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【 CASE REPORT 】

Progressive Restrictive Ventilatory Impairment in Idiopathic Diffuse Pulmonary Ossification

Hidemasa Matsuo[1,2], Tomohiro Handa[3], Michiko Tsuchiya[4], Takeshi Kubo[5], Akihiko Yoshizawa[6], Yuko Nakayama[1], Shuichi Shiga[1], Takefumi Hitomi[7,8], Souichi Adachi[2], Hiroshi Date[9], Toyohiro Hirai[3] and Satoshi Ichiyama[7]

Abstract:
Diffuse pulmonary ossification (DPO) is a rare disease characterized by metaplastic bone formation in the lung. There are few reports with a long-term follow-up of this disease. We herein report a 47-year-old man diagnosed with idiopathic DPO at 30 years of age. The patient's vital capacity was normal until 36 years of age (3.39 L, 82.4% predicted), but it was severely decreased when he visited the hospital again at 47 years of age due to cough and dyspnea (1.98 L, 44.6% predicted). Chest computed tomography showed a significant increase in the number of high-density nodules, suggesting that the progression of DPO had caused restrictive ventilatory impairment.

Key words: pulmonary ossification, restrictive ventilatory impairment, prognosis

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Introduction

Diffuse pulmonary ossification (DPO) is a rare disease characterized by the ectopic formation of mature bone in the bilateral lung parenchyma. This disease was first reported by Luschka in 1856 (1). There are few cases in which living patients are diagnosed with DPO, as the symptoms are generally subclinical, and radiographical abnormalities are usually masked by other pulmonary diseases. According to autopsy data, the incidence of DPO ranges from 0.16% to 1.6% (2-4).

DPO can be classified into two subtypes: nodular and dendriform DPO, both of which have secondary and idiopathic forms (2, 5). Most cases of dendriform DPO arise secondary to acute or chronic damage of the lung, such as idiopathic pulmonary fibrosis, acute respiratory distress syndrome, and chronic obstructive pulmonary disease (6). In contrast, idiopathic DPO is extremely rare: to our knowledge, only around 20 cases have been reported, even including possible cases (5, 7-21). Few of these reports included detailed pulmonary function data, and even the reports with available data showed inconsistent results. Among them, only one report presented the long-term follow-up data (10). In that case report, the lung volumes and diffusing capacity of the lung for carbon monoxide (D_{LCO}) declined slightly over 14 years (detailed data were lacking), suggesting that idiopathic dendriform DPO may progress very slowly.

We herein report a case of idiopathic dendriform DPO that progressed over 11 years and resulted in severe restrictive ventilatory impairment.

[1]Department of Clinical Laboratory, Kyoto University Hospital, Japan, [2]Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Japan, [3]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Japan, [4]Respiratory Medicine, Rakuwakai Otowa Hospital, Japan, [5]Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University, Japan, [6]Department of Diagnostic Pathology, Kyoto University Hospital, Japan, [7]Department of Clinical Laboratory Medicine, Graduate School of Medicine, Kyoto University, Japan, [8]Department of Neurology, Graduate School of Medicine, Kyoto University, Japan and [9]Department of Thoracic Surgery, Graduate School of Medicine, Kyoto University, Japan
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Correspondence to Dr. Tomohiro Handa, hanta@kuhp.kyoto-u.ac.jp

Case Report

The patient was a 47-year old man (height, 172.9 cm; weight, 75.6 kg). He was admitted with spontaneous pneumothorax at 27 years of age. His pneumothorax was cured by chest drainage, but chest X-ray and computed tomography (CT) revealed bilateral diffuse nodular opacities. A transbronchial lung biopsy was performed, but a definitive diagnosis could not be reached.

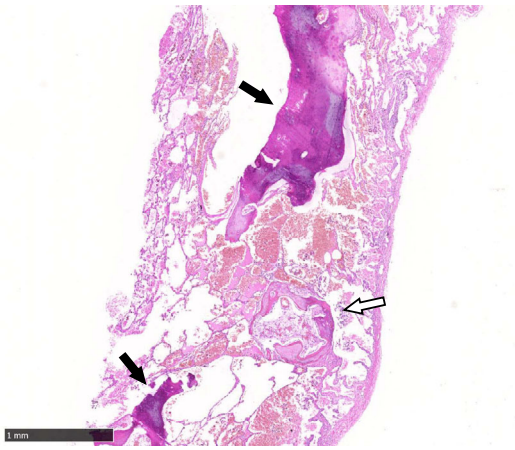

Figure 1. A surgical lung biopsy specimen shows multiple bone formations in the alveolar spaces (arrows).

He presented to the hospital again with diffuse nodular opacities at 30 years of age. A video-assisted thoracoscopic lung biopsy of the right lobe was performed. Multiple dendric foci of bone were observed in the alveolar spaces (Fig. 1). The histopathological image showed subpleural fibrosis, predominantly around the ossified areas, but it was not specific. There were no findings of interstitial lung disease associated with these lesions. Other underlying heart and pulmonary diseases were excluded, so he was diagnosed with idiopathic dendriform DPO. He had a history of hypertension. He had been a smoker from age 16 and quit smoking at age 45 (29 pack-years). He had been working as a plumber from 26 years of age and then started working in industrial waste disposal at 43 years of age, wearing a dust mask. Regarding his family medical history, his mother has been diagnosed with pulmonary calcification.

The images of chest X-ray and CT at 33 years of age are shown in Fig. 2A-C. Chest X-ray showed bilateral ground-glass opacity, and CT revealed high-density nodules bilaterally in the lower lobes. Despite the abnormal chest images, the pulmonary function test conducted at 36 years of age showed normal results (Table 1): the vital capacity (VC) was 3.39 L (82.4% predicted), and the forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) was 81.9%.

He visited the hospital again at 46 years of age after a 10-year interval due to cough and dyspnea when climbing

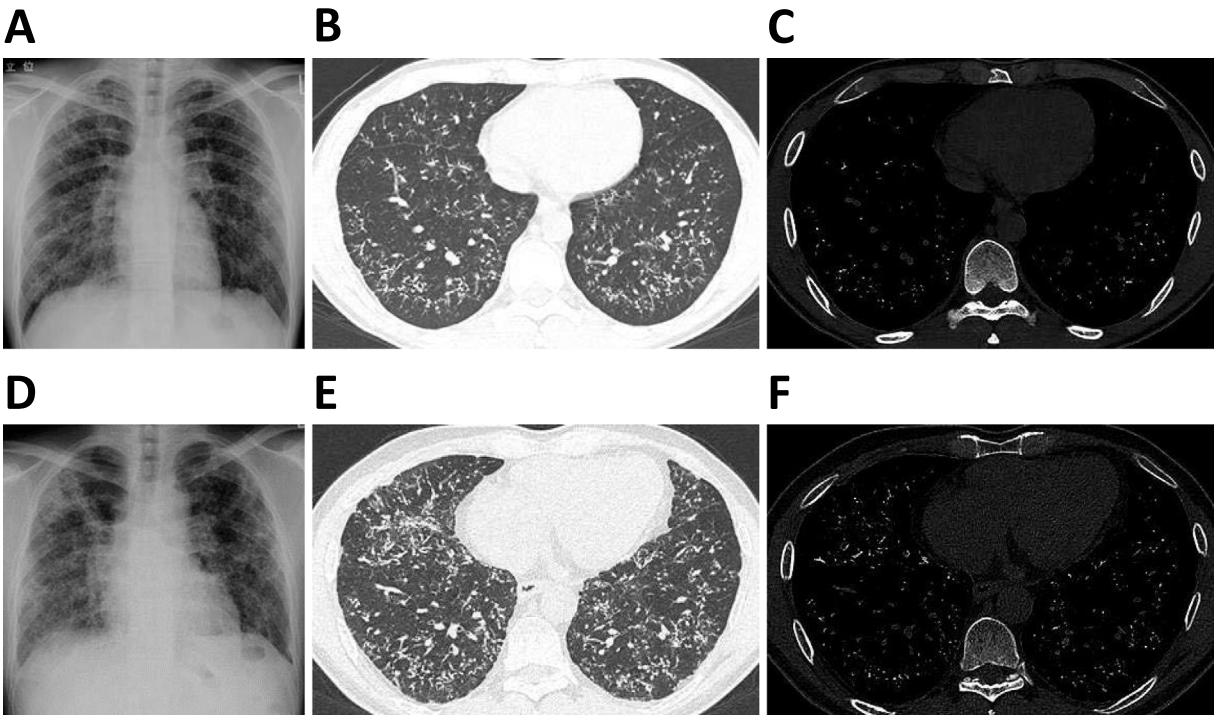

Figure 2. Chest X-ray (A), CT image with lung window (B), and CT image with bone window (C) at 33 years of age. Chest X-ray (D), CT image with lung window (E), and CT image with bone window (F) at 46 years of age. Chest X-ray showed bilateral ground-glass opacity, and CT showed high-density nodules bilaterally in the lower lobes. Compared with the images at 33 years of age, the bilateral ground-glass opacity on chest X-ray had progressed, and the number of high-density nodules on CT had increased significantly at 46 years of age.

Table 1. Pulmonary Function Data at Ages 36 and 47 Years.

		Age: 36		Age: 47	
		Value	% Predicted	Value	% Predicted
VC	(L)	3.39	82.4	1.98	44.6
FVC	(L)	3.20	77.8	1.92	44.1
FEV_1	(L)	2.62	68.9	1.58	42.4
FEV_1/FVC	(%)	81.87	104.4	82.29	96.6
D_{LCO}	(mL/min/mmHg)	N/A	N/A	15.39	53.8
RV/TLC	(%)	N/A	-	45.58	-

VC: vital capacity, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, D_{LCO}: diffusing capacity of the lung for carbon monoxide, RV: residual volume, TLC: total lung capacity, N/A: not available

Table 2. Laboratory Data at Age 46 Years.

Hematology		Biochemistry		Immunology	
WBC	9.77×10^9 /L	AST	22 U/L	PR3-ANCA	<1.0 U/mL
Neutrophil	54.1 %	ALT	15 U/L	MPO-ANCA	<1.0 U/mL
Lymphocyte	31.9 %	LDH	200 U/L	KL-6	870 U/mL
Monocyte	7.4 %	ALP	289 U/L	Anti-ds DNA antibody	<7 IU/mL
Eosinophil	5.9 %	γ-GTP	28 U/L	Anti-centromere antibody	<5.0
Basophil	0.7 %	TP	7.2 g/dL	Anti-nuclear antibody	<1:40
RBC	4.99×10^{12} /L	ALB	4.2 g/dL	SP-D	96.1 ng/mL
HGB	15.3 g/dL	Ch-E	407 U/L	Anti-CCP antibody	<0.6 U/mL
HCT	45.8 %	T-Bil	0.5 mg/dL	Anti-ARS antibody	<5.0 U/mL
MCV	91.8 fL	CRE	0.83 mg/dL	Anti-Sm antibody	<5.0 U/mL
MCH	30.7 pg	eGFR	79.3 mL/min/1.73m^2	Anti-RNP antibody	<5.0 U/mL
MCHC	33.4 %	UA	6.3 mg/dL	Anti-SS-A antibody	<5.0 U/mL
PLT	306×10^9 /L	BUN	10 mg/dL	Anti-SS-B antibody	<5.0 U/mL
		T-CHO	199 mg/dL	Anti-Scl-70 antibody	<5.0 U/mL
Coagulation		TG	54 mg/dL		
PT	11.4 s	CK	147 U/L	Blood gas analysis	
PT-INR	0.99	Na	140 mEq/L	pH	7.37
APTT	43.5 s	K	4.1 mEq/L	PaO_2	91.1 Torr
Fibrinogen	328 mg/dL	Cl	106 mEq/L	$PaCO_2$	40.5 Torr
		Ca	9.5 mg/dL	HCO_3^-	23 mmol/L
		IP	2.7 mg/dL	BE	-2.0 mmol/L
		CRP	<0.1 mg/dL		
		ACE	12.4 U/L	6-min walking distance	555 m
		Aldolase	6 U/L		

WBC: white blood cell, RBC: red blood cell, HGB: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma glutamyl transpeptidase, TP: total protein, ALB: albumin, Ch-E: cholinesterase, T-Bil: total bilirubin, CRE: creatinine, eGFR: epidermal growth factor receptor, UA: uric acid, BUN: blood urea nitrogen, T-CHO: total cholesterol, TG: triglycerides, CK: creatine kinase, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, IP: inorganic phosphorus, CRP: C-reactive protein, ACE: angiotensin-1-converting enzyme, PR3: proteinase3, ANCA: anti neutrophil cytoplasmic antibody, MPO: myeloperoxidase, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, CCP: cyclic citrullinated peptide, ARS: aminoacyl tRNA synthetase, Sm: Smith, RNP: ribonucleoprotein, SS-A: Sjögren syndrome-A, SS-B: Sjögren syndrome-B, BE: base excess

stairs. The laboratory data showed no abnormal results, except for elevation of Krebs von den Lungen (KL)-6 (870 U/mL) (Table 2). Echocardiogram also showed no abnormalities. Chest X-ray revealed the progression of bilateral ground-glass opacity (Fig. 2D). The number of high-density nodules had increased significantly in lower lobes (Fig. 2E, F). Pulmonary function tests revealed that the VC had decreased severely (1.98 L, 44.6% predicted) (Table 1), while the FEV_1/FVC was 82.3% (96.6% predicted). The D_{LCO} was decreased (15.4 mL/min/mmHg, 53.8% predicted), and the residual volume/total lung capacity ratio (RV/TLC) was increased (45.58%). Given these data, we diagnosed the patient with severe restrictive ventilatory impairment due to the progression of DPO. Because there is no established

Table 3. Summary of the Published Cases of Idiopathic Diffuse Pulmonary Ossification.

Case No.	Age, years	Sex	Past medical history	Family history	Smoking history	Environmental / occupational exposures	Pulmonary function test, % predicted	Reference No.
1	34	M	Intermittent hemoptysis	Not mentioned	10 pack-years	Never	FVC: 109%, FEV_1: 87%, D_{LCO}: 72%	5
2	29	M	Pneumothorax	Father: Dendriform pulmonary ossification	Not mentioned	Not mentioned	Not mentioned	9
3	43	M	Allergic rhinitis/ Asthma/ Diabetes mellitus/ Coronary atherosclerotic heart disease	Not mentioned	Never	Never	"Lung volumes and D_{LCO} have declined slightly over 14 years"	10
4	51	M	None	Not mentioned	Not mentioned	Never	"Normal except for an isolated reduction in the transfer factor (73% predicted)"	11
5	26	M	Cleft lip and palate/ Chronic sinusitis	None	Never	Never	"Normal"	12
6	32	M	Pneumonia	Not mentioned	Never	Never	VC: 93%, FVC: 82%, FEV_1: 71%, D_{LCO}: 102%	13
7	47	M	Pneumothorax	Not mentioned	Not mentioned	Exposure to methylmethacrylate, quartz cristobalite, chrome cobalt, alginates, asbestos and silica as a dental technician	"Normal"	14
8	49	M	None	Not mentioned	Never	Not mentioned	"A slow and progressive decline in pulmonary function"	15
9	58	M	Left renal artery stenosis/ Ischemic stroke	Not mentioned	Not mentioned	Never	Not mentioned	16
10	43	M	None	Not mentioned	Never	Never	VC: 110%, FVC: 99%, FEV_1: 92%, D_{LCO}: 71%	17
11	33	M	Pneumothorax/ Asthma	Not mentioned	Never	Not mentioned	Not mentioned	18
12	53	M	Pneumothorax	Not mentioned	Not mentioned	Not mentioned	Not mentioned	19
13	26	M	Pneumothorax	Father: Similar lung condition in his 30s with computed tomography (CT) images	Never	Never	"Normal" (FEV_1: 91%)	20
14	47	F	Hypoplasia and deformity of the middle fingers/ Diabetes mellitus/ Schizophrenia	Father: Multiple small high density nodules by CT	Never	Never	VC: 101%, FEV_1: 71%	21

In addition to the case with "idiopathic" in the publication, the possible cases were included. Some old publications which have only abstracts with little information of the cases on the PubMed were excluded. Not mentioned: No available information in the publication, VC: vital capacity, FVC: forced vital capacity, FEV_1: forced expiratory volume in one second, D_{LCO}: diffusing capacity of the lung for carbon monoxide

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medical treatment, he is now being evaluated for listing for lung transplantation.

Discussion

We encountered a case of idiopathic DPO. Secondary DPO can be derived from not only preexisting disorders but also rare earth metal and heavy metal exposure (22, 23). This patient has an occupational history as a plumber before the diagnosis. The association between his occupation as a plumber and the pathogenesis of DPO is not apparent, as the exposure period until the episode of spontaneous pneumothorax was only one year. We summarized the published cases of idiopathic DPO in Table 3. Some reports have shown that spontaneous pneumothorax can be caused by pulmonary ossification (14, 18-20); therefore, DPO might have been present when our patient suffered from spontaneous pneumothorax. Based on the published cases, idiopathic DPO appears to occur predominantly in younger man, which is compatible with our case.

Idiopathic dendriform DPO has been thought to be an indolent condition (5, 10). Our patient's VC decreased approximately 1.4 L (41.6% of the predicted VC at 36 years of age) over 11 years, which is the most severe case on record of idiopathic dendriform DPO. Although the decreased lung volume based on the images and the decreased D_{LCO} along with the VC suggest the progression of fibrosis, there were no apparent findings of interstitial pneumonia by CT. Based on the histological and radiological findings, we speculate that the non-specific lung fibrosis did not precede ossification but developed secondary to ossification. However, its mechanism remains unclear. During the video-assisted thoracoscopic lung biopsy, the lung showed incomplete collapse, suggesting that lung compliance was decreased. Our patient's chest CT image showed abundant high-density nodules bilaterally compared with the literature cases (5, 11, 14, 17). This result may explain the severity of the restrictive ventilatory impairment in our case. The pulmonary function test also showed an impaired diffusing capacity (D_{LCO}), which is compatible with the previous case (10).

Some biological hypotheses of DPO pathogenesis have been proposed. DPO is strongly associated with fibrosing interstitial lung diseases (24); however, the pathogenesis of idiopathic DPO is still uncertain. As a candidate, transforming growth factor-beta (TGF-β)/bone morphogenetic protein (BMP) is known to be associated with ectopic bone formation, as well as normal bone organogenesis (25). Furthermore, three reports of familial DPO have been published (9, 20, 21). Interestingly, two of these reports are from Japan. In all three cases, the patients' fathers suffered from DPO. Some genetic abnormalities may be involved in DPO pathogenesis; therefore, when a patient is diagnosed with idiopathic DPO, the patient's family should also be checked, especially male relatives. We examined the present patient's mother, who had been diagnosed with pulmonary calcification, but her chest CT image showed only mild calcification, suggesting old inflammatory change. Unfortunately, we have no data for the patient's father or son at present.

In this case, the follow-up period from the first diagnosis was approximately 17 years, which is the longest period yet among such reports. However, it should be noted that whether the restrictive ventilatory impairment progressed gradually through the entire period or progressed rapidly in recent years is unknown, as the patient had missed appointments for approximately 10 years. In a previous report, lung transplantation was performed for end-stage pulmonary fibrosis, and the patient was diagnosed with DPO based on an examination of the extirpated lung (26); however, the prognosis after the transplantation is unknown. Further reports of idiopathic dendriform DPO with long-term follow-up data are required to determine the optimum timing for lung transplantation.

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

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