Unilateral Upper Lung Field Pulmonary Fibrosis Radiologically Consistent with Pleuroparenchymal Fibroelastosis after Thoracotomy: A New Disease Entity Related to Thoracotomy

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Keywords

Apical cap · Pleuroparenchymal fibroelastosis · Thoracotomy · Magnetic resonance imaging

Abstract

Background: Pleuroparenchymal fibroelastosis (PPFE) is a rare bilateral idiopathic interstitial pneumonia defined by pleural-parenchymal involvement. In clinical practice, we encountered patients with upper lung field pulmonary fibrosis (Upper-PF), which was radiologically consistent with PPFE, but apparently limited to the unilateral lung. **Objectives:** The purpose of the study was to clarify the clinical characteristics in those patients. **Methods:** We examined the medical records of all the consecutive patients from 2012 to 2016 to see whether there were patients having unilateral Upper-PF. **Results:** We found 6 patients with unilateral Upper-PF. The most common symptom was dyspnea, and all patients had a low body mass index and severe restrictive

pulmonary impairment. Notably, all patients had a history of thoracotomy for resecting lung or esophageal cancer, and the lesions were limited to the operated side. Dynamic breathing chest MRI showed an impaired thoracic movement in the operated side. Serial chest CT from prethoracotomy to the first visit was obtained in 5 patients: before thoracotomy, only a slight apical cap, defined as a wedge- and triangle-shaped opacity with broad pleural contact, was observed only in the operated side, but progressed into the lesion after a median of 8.4 years following thoracotomy. After the first visit, the unilateral lesion rapidly deteriorated in all patients. **Conclusions:** Unilateral Upper-PF had some characteristics in common with PPFE. Because the lesion was limited to the operated side, unilateral Upper-PF would be a new disease entity related to thoracotomy. Our results indicate that thoracotomy impairs thoracic movement in the operated side and subsequently triggers unilateral Upper-PF development, especially in patients with an apical cap.

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Introduction

Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare form of bilateral interstitial pneumonia and characterized as marked pleural and parenchymal involvement predominantly in the upper lobe [1]. Radiologically, PPFE is defined as a presentation of pleural thickening with associated subpleural fibrosis [2, 3]. In our clinical practice, we have encountered cases of upper lung field pulmonary fibrosis (Upper-PF) that are limited to the unilateral lung but are similar to PPFE in their radiological manifestations. We also took notice of the presence of apical caps, defined as a wedge- and triangle-shaped opacity with broad pleural contact in the apex of the lung in those patients [4]. We supposed that there would be a relationship between Upper-PF and the presence of apical cap. To clarify this relationship and the characteristics of unilateral Upper-PF, we performed a retrospective study.

Method

We examined the medical records of all consecutive patients who presented to our department from March 2012 to December 2016 to see whether there were patients displaying features of unilateral pleuroparenchymal disease. We gathered them and reviewed their clinical features.

Radiological findings of the unilateral lung with the lesion must be the same as those for “definite PPFE” or “consistent with PPFE.” Patients who had apparent abnormal shadows in the contralateral lung on chest radiography were excluded. According to the previous report by Reddy et al. [2], “definite PPFE” was defined as demonstrating pleural thickening with associated subpleural fibrosis concentrated in the upper lobes, with involvement of the lower lobes being less marked or absent. “Consistent with PPFE” was defined as pleural thickening in the upper lobes with associated subpleural fibrosis present; however, the distribution of these changes is not concentrated in the upper lobes or the features of coexistent disease present elsewhere. Patients who were considered to have pulmonary aspergillosis and mycobacterial lung disease based on the results of sputum and serological examination were excluded. Patients were selected using medical charts and imaging studies on the basis of consensus of at least chest physicians or radiologists who had board certification of respiratory or radiology.

Patients’ characteristics including age, sex, smoking habit, previous history, and body mass index (BMI) were collected from medical records. In addition, the results of laboratory data includ-

ing Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D), chest high-resolution CT findings, lung perfusion scintigraphy, and pulmonary functional test were assessed. With regard to chest high-resolution CT, we took notice of the presence of an apical cap and the radiological change of the apical cap in the clinical course and, therefore, also evaluated serial CT scans before and after the time of the first visit. Besides, the motion of the diaphragm and chest wall was evaluated using dynamic breathing MRI.

Dynamic Breathing MRI and Statistics

All MRI studies were performed on a 1.5-T Achiva (Philips Medical Systems, Amsterdam, The Netherlands) using a 32-channel Torso coil. A balanced fast-field echo sequencing was used (echo time 1.1 ms, repetition time 2.1 ms, flip angle 50°, parallel imaging factor 2). The field of view was 450 mm, and the matrix size was 256 × 256. The image slice thickness was 10 mm, and acquisition time per image was 0.28 s.

Coronal and sagittal imaging of the patient’s thorax in the supine position was performed. Each patient was instructed to repeat breathing deeply from maximal inspiration to maximal expiration with as much effort as possible. Dynamic breathing MRI was performed at a fixed mid-coronal plane through the trachea and at two fixed mid-sagittal planes through the middle of each lung. Respiratory diaphragm and chest wall motion were evaluated by a cine-loop view of the sequential MR images according to the paper reported by Suga et al. [5]. Respiratory diaphragm motions were evaluated measuring the maximal and minimal dimensions from the top of the apex to the diaphragm on a mid-coronal, and those of the transvertical anteroposterior dimension of the chest at the two fixed levels through the upper and lower thoraces (at 5 cm below the lung apex and at 5 cm above the diaphragm in the maximal inspiration) on mid-sagittal planes. The maximum anteroposterior diameter of the thorax (MDT) and the maximum amplitude of respiratory motions (the maximum dimension – the minimum dimension) of the chest walls (MACW) and diaphragm (MAD) were measured in each thorax as shown in Figure 1a. The parameters of MDT, MACW and MAD were compared between the right and left thorax, using the paired Student *t* test, and *p* values less than 0.05 were considered statistically significant. The software used for all analyses was JMP 10 software (SAS Institute, Cary, NC, USA). This study was approved by the Institutional Ethical Review Board (IRB: H27-25).

Results

Patients’ Characteristics

Six patients were found to have the above-mentioned conditions (see the Methods). The patients’ characteristics are described in Table 1. The median age was 74.5

Fig. 1. a MDT is shown in a’ and b’. Chest wall motion is evaluated measuring the transvertical anteroposterior dimension of the upper and lower thoraces at mid-sagittal planes. The MACW was calculated as a’ – c’ and b’ – d’. Respiratory motion of the diaphragm is also evaluated measuring the vertical length from the apex to each hemidiaphragm at a mid-coronal plane of breathing

MRI. The MAD was calculated as e’ – f’. **b–d** The details of the respiratory motion of the chest wall and diaphragm in case 1 (**b**), case 2 (**c**), and case 4 (**d**). MDT, maximum anteroposterior diameter of the thorax; MACW, maximum amplitude of respiratory motions of the chest walls; MAD, maximum amplitude of respiratory motions of the diaphragm.

(For figure see next page.)

Table 1. Patient characteristics of 6 cases

Case	Age, years/ sex	Chief complaint	Smoking history (pack-years)	Previous history	History of surgery	Resected lung	Interval from thoracic surgery to first visit, years	BMI	KL-6	SP-D
1	70/M	Dyspnea	Former (23)	Lung ca, gastric ca	Thoracotomy, gastrectomy	Rt lower lobe	11.8	18.2	342	145.2
2	73/M	Rt back pain	Never	Lung ca	Thoracotomy	Rt upper lobe Rt middle lobe ^a	4.2	20.2	439	44.0
3	78/F	Dyspnea, cough, sputum	Never	Lung ca	Thoracotomy	Rt middle lobe S6	14.3	19.6	ne	ne
4	75/M	Dyspnea, cough, sputum	Former (5)	Esophageal ca	Thoracotomy, esophagectomy		2.8	19.1	359	316.8
5	84/M	Cough	Former (36)	Esophageal ca	Thoracotomy, esophagectomy		10.5	18.7	581	221.1
6	74/F	Dyspnea	Never	Lung ca	Minithoracotomy ^b	Rt lower lobe	6.2	20.7	475	120.1
Median	74.5						8.4	19.4	439	145.2

Rt, right; ca, carcinoma; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; ne, not evaluated; BMI, body mass index. ^a Partial resection. ^b Minithoracotomy with video assistance (5 cm incision).

Table 2. Radiological findings of chest CT and lung perfusion scintigraphy, and results of pulmonary functional analysis

Case	Lesion location	Apical cap in the left lung		Lung perfusion scintigraphy, %		Pulmonary functional analysis			
		first visit	disease course after first visit	right	left	%FVC	FEV1, %	%RV/TLC	%DLCO
1	Right	Present	Deteriorated	12	88	34.1	98.4	175.4	165.3
2	Right	Present	Stable	9	91	59.4	88.1	ne	ne
3	Right	Present	Stable	27	73	74.8	70.6	131.1	115
4	Right	Present	Deteriorated	20	80	46.9	97.2	145.5	137.4
5	Right	Present	Deteriorated	34	66	64.2	91.8	ne	ne
6	Right	Present	Stable	ne	ne	75.9	69.3	97.5	89.8
Median				20	80	61.8	90.0	138.3	126.2

CT, computed tomography; ne, not evaluated; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusing lung capacity for carbon monoxide.

years. Four of the 6 patients were male and 3 patients were former smokers. The most common symptom was dyspnea, and all patients had a history of surgical treatment for various cancers: lung cancer in 4 patients, esophageal cancer in 2 patients, and gastric cancer in 1 patient. Last surgical treatment was for lung cancer in 3 patients, esophageal cancer in 2 patients, and gastric cancer in 1 patient. Of note, all patients had undergone right thoracotomy for resecting lung or esophageal cancer. Surgical lung resection was performed in 4 patients: right lower lobectomy in 2 patients, right upper lobectomy and mid-

dle lobe partial resection in 1 patient, and right middle lobectomy and S6 segmentectomy in the remaining patient. The median interval from thoracotomy to the first visit to our hospital was 8.4 years. In all patients, BMI was low, with a median of 19.4. Regarding markers for interstitial lung disease, KL-6 was within the normal range whereas SP-D was elevated in almost all patients. The presence of antinuclear antibody was assessed in all patients, but it was positive in only 1 patient. This patient did not display features suggestive of an underlying connective tissue disease.

Fig. 2. a No abnormal shadow was detected 1 year after surgical resection of the right upper lobectomy and middle lobe partial resection. **b** A subpleural and parenchymal lesion developed in the remaining right lung 4 years after surgical lung resection.

Serial Chest CT Finding and the Relationship of Apical Cap and Pleuroparenchymal Involvement (Table 2)

All patients were evaluated with chest high-resolution CT on the first visit. Importantly, in all patients, pleuroparenchymal involvement was present in the right side (operated side). Five patients had pleural thickening and subpleural fibrosis limited to the right upper lobe, which radiologically met the criteria of definite PPFE. In the remaining patient with a history of right upper lobectomy and middle-lobe partial resection, pleural thickening and subpleural fibrosis was present in the right middle and lower lobes, which met the criteria of consistent with PPFE (Fig. 2). With regard to the left lung (nonoperated side), only a pulmonary apical cap was present in all patients, although the degree was slight. The previous CT before thoracotomy was obtained in 5 patients. Notably, all of them had a right apical cap (operated side), which apparently deteriorated and progressed into the lesion by the time of the first visit to our hospital. After the first visit, the right lesion in the operated side rapidly deteriorated in all patients. However, with respect to the radiological course of the left apical cap (nonoperated side), the

progression was observed only in the 3 patients with a history of gastric or esophageal resection, whereas the remaining 3 patients without those histories presented stable disease. In Figure 3, we present the radiological course of case 4 with a history of thoracotomy for esophagectomy. Before right thoracotomy, a slight apical cap was only present in the operated side (Fig. 3a), but it deteriorated and resulted in pleural-parenchymal involvement with an emergence of a left apical cap (Fig. 3b). During the clinical course, the right lesion and left apical cap apparently aggravated (Fig. 3c).

Lung Perfusion Scintigraphy and Pulmonary Function Analysis

In 5 of 6 patients, lung perfusion scintigraphy was performed and showed a drastic reduction of the right perfusion rate, which ranged from 9 to 34% with a median of 20%. In all evaluated patients, reduced perfusion was evident in the right upper lung field.

With regard to pulmonary function analysis, all patients presented a remarkable restrictive dysfunction with a normal range of forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC). %FVC was low and ranged

Fig. 3. **a** Before thoracotomy for esophagectomy; chest CT in February 2011 demonstrating normal lung with a subtle right pulmonary apical cap (black arrowhead). **b** Chest CT on the first visit (in December 2013) revealing a slight subpleural lesion in the right lung (black arrowhead) with a slight pulmonary apical cap in the

left lung (white arrowhead). In the dilated uplifted stomach, an air-fluid interface was visible (arrow). **c** Chest CT in February 2015 showing a progression of the right lung lesion and left pulmonary apical cap (arrowheads) with a full stomach (arrow).

from 34.1 to 75.9%, with a median of 61.8%. Almost all patients presented normal FEV1% with a median of 90.0%. On the other hand, percent residual volume/total lung capacity and percent diffusing capacity of the lung carbon monoxide were greater, with medians of 138.3 and 126.2%, respectively.

Dynamic Breathing MRI

In 5 patients, dynamic breathing MRI was performed to analyze the movement of the diaphragm and chest wall as shown in Figure 1 and Table 3. Right MDT was signifi-

cantly smaller than left MDT at both upper and lower thoracic levels ($p = 0.011, 0.045$), indicating that the patients had a flattened chest in the operated right side. With regard to chest wall movement, right MACW was smaller compared to left MACW at both the upper and lower thoracic levels ($p = 0.028, 0.047$). Regarding diaphragm movement, MAD was also smaller in the right thorax than in the left thorax ($p = 0.028$). These results showed an impaired movement of the chest wall and diaphragm in the operated right side. The details of respiratory motion of cases 1, 2, and 4 are presented in Figure 1b–d.

Fig. 4. **a** Chest radiograph showing a lesion in the right upper lung field. **b** Chest CT demonstrating subpleural parenchymal involvement in the right upper lobe, with a slight pulmonary apical cap in left upper lobe (arrowhead).

Table 3. Dynamic breathing magnetic resonance imaging

Case	MDT, mm				MACW, mm				MAD, mm	
	upper		lower		upper		lower			
	right	left	right	left	right	left	right	left	right	left
1	110	144	125	172	9	9	5	6	7	25
2	94	114	110	144	6	15	4	10	15	57
3	142	166	146	175	19	25	15	18	42	58
4	95	104	123	149	4	6	4	9	16	30
5	114	126	157	150	6	15	4	9	22	22
6	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Mean $\pm$ SEM	111 $\pm$ 9	131 $\pm$ 11	132 $\pm$ 8	158 $\pm$ 6	8.8 $\pm$ 2.7	14 $\pm$ 3.3	6.4 $\pm$ 2.2	10.4 $\pm$ 2.0	20.4 $\pm$ 5.9	38.4 $\pm$ 7.9
Median	110	126	125	150	6	15	4	9	16	30

MDT, maximum anteroposterior diameter of the thorax; MACW, maximum amplitude of respiratory motions of chest walls; MAD, maximum amplitude of respiratory motions of the diaphragm; ne, not evaluated.

Case Presentation (Case 1)

In July 2014, a 70-year-old man visited our hospital complaining of gradually deteriorating dyspnea on exertion. He had a previous history of right lower lobectomy for lung adenocarcinoma in September 2002 and distal gastrectomy for gastric cancer in November 2011. After

gastrectomy, his body weight decreased by 10 kg over 3 years. Chest radiography on the first visit to our hospital showed a volume loss in the right lung, and chest high-resolution CT demonstrated pleural and parenchymal involvement in the right upper lobe with a subtle apical cap in the left lung (Fig. 4). Notably, although there was no

Fig. 5. Serial chest CTs between October 2007 (**a**) and January 2012 (**b**) demonstrating only a slight pulmonary apical cap in the right upper lobe (arrowhead) with no apparent change. In February

2016, a subpleural parenchymal involvement with an emphysematous change developed in the right lung and the left pulmonary apical cap (arrow) apparently aggravated (**c**).

apparent difference of chest CT findings between 2007 and 2012 (Fig. 5a, b), serial chest CT showed that the right apical cap rapidly deteriorated and progressed into the lesion after gastrectomy (Fig. 4b). A pulmonary function test on the first visit showed a decreased %FVC of 34.3% with an elevated percent residual volume/total lung capacity of 175.4%, whereas %FVC in November 2011 was 69.2%. In lung perfusion scintigraphy, the perfusion rate of the right lung was extremely low at 12%. Dynamic breathing MRI showed that the right MDT and MAD were smaller compared to the left ones, whereas the upper and lower MACW was equal on both sides of the chest wall (Fig. 1b). Because the arterial blood gas analysis showed hypercapnia, we initiated noninvasive positive pressure ventilation and rehabilitation to improve right thoracic movement, resulting in an increase in FVC from 1.28 to 1.53 L over a week. With nutrition therapy, non-invasive positive pressure ventilation, and pulmonary re-

habilitation, the patient presented a stable disease course without body weight loss until July 2015. However, a subpleural emphysematous-like change appeared in the right upper lobe, and the left apical cap apparently deteriorated in February 2016 (Fig. 5c).

Discussion

We reported on 6 consecutive cases of unilateral Upper-PF that radiologically met the criterion “definite PPFE” or “consistent with PPFE.” To date, PPFE patients have been reported to present a low BMI with a flattened chest and a restrictive pulmonary impairment, which was observed in all our patients [6–9]. These results indicate that one of the differences between our patients and patients with PPFE was whether a lesion existed in the unilateral lung or bilateral lungs. The lesion was apparently

Fig. 6. Schema of the possible mechanism of development of unilateral upper lung field pulmonary fibrosis (Upper-PF). GERD, Gastroesophageal reflux disease.

located in the operated side and therefore, unilateral Upper-PF would be a new disease entity related to thoracotomy. Of note, although unilateral Upper-PF developed in the upper lobe in 5 of 6 patients, the remaining patient with a history of upper lobectomy and middle lobe partial resection developed unilateral Upper-PF in the middle and lower lobes (case 2, Fig. 2). These results indicate that unilateral Upper-PF development is correlated with upper lung location, not with upper lobe. Although the mechanism of unilateral Upper-PF development remains unclear, our results suggest the following two possibilities.

Firstly, thoracotomy could cause unilateral Upper-PF, which would arise from impaired thoracic movement in the operated side, especially in patients with an apical cap. In fact, all patients had a history of right thoracotomy, and the lesions were located on the operated side. Importantly, 2 of them had an esophageal cancer, and therefore, lung resection was not performed (cases 4 and 5). These results strongly indicate that thoracotomy itself is an important factor for developing unilateral Upper-PF. Generally, thoracotomy causes a restrictive pulmonary impairment compared to complete video-assisted thoracic surgery, because ribs, the latissimus dorsi, and the serratus anterior muscles are dissected [10, 11]. Indeed, all patients in this study presented a restrictive pulmonary impairment, and dynamic breathing MRI revealed an impaired movement of the chest wall and diaphragm in the operated side. These results suggest that thoracotomy has a substantial negative impact on thoracic movement in the operated side. However, we believe that impaired tho-

racic movement alone would not cause unilateral Upper-PF, because the majority of patients treated with thoracotomy do not develop unilateral Upper-PF. The important finding in the present study is that all radiologically evaluated patients before thoracotomy had an apical cap in the operated side, which apparently deteriorated and progressed into the lesion during their clinical courses. These results imply that the presence of an apical cap in the operated side is particularly important for unilateral Upper-PF development. More recently, apical cap, which is pathologically identical to PPFE, has been reported to be potentially caused by relative ischemia in the upper lobe and low-grade inflammation in the lung parenchyma [2, 12]. Besides, relative ischemia in the upper lobe can impair the resolution of inflammation, which would also facilitate the development of apical cap and PPFE [4, 13, 14]. Taking those reports into consideration, together with our results, the patients with an apical cap would have a potential pathophysiological factor change of relative ischemia and low-grade inflammation to some extent, and thoracotomy would strongly affect those patients.

Secondly, gastroesophageal resection may partially contribute to pulmonary fibrosis development. Indeed, in case 1, unilateral Upper-PF developed soon after gastrectomy, although both lungs remained normal for 7 years after thoracotomy (Fig. 5a, b). Therefore, mechanisms other than an impaired thoracic movement should also contribute to the development of unilateral Upper-PF. We believe that the clinical courses of an apical cap in the non-operated side, which was observed during the first visit in

all patients, is important to clarify those mechanisms. Of note, apical caps in the nonoperated side apparently aggravated in the 3 patients with a history of gastrectomy or esophagectomy during their clinical course (cases 1, 4, and 5). These results indicate that gastroesophagectomy itself potentially aggravates the apical cap. Considering the previously mentioned reports that apical cap development was potentially correlated with low-grade inflammation [2, 12], we believe that our 3 patients with a history of gastroesophageal resection potentially had a mechanism of microaspiration, which resulted in repeated low-grade inflammation. Generally, gastroesophageal reflux disease (GERD) and delayed gastric emptying easily develop in patients with a history of gastrectomy or esophagectomy [15–17] and can cause aspiration pneumonia [18]. In fact, 2 patients treated with esophagectomy (cases 4 and 5) had an apparent air-fluid level in the remaining esophagus and intrathoracic stomach (Fig. 3b, c), suggesting that GERD and microaspiration frequently occur. Importantly, many recent studies have shown that microaspiration following GERD can cause interstitial lung disease [19, 20], which is predominant in the right lung as observed in our cases [21]. In addition, GERD-related microaspiration has been reported to potentially cause upper lobe dominant interstitial lung disease [22]. Probably, restrictive thoracic movement in the operated side would also contribute to aggravate the impaired airway clearance following microaspiration. The schema of this hypothesis of possible mechanisms for unilateral Upper-PF development is shown in Figure 6.

Despite these important results, our study had several limitations. Firstly, this was a small-sized retrospective study at a single institution. Secondly, it remains unclear how often unilateral Upper-PF actually developed in patients with apical cap, who underwent thoracotomy, be-

cause only 2 patients who underwent thoracotomy were not treated in our hospital. Thirdly, no pathological specimens could be obtained, because the pulmonary functional results of the patients were not good enough to perform surgical lung biopsy in all patients. Therefore, it would be important in future research to investigate whether the pathological findings in unilateral upper-PF are same as those in PPFE.

In conclusion, we have reported on 6 consecutive cases of unilateral Upper-PF, which had some characteristics commonly observed in patients with PPFE. Because the lesion was limited to the operated side, unilateral Upper-PF would be a new disease entity related to thoracotomy. Although the mechanism of unilateral Upper-PF remains unclear, thoracotomy impairs thoracic movement in the operated side and subsequently would trigger unilateral Upper-PF development, especially in patients with an apical cap. Accumulation of knowledge about unilateral Upper-PF will help clarify the mechanisms of PPFE development.

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Financial Disclosure and Conflicts of Interest

The authors declare that there are no conflicts of interest related to this article.

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