Supplementary Table 1. Survey form of idiopathic DPO

Institution　　Depertment　　Description　　Date of description

Case No.							
Characteristics of patient	Sex	Male / Female	age at diagnosis : (years old)	Date of diagnosis :			
	Diagnostic opportunity	Medical checkup / Examination for Respiratory symptoms / Accidentally while observing other diseases / other					
	Method of diagnosis	Pathological / Only radiologicaly / Pathological anatomy / other					
	Comorbidities	No / Yes	If yes, disease names:				
	Past medical history	No / Yes	If yes, disease names:				
	Family history	No / Yes	If yes, relatives:				
	Smoking history	No / Yes	If yes, (packs / day) × (years)		Age when smoking cessation : (years old)		
	Occupation						
Data on diagnosis	Symptons	No / Yes	If yes, symptoms :				
	Physical findings	Height (cm)		Body weight(kg)			
		Blood pressure(mmH	systolic phase ／diastolic phase	Heart rate(bpm)			
		Respiratory rate(bpm)		SpO2(%)		Oxygen : No / Yes	Oxygen dose :
		Auscultatory findings of the lungs		Other special physical findings :			
	Blood test findings	WBC(/μL)		Leukocyte fraction	Neu( )(%) Lym( )(%) Eos( )(%) Mon( )(%) Bas( )(%)		
		RBC(/μL)		Hb(g/dL)		Platelet(/μL)	
		AST(U/L)		ALT(U/L)		LDH(U/L)	
		ALP(U/L)		T-Bil(mg/dL)		CK(mg/dL)	
		BUN(mg/dL)		Cre(mg/dL)		CRP(mg/dL)	
		alubmin(mg/dL)		Ca(mg/dL)		P(mg/dL)	
		intact PTH(pg/mL)		Calcitonin(pg/mL)		25-OH vitaminD(ng/mL)	
		HbA1c(NGSP) (%)		BNP(pg/mL)		KL-6(U/L)	
		TSH(μIU/mL)		free T4(ng/dL)		free T3(ng/mL)	
		ACE (mU/mL)					
		Positive autoimmune antibody and its value					
	Uriac findings	Urine occult blood	Urine protein	Urine sediment :			
		Urin Cre(mg/dL)		Urine protein(mg/dL)		Urine Ca(mg/dL)	
	Arterial blood gas analysis	Room air or oxygen	[(L/min)]	pH ( ) PaO2 ( ) PaCO2 ( )		HCO3-( ) BE ( )	
	Pulmonary function test	VC ( )(L) %VC ( )(%) FVC ( )(L) %FVC ( )(%) FEV1.0 ( )(L) %FEV1( )(%) FEV1.0% ( )(%) TLC ( )(L) RV ( )(L)					
		DLCO ( )(mL/min/mmHg) %DLCO( ) (%) DLCO/VA( ) (mL/min/mmHg/L) %DLCO/VA( )(%)					
	Electro-cardiogram	Normal / Abnormal	Findings :				
	Echocardiographic findings	Normal / Abnormal	Findings :				
	Chest plain x-ray	Date :		＊CD-ROM			
	Chest simple CT	Date :		＊CD-ROM			
	Transbronchial lung biopsy	No / Yes					
	Bronchoalveolar lavage	No / Yes	BALF : Site of BAL ( )	In ( ) mL, collection ( ) mL			CD4/8 ratio :
			Fraction macrophage ( ) (%) Lym( )(%) Neu( )(%) Eos( )(%) Mon( )(%) Bas( )(%)				
	Surgical lung biopsy	No / Yes					
	Pathological anatomy	No / Yes					
Latest data	Recent confirmation date :		Age : (years old)	SpO2(%)	(%)	Oxygen : No / Yes	Oxygen dose :
	Arterial blood gas analysis	Room air or oxygen	[(L/min)]	pH ( ) PaO2 ( ) PaCO2 ( )		HCO3-( ) BE ( )	
	Drug therapy	No / Yes	If yes, drugs :				
	Oxygen therapy	No / Yes	If yes, date of starting oxygen :	Age of starting oxygen : (years old)			
	Latest chest plain x-ray	Date :		＊CD-ROM			
	Latest chest simple CT	Date :		＊CD-ROM			
	Latest pulmonary function test	VC ( )(L) %VC ( )(%) FVC ( )(L) %FVC ( )(%) FEV1.0 ( )(L) %FEV1( )(%) FEV1.0% ( )(%) TLC ( )(L) RV ( )(L)					
		DLCO ( )(mL/min/mmHg) %DLCO( ) (%) DLCO/VA( ) (mL/min/mmHg/L) %DLCO/VA( )(%)					
	Survival	Alive / Dead/ Unknow	If dead, date of death :	Age at death : (years old)		Cause of death :	
Please write briefly clinical course after diagnosis.							

Supplementary Table 2. The score sheet of radiological findings of HRCT of IDPO patients

Case	Distribution			Radiological findings 0: none, 1: < 10%, 2: 10-30%, 3: 30-50%, 4: > 50%													Degree of progress
	Craniocaudal	Axial															
No.	1: Upper and middle fields predominance 2: Lower fields predominance 3: Diffuse / Random	1: Peripheral 2: Peribroncho-vascular 3: Diffuse 4: Random 5: Dependent 6: Central		Fine calcified nodules	Calcified short lines	Calcified branching structures	Fine nodules	Short lines	Branching structures	Interlobular Septal thickening	Thickening of bronchova-scular budles	Pleural thickening or irregularity	Non-septal linear opacity	Subpleural curve-linear shadow/line	cyst	Ground-glass attenuation	Consoli-dation	0: Incomparable 1: Stable 2: Mild progress 3: Progress
1	2	2	3	2	1	2	1	1	1	1	1	0	0	0	0	0	0	3
2	2	3		1	1	2	1	1	1	1	0	0	0	0	0	0	0	0
3	2	3		1	1	1	1	1	1	0	0	1	0	0	0	0	0	0
4	3	3		2	1	2	1	1	1	1	0	1	0	0	1	0	0	3
6	2	3		2	1	2	1	1	1	1	0	1	0	0	1	0	0	3
8	2	3		2	1	2	1	1	1	1	0	0	0	0	0	0	0	0
10	3	3		1	1	1	2	1	2	0	0	0	1	0	0	0	0	3
11	2	3		2	1	1	1	1	1	1	0	0	1	0	0	0	0	3
14	2	2	3	1	1	2	1	1	1	1	1	1	0	0	0	0	0	3
15	2	2	3	1	1	2	1	1	1	1	0	1	0	0	0	0	0	0
16	2	2	3	2	1	1	1	1	1	1	0	0	1	0	0	0	0	3
19	3	3		2	1	2	1	1	1	1	0	1	0	0	0	0	0	3
20	2	3		1	1	1	1	1	1	1	0	0	0	0	0	0	0	1
21	2	2		1	1	1	1	1	1	0	0	0	0	0	0	0	0	3
25	2	3		2	1	2	1	1	1	1	0	1	1	0	0	0	0	3
28	2	3		2	1	2	1	1	1	1	1	1	1	0	0	0	0	3
29	2	3		2	1	2	1	1	1	1	1	1	1	0	0	0	0	3
30	2	3		2	1	2	1	1	1	1	1	1	1	0	1	0	0	3
33	2	3		1	1	1	2	1	1	1	1	1	1	0	0	0	0	3
34	2	2		1	1	1	1	1	1	1	1	1	0	0	0	1	0	0
35	2	1		2	1	1	1	1	1	0	0	0	0	0	0	0	0	3
37	3	3	4	1	1	1	2	0	1	1	0	0	1	0	0	0	0	1

Supplementary Table 3. The score sheet of pathological findings of IDPO

Case No.	Types of ossified lesion 1: Dendriform 2: Nodular 3: Mixed	Distribution of ossified lesion 1: Peribronchial 2: Perivascular 3: Subpleural 4: Interlobular 5: Intraalveolar	Maximum size of ossified lesion (mm)	Number of ossified lesions	Bone marrow 1: Exist 2: Few	Grade of pathological findings					
						Fibrosis around ossified lesion	Subpleural fibrosis	Inflammatory cell infiltration	Emphysema	Histiocyte containing hemosiderin	Histiocyte containing brown pigment granules
1	1	1, 2, 3, 5	2.0	6	1	1	0-1+	1+	0+	0+	1+
2	3	1, 2, 3, 4	3.0	32	1	1	0-1+	1+	0+	0+	1+
3	3	1, 2, 3	3.0	15	1	1	0-1+	1+	0+	0+	0+
4	1	3, 4	3.0	3	1	1	0-1+	1+	0+	2+	2+
6	3	1, 2, 3, 4	5.0	15	1	1	1+	1+	0+	1+	1+
8	1	1, 2, 3, 4	1.0	7	1	1	0+	0-1+	1+	1+	1+
10	1	1, 2, 3, 5	6.0	15	1	1	1+	1+	1+	0+	1+
11	1	1, 2, 3, 4	3.0	6.75	1	1	0-1+	1+	0+	1+	2+
14	1	1, 2, 3, 4, 5	6.0	17	1	1	1+	1+	0+	0+	1+
15	1	1, 2, 3	N.E.	5	1	0	0+	1+	N.E.	N.E.	N.E.
16	1	3, 5	N.E.	3	1	1	0+	1+	N.E.	N.E.	N.E.
19	1	1, 2, 5	N.E.	10	1	1	0+	N.E.	N.E.	N.E.	N.E.
20	1	1, 2, 3, 5	4.0	55	1	1	0+	1+	0+	0+	0-1+
21	3	2, 5	1.0	6	2	1	0	0+	0+	0+	1+
25	1	1, 3, 4, 5	3.0	9.5	1	1	1+	1+	0+	N.E.	1-2+
28	3	3, 5	5.0	7	1	1	1+	1+	0+	0+	1+
29	1	1, 3, 5	5.0	4	1	1	0-1+	1+	0+	2+	2+
30	1	2	3.0	2	1	1	0-1+	1+	0+	2+	0-1+
33	1	1, 3, 4, 5	1.0	5	1	1	0-1+	1+	0+	0+	1+
34	1	1, 3, 5	1.0	5	1	1	N.E.	N.E.	N.E.	N.E.	N.E.
35	1	1, 3	2.0	25	1	2	0-1+	1+	N.E.	N.E.	1+
37	1	1, 3, 5	2.5	23	1	1	N.E.	1+	N.E.	1+	1+

N.E. not evaluable

Supplementary Table 4. The data of pulmonary function tests at the diagnosis and latest follow-up

	Initial value at diagnosis		Latest value		Change/year	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
FVC (mL)	22	3379 (724)	17	3143 (774)	17	-114.5 (192.2)
FVC, %predicted (%)	22	85.0 (17.0)	17	77.0 (16.8)	17	-3.1 (5.1)*
FEV_1 (mL)	22	2729 (626)	17	2490 (595)	17	-97.3 (98.5)
FEV_1, %predicted (%)	22	80.0 (17.5)	17	71.8 (13.8)	17	-2.7 (3.9)*
FEV_1/FVC (%)	22	80.5 (7.2)	17	78.3 (9.1)	17	-0.2 (3.6)
DL_{CO}, %predicted (%)	16	74.9 (17.7)	11	68.5 (12.4)	11	-1.3 (1.5)*
Observation period of pulmonary function tests (years)				6.78 (4.84)		
FVC, %predicted < 80%	8 (36.3%)		9 (52.9%)			
FEV_1/FVC (%) < 70%	2 (9.1%)		2 (11.8%)			
DL_{CO}, %predicted (%) < 80%	10 (62.5%)		9 (81.8%)			

Data are mean (SD) or n (%)

*Relative change

Supplementary Table 5. Comparison between stable and progressive groups of IDPO in the decline of FVC.

	Decline of FVC < 50 mL/year (n=7)	Decline of FVC ≥ 50 mL/year (n=10)	*P* value
Mean age at diagnosis of DPO (years)	34.0 (8.8)	35.3 (6.8)	0.749 *
Sex male	6 (86%)	9 (90%)	1 **
Pulmonary function test on diagnosis			
FVC (mL)	3576 (838)	3507 (610)	0.857 *
FVC, %predicted (%)	97.8 (17.9)	84.8 (10.8)	0.697 *
FEV_1 (mL)	3000 (675)	2775 (574)	0.481 *
FEV_1, %predicted (%)	80.5 (15.6)	79.9 (9.6)	0.604 *
Median ossification score of HRCT	4.0	4.5	0.916 ^
Number of ossification lesion of pathological specimen	11.7 (7.5)	8.0 (6.6)	0.308 *
PaO_2 (mmHg) #	92.8 (23.8)	85.6 (4.3)	0.54 *
WBC (cells/μL)	7050 (2841)	6556 (2524)	0.718 *
LDH (U/mL)	176.3 (41.5)	185.4 (27.9)	0.624 *
KL-6 (U/mL) #	227.4 (96.2)	479.4 (285.7)	0.0466 *

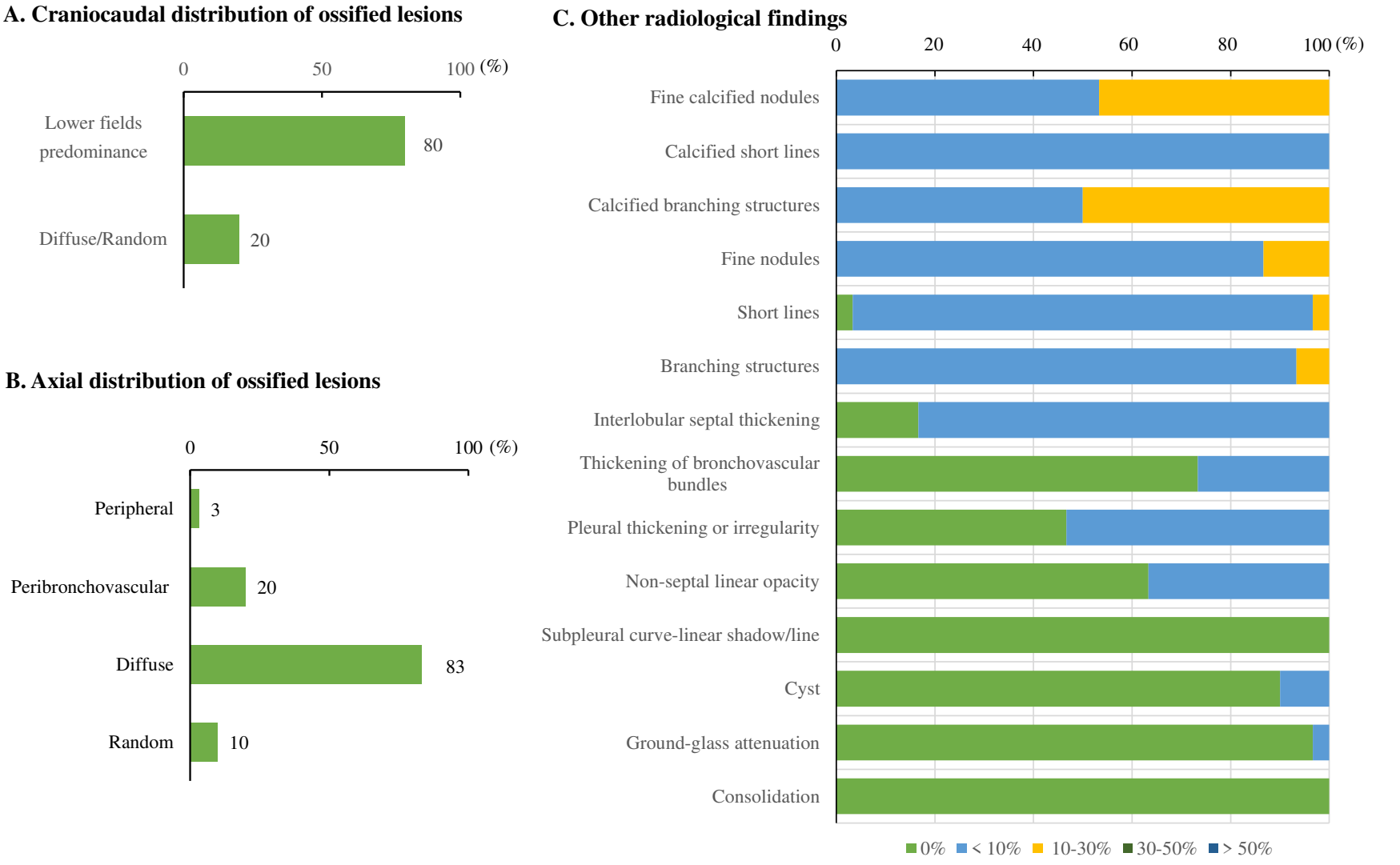
Data are mean(SD) or n of 17 IDPO cases (%).

*Welch Two Sample t-test

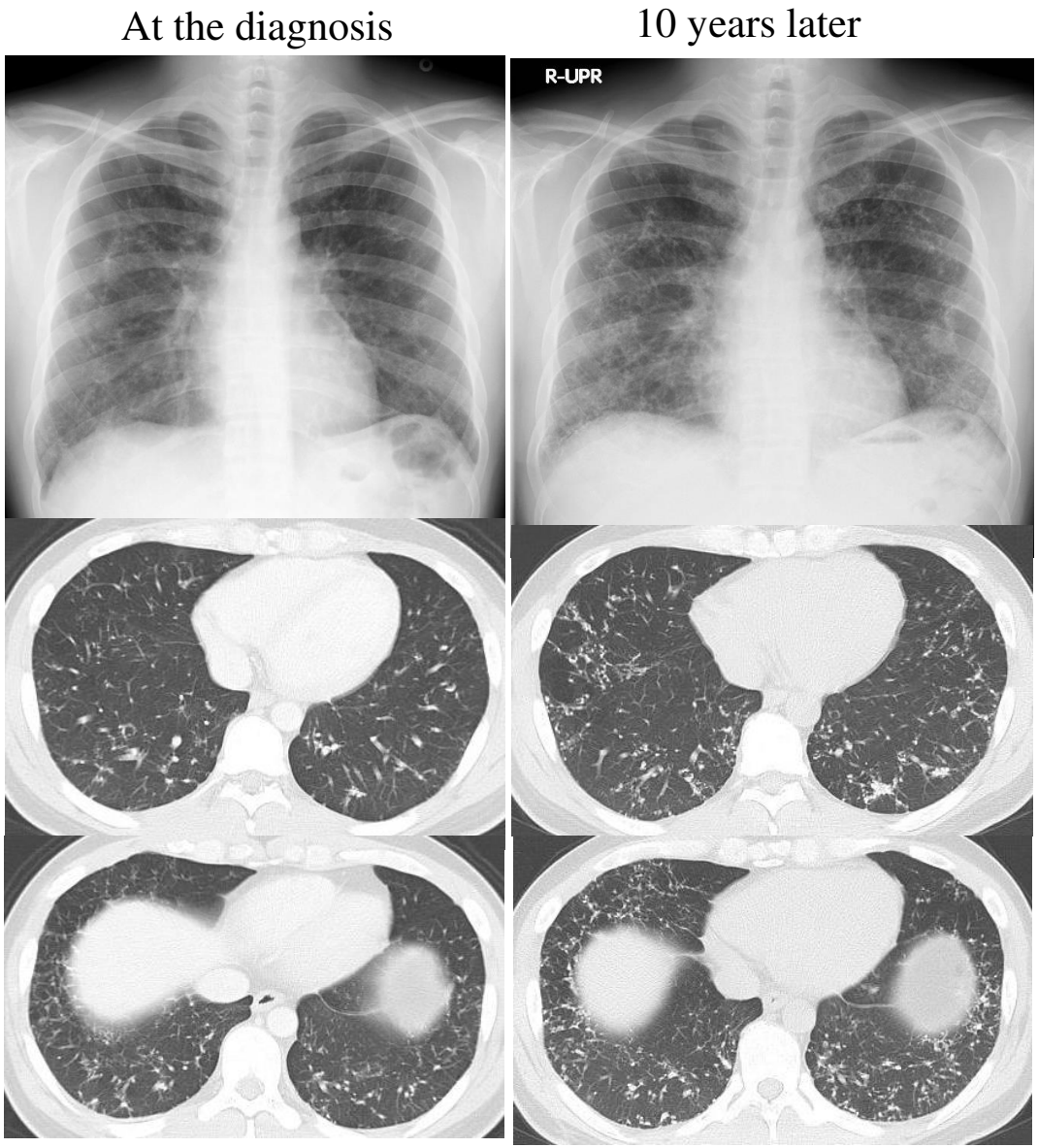
** Fisher test

^Mann-Whitney U test

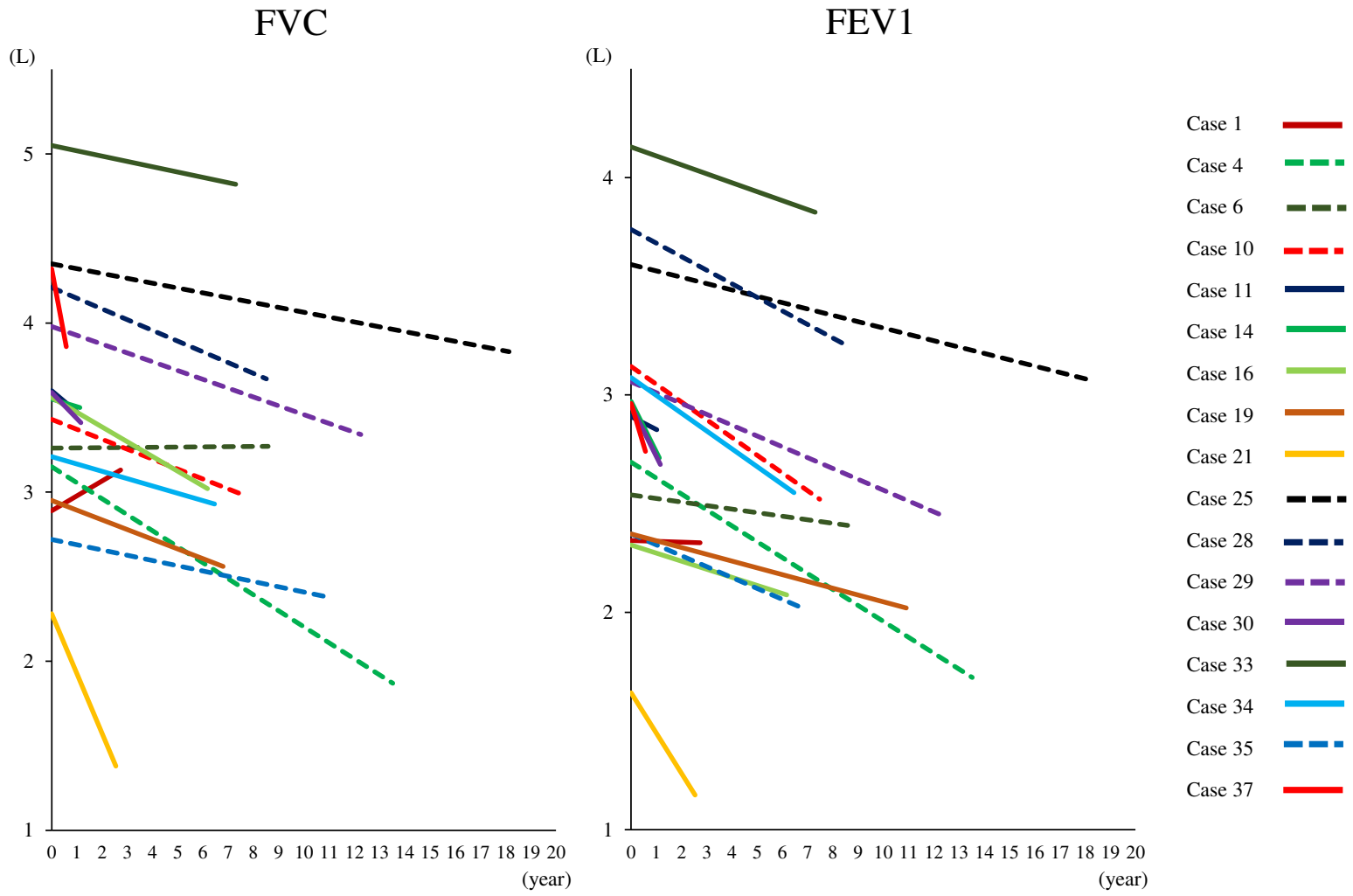
n=18



Supplementary Figure 1. Features of radiological IDPO in HRCT



Supplementary Figure 2. The representative case showing deterioration of the radiological findings on chest radipgraphy and HRCT



Supplementary Figure 3. Serial changes in pulmonary function tests in patients with IDPO

Supplementary figures

Supplementary Figure 1. Radiological features of radiological IDPO in chest HRCT

Two radiologists evaluated the HRCT findings of 30 cases of radiological IDPO by using the score sheet (see the Supplementary Table 2). The data of craniocaudal distribution (A) and axial distribution (B) of ossified lesions were examined. Quantitative and qualitative assessments of calcified lesions, interstitial changes, and other findings were performed (C).

Supplementary Figure 2. The representative case showing deterioration of the radiological findings on chest radiography and HRCT

Supplementary Figure 3. Serial changes of pulmonary function tests in patients with IDPO

The PFT data of 17 cases with IDPO were collected at two time points: at the diagnosis and latest follow-up. The changes in FVC (L) and FEV1 (L) were plotted.

A nationwide epidemiological survey of idiopathic dendriform pulmonary ossification

(Primary survey)

Principal investigator: Yasuhiko Nishioka, M.D., Ph.D.
Professor and Chairman
Department of Respiratory Medicine and Rheumatology
Graduate School of Biomedical Sciences, Tokushima University

January 4, 2018

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1.INTRODUCTION AND RATIONALE

Pulmonary ossification was pathologically noticed as the condition showing bone formation with or without marrow components appeared in the bilateral lung parenchyma1. A first case was reported in 1856 by Luschka[1)]. The early representative reports of autopsy cases showed that most were affected by underlying diseases[2, 3)]. However, since 1970s, the number of reports for idiopathic cases with diffuse pulmonary ossification have been increased[4-7)]. In the 2000s, several case reports have shown idiopathic cases of pulmonary ossification without underlying pulmonary or systemic diseases[6-8)]. The information from these reports suggested the quite homogenous clinical features such as male-predominant, asymptomatic and a branching type of ossification in HRCT and/or histology, whereas there is no comprehensive study to analyze the clinical features including onset, pulmonary function, complication, clinical course and prognosis in addition to radiological and histopathological details.

We, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases in Japan, here conducted a nationwide study to clarify the clinical findings of idiopathic cases of pulmonary ossification in Japan. Therefore, we used a term of idiopathic pulmonary dendriform ossification (IDPO) in the present study.

2. OBJECT

We conducted a nationwide survey in Japan from 2017 to 2019 to understand and clarify the pathophysiology of IDPO. The questionnaire by mail inquired into the number of cases of suspected IDPO to 1,791 hospitals, that have over 200 beds in Japan.

3. PARTICIPANTS

3-1 Inclusion criteria

Patients with diffuse pulmonary ossification diagnosed pathologically without any underlying disease

3-2 Exclusion criteria

1) Patients with diffuse pulmonary ossification diagnosed pathologically with any underlying disease as follows;[9)]

I. Preexisting pulmonary disorder

A. Idiopathic pulmonary fibrosis

B. Pulmonary amyloidosis

C. Chronic busulfan therapy

D. Acute respiratory distress syndrome

E. Hamman-Rich syndrome

F. Sarcoidosis

G. Histoplasmosis

H. Tuberculosis

I. Metastatic breast cancer

J. Pulmonary metastases of osteogenic sarcoma

K. Metastatic melanoma

II. Preexisting cardiac disorder

A. Mitral stenosis

B. Chronic left ventricular failure

C. Idiopathic hypertrophic subaortic stenosis

III. Preexisting extracardiopulmonary disorder

A. Primary and secondary hyperparathyroidism

B. Hypervitaminosis D

C. Pyloric stenosis with alkalosis

2) Patients with other pulmonary diseases except pulmonary ossification

3-3 Dropout criteria

Patients to be decided to dropout and cancel by the principal investigator(PI).

4. METHODS

4-1 Collecting data

The number of cases suspected IDPO in participating institutions. The data does not include personal information of patients.

4-2 The way to collect and evaluate the data

The questionnaire by mail.

*Data

1) The number of cases of IDPO by histopathological diagnosis that experienced

2) The timing of diagnosis of IDPO

3) The number of cases of IDPO diagnosed by only chest CT and no histopathological findings that experienced.

4) Whether or not survey cooperation is possible.

We aggregate the results.

4-3 Period of study

From the date approved by the institutional ethics committee in Tokushima University to March 31,2019.

4-4 Data management

PI storages the answer sheets in lockable shelfs. Only this study can use these answers.

4-5 Data transfer

Not applicable

5. BURDEN, BENEFIT AND RISK FOR PRTCIPANTS

Not applicable

6. INFORMED CONSENT

6-1 The way of consent

Not applicable

6-2 The document of consent

Not applicable

7. PRIVACY PROTECTION

The answer sheets are storage in lockable shelfs.

8. HEALTH DAMAGE COMPESATION

Not applicable

9. CHANGES OF STUDY

When this protocol is changed something, principal investigator reports the change to the director of Tokushima university hospital. This study will continue after another approval.

10. END, DISCONTINUATION AND INTERRUPTION OF STUDY

When PI terminates or stops this study, he reports it to the director of Tokushima university hospital with documents within three months.

11. HANDOLING AND STORAGE OF DATA AND DOCUMENTS

The storage manager, PI handholds and storages all data and documents in lockable shelfs for five years from termination of this study.

12. PUBLIC DISCLOSURE AND PUBLICATION POLICY

Publication is the responsibility of PI.

13. ANNUAL PROGRESS REPORT

PI reports the research status report to the director of Tokushima university hospital each year.

14. FUNDING AND CONFLICT OF INTEREST

This work was partly supported by a grant to the Ministry of Health, Labour and Welfare, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases in Japan. Clinical Research Conflict of Interest Review Committee in Tokushima university hospital approves conflict of interest of this study.

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A nationwide epidemiological survey of idiopathic dendriform pulmonary ossification

(Secondary survey)

Principal investigator: Yasuhiko Nishioka，M.D., Ph.D.
Professor and Chairman
Department of Respiratory Medicine and Rheumatology
Graduate School of Biomedical Sciences, Tokushima University

July 7, 2018

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1.INTRODUCTION AND RATIONALE

Pulmonary ossification was pathologically noticed as the condition showing bone formation with or without marrow components appeared in the bilateral lung parenchyma[1]. The first case was reported in 1856 by Luschka[1]. The early representative reports of autopsy cases showed that most were affected by underlying diseases[2, 3]. However, since the 1970s, the number of reports of idiopathic cases with diffuse pulmonary ossification have been increasing[4-7]. In the 2000s, several case reports have reported idiopathic pulmonary ossification without underlying pulmonary or systemic diseases[6-8]. The information from these reports suggested quite homogenous clinical features such as male-predominance, asymptomatic disease, and branching-type ossification on HRCT and/or histological studies, but there is no comprehensive study that analyzed the clinical features including onset, pulmonary function, complication, clinical course, and prognosis in addition to radiological and histopathological details.

We, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases in Japan, conducted a nationwide study to clarify the clinical findings of idiopathic cases of pulmonary ossification in Japan. Therefore, we used the term idiopathic pulmonary dendriform ossification (IDPO) in the present study. The primary survey revealed 50 cases in 32 institutions.

2. OBJECT

We collected the data of these cases: clinical feature, examined data of blood and pulmonary function test (PFT), chest radiography and high-resolution CT (HRCT) scans, and pathological specimens. We aimed to reveal the features of IDPO and present diagnostic guidelines for IDPO.

3. PARTICIPANTS

3-1 Inclusion criteria

Patients with diffuse pulmonary ossification diagnosed pathologically without any underlying disease were included.

3-2 Exclusion criteria

3) Patients with diffuse pulmonary ossification diagnosed pathologically with any underlying disease as follows: [9]

I. Preexisting pulmonary disorder

A. Idiopathic pulmonary fibrosis
B. Pulmonary amyloidosis
C. Chronic busulfan therapy
D. Acute respiratory distress syndrome
E. Hamman-Rich syndrome
F. Sarcoidosis
G. Histoplasmosis
H. Tuberculosis
I. Metastatic breast cancer
J. Pulmonary metastases of osteogenic sarcoma
K. Metastatic melanoma

II. Preexisting cardiac disorder

A. Mitral stenosis

Nishioka Y, *et al. BMJ Open Resp Res* 2022; 9:e001337. doi: 10.1136/bmjresp-2022-001337

B. Chronic left ventricular failure

C. Idiopathic hypertrophic subaortic stenosis

III. Preexisting extracardiopulmonary disorder

A. Primary and secondary hyperparathyroidism

B. Hypervitaminosis D

C. Pyloric stenosis with alkalosis

Patients with other pulmonary diseases except pulmonary ossification

3-3 Dropout criteria

Patients to be decided as dropouts and cancelled by the principal investigator (PI).

4. METHODS

4-1 Data collection

4-1-1 Data

The following data at both the diagnosis and latest follow-up were collected (see the data sheet shown in the Supplementary Table 1). All data were already existing and not tested only for this study.

1) Background of patients
2) Physical findings
3) Laboratory data
4) Chest image (chest radiography and HRCT)
5) Pathological slides

Any identifying data were removed and anonymized. Each institution managed the data using the correspondence table. This study was approved by the ethics committee in each institution for using the patients' data.

4-1-2 The detailed data

1) Background of patients

   Sex, date of diagnosis, age at diagnosis, diagnostic opportunity, method of diagnosis, complications, medical history, family history of IDPO, smoking history, occupational history, et al.

2) Findings at diagnosis

   Symptoms

   Physical findings (height, body weight, blood pressure, heart rate, lung sounds, SpO_2, et al.)

   Blood test data (CBC, liver function, renal function, thyroid function, intact PTH, calcitonin, vitamin D, HbA1c, BNP, KL-6, et al.)

   Urinary test data, arterial blood gas analysis, pulmonary function test, electro-cardiogram, echocardiography

   Chest radiography, HRCT

   Transbronchial biopsy, bronchoalveolar lavage, surgical lung biopsy, autopsy

3) Findings at the latest follow-up

   Last confirmation date, age, SpO_2, arterial blood gas analysis, drug therapy, oxygen therapy, recent chest radiography, recent HRCT, recent pulmonary function test, survival

4-1-3 Evaluation of data

The data were aggregated and analyzed clinically, radiologically and histopathologically by specialists of the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable

Diseases

4-2 Period of study

From the date approved by the institutional ethics committee in Tokushima University to March 31, 2022.

4-3 Data management

PI will store the answer sheets in lockable shelfs. The collected data will be used only for this study.

4-4 Data transfer

The questionnaire sheet was sent by mail or via the internet. Chest images were copied on CD-ROM and sent by mail. The pathological slides were sent by mail. All data were anonymized. The principal investigator (PI) stored them in lockable shelfs.

5. BURDEN, BENEFIT AND RISK FOR PRTCIPANTS

Not applicable for observational study

6. STATISTICAL ANALYSIS

Not applicable

7. INFORMED CONSENT

7-1 The way of consent

By opt-out because all the collected data were already existing and anonymized.

7-2 The document of consent

Each institution has the documents for opt-out, following the rules.

8. PRIVACY PROTECTION

We protected the privacy of subjects by identifying them with a research subject identification code. When publishing the results of this research, the privacy of the research subjects will be protected as well.

9. HEALTH DAMAGE COMPESATION

Not applicable

10. CHANGES OF STUDY

When this protocol is changed, the PI will report the change to the director of Tokushima university hospital. This study will continue after another approval.

11. END, DISCONTINUATION AND INTERRUPTION OF STUDY

When the PI terminates or stops this study, he will report it to the director of Tokushima university hospital with documents within 3 months.

12. HANDLING AND STORAGE OF DATA AND DOCUMENTS

The storage manager, i.e., the PI, will retain and store all data and documents in lockable shelfs for 5 years

from termination of this study.

13. PUBLIC DISCLOSURE AND PUBLICATION POLICY

Publication is the responsibility of PI.

14. ANNUAL PROGRESS REPORT

PI will report the research status to the director of Tokushima university hospital each year.

15. FUNDING AND CONFLICT OF INTEREST

This work was partly supported by a grant to the Ministry of Health, Labour and Welfare, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases in Japan. The Clinical Research Conflict of Interest Review Committee in Tokushima university hospital approved the conflict of interest of this study.

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