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【 CASE REPORT 】

Three Cases of Idiopathic Diffuse Pulmonary Ossification

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Abstract:
Diffuse pulmonary ossification (DPO) is an uncommon diffuse lung disease characterized by metaplastic bone formation in the lung parenchyma and is rarely diagnosed in life. While DPO usually occurs as a secondary disease, idiopathic cases are extremely rare. We describe three cases of idiopathic DPO, two of which were definitively diagnosed by surgical lung biopsy. One case was observed in a 43-year-old man with a history of recurrent pneumothorax who developed pneumothorax after the surgical biopsy. Few reports have described cases of DPO with recurrent pneumothorax; however, pneumothorax should be considered as a potential complication when such patients are encountered.

Key words: pulmonary ossification, ectopic bone formation, pneumothorax, diffuse lung disease

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Introduction

Diffuse pulmonary ossification (DPO) is an uncommon diffuse lung disease characterized by metaplastic bone formation in the lung parenchyma (1, 2). Since DPO is usually an asymptomatic disease, it is typically discovered at autopsy in patients with other pulmonary injuries; living cases are rarely encountered (2). DPO usually occurs in patients with a pre-existing pulmonary or cardiac disorder (3); idiopathic cases are extremely rare (3).

We herein describe three cases of idiopathic DPO, two of which were definitively diagnosed by surgical lung biopsy using video-assisted thoracoscopy surgery (VATS). One patient showed recurrent pneumothorax during follow-up.

Case Reports

Case 1

A 43-year-old man visited our hospital due to dyspnea on exertion. An abnormality on a chest radiograph had been noted at a medical checkup when he was 37 years of age, but he did not undergo any further investigation. He was a never-smoker who had developed right pneumothorax twice (at 41 and 42 years of age), and who had a history of atopic dermatitis. He had no remarkable family medical history. The patient was unemployed and had no history of exposure to any relevant environmental factors.

His respiratory rate was 19 breaths/min, and his percutaneous oxygen saturation was 95% (on room air). A physical examination revealed no abnormalities. A peripheral blood test showed elevated Hb, eosinophil and IgE levels (Table 1). An electrocardiogram and echocardiogram showed no abnormalities. A pulmonary function test revealed a restrictive pattern and decreased diffusing capacity (Table 2). Chest X-ray showed small, diffuse linear opacities in the bilateral lower lung fields but almost no changes over the past six years (Fig. 1A and B). High-resolution computed tomography (HRCT) revealed linear and reticular opacities with diffuse calcification, mainly in the bilateral lower lobes (Fig. 1C and D).

A VATS lung biopsy was performed to make a diagnosis (Fig. 2). The histological examination of the biopsy specimen revealed multiple foci of bone in a branching pattern, randomly located within the alveolar airspaces (Fig. 3A and B). Some of the bone in the foci contained fat components, probably derived from the bone marrow. Al-

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Table 1. Laboratory Findings.

		Case 1	Case 2	Case 3			Case 1	Case 2	Case 3
Hematology					Serology				
WBC	/μL	7,140	11,350	4,560	CRP	mg/dL	0.16	0.37	0.10
Neut	%	63.9	75.2	57.7	ESR	mm/hr	1	8	4
Ly	%	11.7	16.3	34.5	IgG	mg/dL	1,551	1,566	n/a
Mo	%	11.7	4.4	5.4	IgA	mg/dL	314	291	n/a
Eo	%	10.2	3.7	1.9	IgM	mg/dL	n/a	96	n/a
RBC	$\times10^4$/μL	608	563	506	IgE	IU/mL	15,596	86	n/a
Hb	g/dL	18.7	16.1	15.9	KL-6	U/mL	443.7	659.8	142.3
Ht	%	58.4	48.8	47.5	CEA	ng/mL	2.6	2.0	1.3
Plt	$\times10^4$/μL	20.1	29.2	29.2	CYFRA	ng/mL	1.2	1.7	0.8
					ProGRP	pg/mL	55.7	17.5	32.0
Biochemistry					SCC	ng/mL	11.4	n/a	n/a
AST	U/L	27	30	24	sIL-2R	U/mL	482	335	n/a
ALT	U/L	21	47	37	BNP	pg/mL	11.1	n/a	n/a
γ-GTP	U/L	44	63	n/a	RF	IU/mL	<20	<20	n/a
ALP	U/L	243	307	260	ANA		<40×	<40×	n/a
T-Bil	mg/dL	3.2	0.68	n/a	PR3-ANCA	EU	n/a	<10	n/a
LDH	U/L	337	216	n/a	MPO-ANCA	EU	<1.0	<10	n/a
TP	g/dL	7.4	8.5	7.9	β-D Glucan	pg/mL	6.5	15.2	<5.0
Cre	mg/dL	0.73	0.81	0.76	IGRA		Negative	n/a	Negative
Na	mmol/L	138	136	139					
K	mmol/L	3.6	4.5	4.3					
Cl	mmol/L	101.9	96.6	102.7					
Ca	mg/dL	9.7	9.8	9.3					
P	mg/dL	2.1	n/a	n/a					
HbA1c	%	4.9	8.5	n/a					

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, T-Bil: total bilirubin, LDH: lactate dehydrogenase, TP: total protein, Cre: creatinine, HbA1c: hemoglobin A1c, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, KL-6: Krebs von den Lungen-6, CEA: carcinoembryonic antigen, CYFRA: cytokeratin 19 fragment, ProGRP: pro-gastrin releasing peptide, SCC: squamous cell carcinoma-related antigen, sIL-2R: soluble interleukin-2 receptor, BNP: brain natriuretic peptide, RF: rheumatoid factor, ANA: antinuclear antibody, IGRA: interferon-gamma release assays, n/a: not available

Table 2. Results of Pulmonary Function Tests.

Parameters		Case 1	Case 2
VC	mL	3,100	3,450
%VC	%	68.3	75.2
FVC	mL	3,000	3,560
%FVC	%	67.4	78.8
FEV_1	mL	2,220	2,310
$\%FEV_1$	%	57.7	58.3
$FEV_1\%$	%	74.0	64.9
RV/TLC	%	33.8	30.3
$\%DL_{CO}$	%	66.8	71.7
$\%DL_{CO}/V_A$	%	87.7	86.4

though there was some evidence of interstitial fibrosis, the fibrosis was minimal and not significant enough to be regarded as interstitial pneumonia. These findings were compatible with DPO. Because of the lack of any underlying disease, we diagnosed the patient with idiopathic DPO.

We observed the patient without treatment, and he experienced right chest pain and dyspnea two months after VATS. Chest X-ray and CT showed right pneumothorax (Fig. 1E). The pneumothorax was relieved with two weeks of rest.

Case 2

A 35-year-old man visited our hospital due to dry cough, which had persisted for several months. An abnormality was noted on chest radiography, but he was followed without treatment. He was an ex-smoker (from 22-28 years of age) and had diabetes mellitus. He had no remarkable family medical history. The patient worked as a systems engineer and had no history of exposure to any relevant environmental factors.

A physical examination revealed no abnormalities. A peripheral blood test showed elevated Krebs von den Lungen (KL)-6 and HbA1c values (Table 1). A pulmonary function test revealed a restrictive and obstructive pattern and decreased diffusion capacity (Table 2). Chest X-ray showed linear, reticular shadows, principally in the right middle and lower lung fields (Fig. 4A). HRCT revealed linear and reticular opacities with diffuse calcification, mainly in the bi-

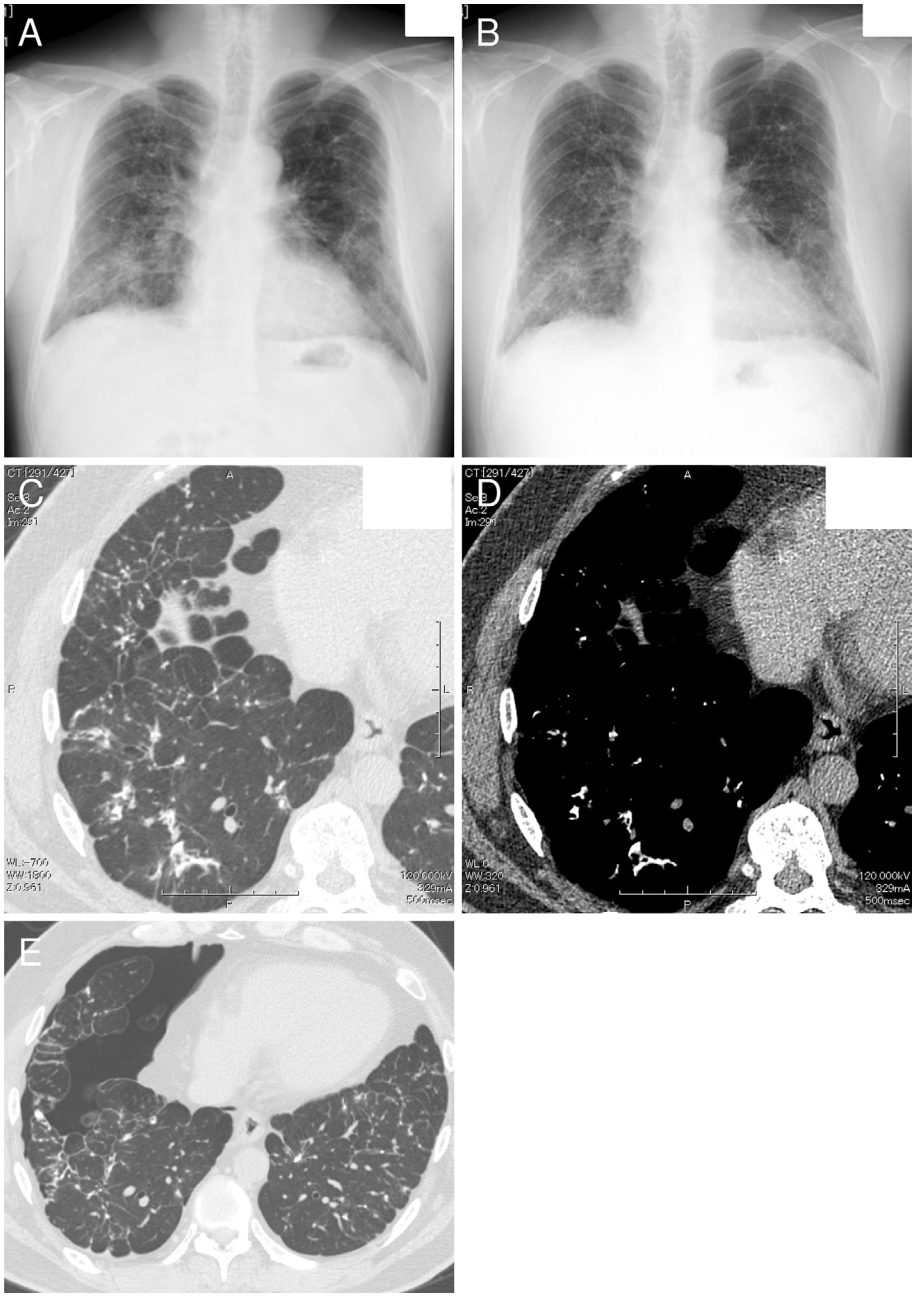

Figure 1. **Chest X-ray in Case 1 taken six years prior to the first visit (A) and at the first visit (B) showed small, diffuse linear opacities that were mainly located in the bilateral middle and lower lung fields, with almost no changes over six years. Chest computed tomography of Case 1 revealed linear and reticular opacities in the parenchymal window (C) and calcified lines and micronodules in the mediastinal window (D). Chest computed tomography showed right pneumothorax two months after surgery (E).**

lateral middle and lower lobes (Fig. 4B and C).

An examination of the bronchoalveolar lavage fluid (BALF) showed a significant lymphocyte predominance with a normal total cell count and decreased CD4/CD8 ratio (Table 3). The findings on a transbronchial lung biopsy (TBLB) were unremarkable; thus, a VATS lung biopsy was performed. Bone tissue in a branching pattern was observed within the alveolar spaces. Bone marrow was identified within some fragments (Fig. 3C and D). There was no significant evidence of fibrosis or inflammation. As in Case 1, these findings were compatible with DPO, and patient had no underlying lung or heart disease. Consequently, the patient was diagnosed with idiopathic DPO. He is currently being followed closely without treatment.

Case 3

A 35-year-old man visited our hospital because of an abnormality on chest radiography that had worsened over the past 6 years. He was asymptomatic. He was an ex-smoker (18-45 years of age) and had no underlying disease. The pa-

tient was a clerical worker and had no history of exposure to any relevant environmental factors.

The findings of a physical examination and peripheral blood test were normal (Table 1). Chest X-ray showed linear, reticular shadows mainly in the right lung field (Fig. 5A). HRCT revealed linear and reticular opacities with diffuse calcification predominantly in the right lung; the abnormalities had progressed over the six years prior to his presentation (Fig. 5B-E).

An examination of the BALF showed the predominance of macrophages and an increased CD4/CD8 ratio (Table 3). The findings on a TBLB were unremarkable, but he refused to undergo VATS lung biopsy. The HRCT findings were compatible with dendriform-type DPO, and he had no underlying lung or heart disease. Thus, the clinical diagnosis was idiopathic DPO. The patient is currently being followed without treatment.

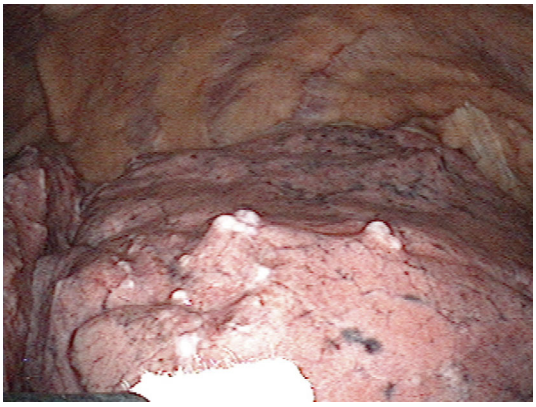

Figure 2. A photograph taken during video-assisted thoracoscopic surgery in Case 1 showed an irregular lung surface with multiple white elevations. These elevations might have caused the recurrent pneumothorax in Case 1.

Discussion

DPO is histologically categorized into two forms: a nodular type and a dendriform type (1). The nodular type is characterized by lamellar deposits of calcified osteoid material situated within the alveolar spaces, often without marrow elements; the dendriform type is characterized by interstitial branching spicules of bone and marrow elements that may protrude into the alveoli. The nodular type is typically associated with pre-existing cardiac disorders that result in chronic pulmonary venous congestion (1). In contrast, the dendriform type is less common and is generally found in DPO (1). Although the pathogenesis of pulmonary ossification is unclear (4, 5), it is hypothesized that ectopic ossification occurs as a result of various factors, including cell and tissue injury, an alkaline environment, the cessation of pul-

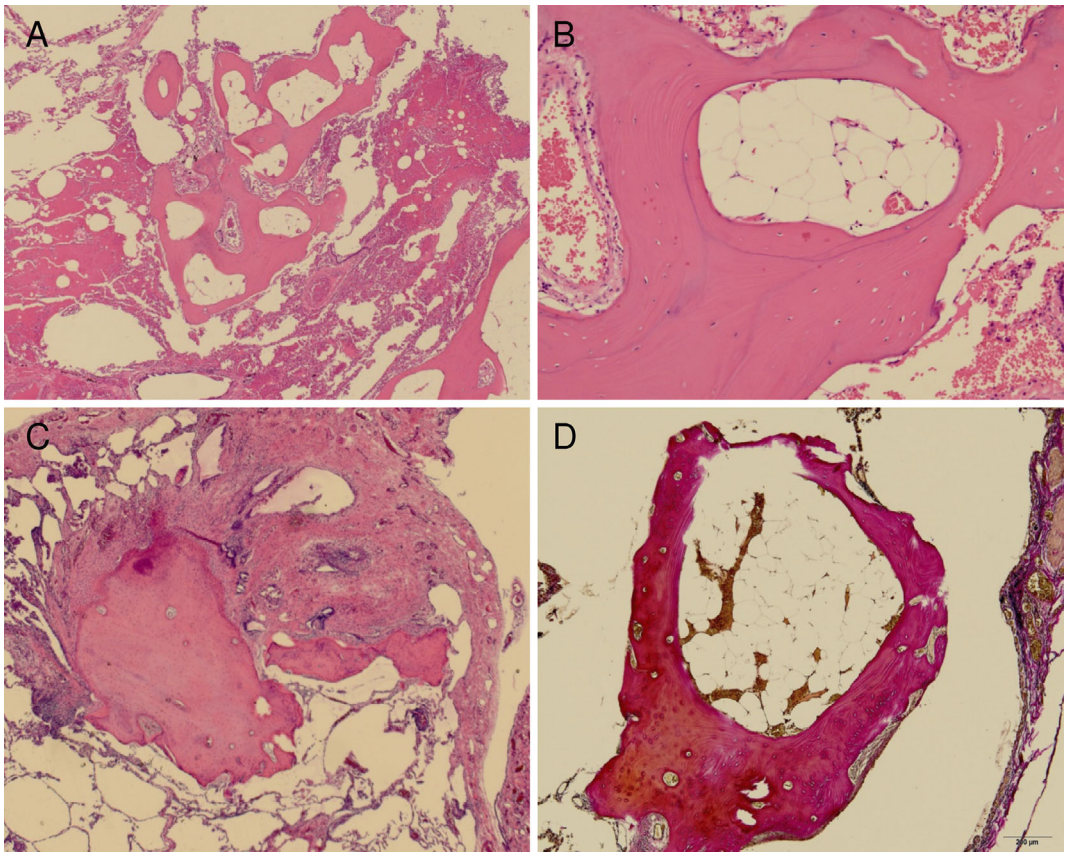

Figure 3. The histological examination of biopsy specimens obtained during video-assisted thoracoscopic surgery showed bone tissue within the alveolar airspaces, some containing marrow elements. (A) and (B): Case 1, (C) and (D): Case 2.

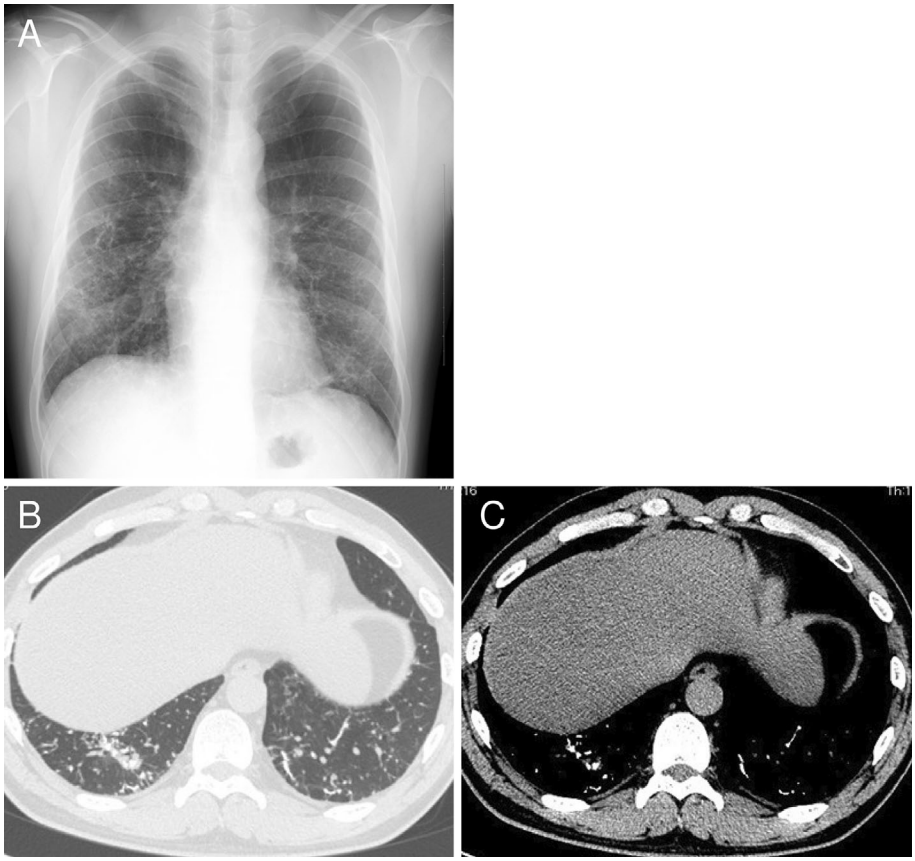

Figure 4. **Chest X-ray in Case 2 showed diffuse reticulonodular shadows, predominantly in the right middle and lower lung fields (A). Chest computed tomography of Case 2 revealed linear and reticular opacities in the parenchymal window (B) and calcified lines and micronodules in the mediastinal window (C).**

Table 3. **Results of Bronchoalveolar Lavage Fluid Examinations.**

		Case 2	Case 3
Total cell count	$\times 10^4$/mL	5.9	8.5
Macrophage	%	24.0	90.0
Neutrophil	%	1.0	0.0
Lymphocyte	%	73.0	9.0
Monocyte	%	2.0	1.0
CD4/CD8 ratio		0.85	3.2

monary blood flow, the presence of collagen and profibrogenic cytokines, extravasation, and metallic deposition (6). In addition, there are the reports of familial clustering of dendriform ossification, which suggests a genetic factor predisposes patients to the pathogenesis of this disease (7-9).

With advances in CT technology and the widespread use of CT in the evaluation of lung disease, DPO is more frequently diagnosed by imaging (10). Our three cases had abnormal radiographic findings on chest X-rays; thus, we performed HRCT and found isolated or confluent calcified lines and micronodules in every case. In the two cases in which lung biopsy was performed by VATS, the results were histologically compatible with dendriform type DPO. None of the cases had heart or pulmonary disease, and all patients were diagnosed with idiopathic DPO.

DPO is generally considered to be indolent or slowly progressive, inducing a gradual decline in the pulmonary function (4-6). However, there was a case report of a patient with idiopathic DPO who showed no significant deterioration for one decade (11), and another case with progressive restrictive ventilatory impairment due to idiopathic DPO (12). No proven treatment has been developed for pulmonary ossification (1, 4, 6), and remission has yet to be described (4). The BALF of Case 2 showed a lymphocytic predominance, and that of Case 3 showed an elevated CD4/CD8 ratio. There are few reports on the BALF characteristics of patients with idiopathic DPO, and no consistent findings have been reported. However, increases in the lymphocyte numbers and CD4/CD8 ratio were described in a previous report (11). This suggests the potential involvement of immunologic reactions in idiopathic DPO. Further studies are warranted to investigate the BALF characteristics of patients with idiopathic DPO.

To our knowledge, eight other cases of DPO with pneumothorax have been reported (9, 12-18). One case occurred in a pilot (13), and another developed pneumothorax following air travel (14). Tsai et al. (9) reported on a histopathological section in which tiny bone trabeculae had inserted themselves within the alveolar interstitium and elevated the

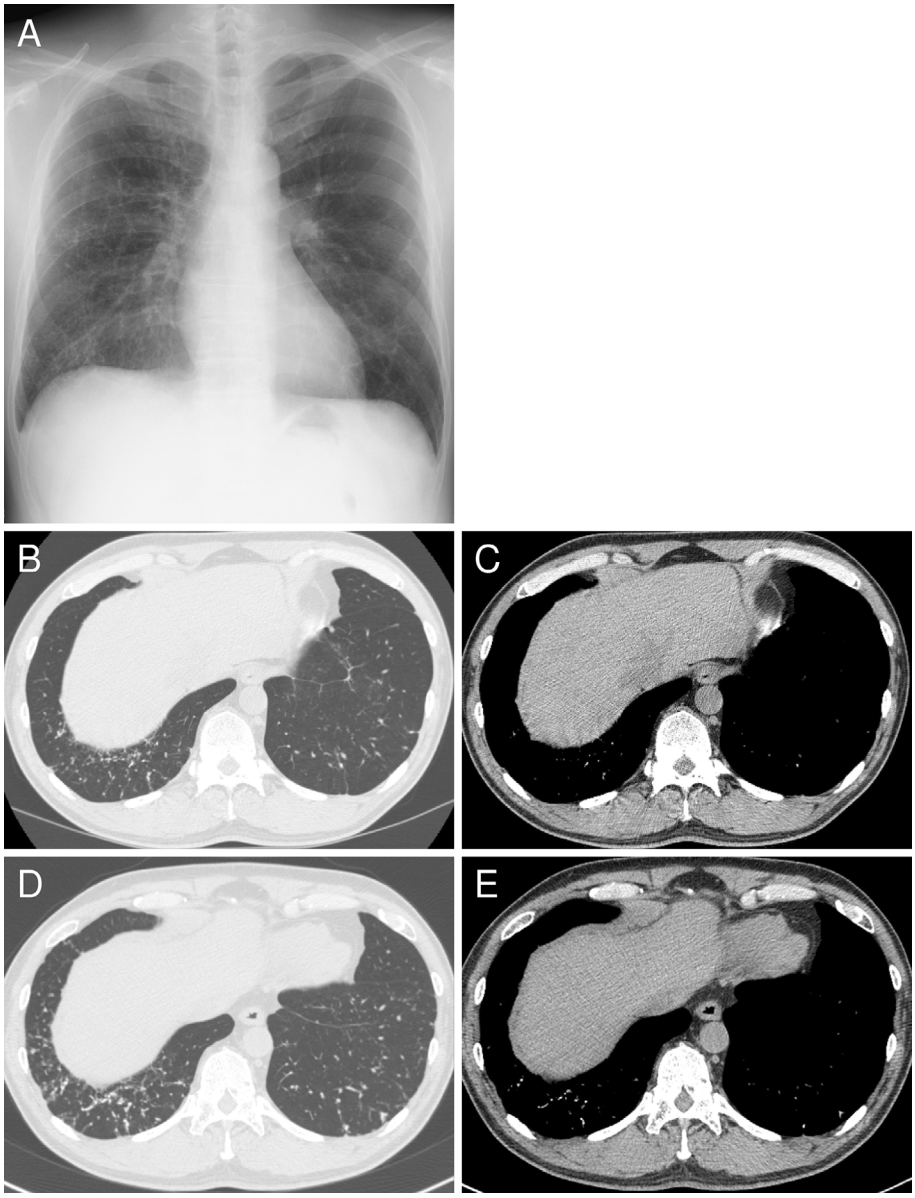

Figure 5. **Chest X-ray in Case 3 showed linear and reticular shadows, principally in the right middle and lower lung fields (A). Chest computed tomography performed six years prior to the first visit showed slightly linear and reticular opacities in the parenchymal window (B) and calcified lines and micronodules in the mediastinal window (C). Chest computed tomography at the first visit showed that the abnormalities had progressed over six years (D, E).**

pleura. Kato et al. (15) showed a deficit in the elastic fiber layer in the visceral pleura caused by bony spicules. They concluded that pneumothorax may occur secondarily to DPO (9, 15). In the biopsy specimen of Case 1, the puncture of the visceral pleura by the bone tissue was not observed. However, CT showed calcified linear reticulations in the subpleural area, and an irregular lung surface with multiple white elevations (Fig. 2) might have been subpleural bone lesions. Case 1 had no bullae or other abnormalities that would cause recurrent pneumothorax. This suggests the possibility that recurrent pneumothorax occurred due to idiopathic DPO in this case. While some studies have reported that pneumothorax did not recur after the operation (15-17), Case 1 had recurrent pneumothorax after VATS. We hypothesize that an area of DPO that was not removed by VATS was responsible for pneumothorax, as his lung had diffuse DPO.

Although patients with DPO are usually asymptomatic (3), Bai et al. (19) reported that spontaneous pneumothorax was the initial presentation in some patients with DPO. Thus, pneumothorax should be considered as a complication of DPO.

In conclusion, we presented three cases of idiopathic DPO. Two cases were definitively diagnosed by VATS, and one had recurrent pneumothorax due to DPO. There are few reports on DPO, especially with long-term follow-up. The further accumulation of DPO cases and the early diagnosis of DPO are required to better understand this entity and its

Table 4. Summary of the Published Cases of Diffuse Pulmonary Ossification with Pneumothorax.

Case No.	Age, years	Sex	Etiology of DPO	Past medical history	occurrence times of pneumothorax	Smoking history	Diagnosis	Reference No.
1	26	M	Familial	None	3	Never	Surgical lung biopsy	9
2	47	M	Idiopathic	Hypertension	1	Ex-smoker	VATS	12
3	51	M	Not mentioned (probably idiopathic)	Urinary stone	1	Not mentioned	Thoracotomy	13
4	83	M	Not mentioned (idiopathic or due to silica)	Hypertension, Carotid and coronary angioplasties	1	Never	VATS	14
5	33	M	Not mentioned (probably idiopathic)	Bronchial asthma	1	Never	Surgical lung biopsy	15
6	42	M	Not mentioned (probably idiopathic)	Bronchial asthma	3	Not mentioned	OLB	16
7	53	M	Not mentioned (probably idiopathic)	None	2	Not mentioned	Thoracotomy	17
8	68	M	Not mentioned (probably idiopathic)	Hypertension, Chronic bronchitis	1	Ex-smoker	VATS	18

Not mentioned: No available information in the publication, DPO: diffuse pulmonary ossification, VATS: video-assisted thoracoscopic surgery, OLB: open lung biopsy

association with preexisting diseases.

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

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