (15), and an improvement of PH is a major objective of treatment. PH with SSc is classified as pulmonary arterial hypertension (PAH) (group 1) (16), but pulmonary veno-occlusive disease (group 1'), PH due to left heart disease (group 2),

and PH due to lung disease (group 3) often coexist. The effectiveness of existing pulmonary vasodilators is limited only to PAH, and pulmonary vasodilators might even exacerbate PH due to the presence of other diseases (17), therefore intense monitoring is necessary. In this case, we needed to take multiple causes of PH as CPFE (group 3), SSc (group 1), and sarcoidosis (group 5) into consideration, and thus the effect of vasodilators is very limited in practice.

It is important to consider the existence of CTD when emphysema and fibrosis are present, even though smoking is the chief cause of CPFE. The incidence of sarcoidosis overlapping with CPFE is a very rare. Furthermore, the causes of this coexistence are not clear. Further research is therefore warranted to determine whether this is a common etiopathogenesis or merely a coincidence.

The authors state that they have no Conflict of Interest (COI).

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