

[CASE REPORT]

Diffuse Pulmonary Ossification with Connective Tissue Weakness Potentially Due to Vascular Ehlers-Danlos Syndrome

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Abstract:

A 30-year-old non-smoking man was referred to our hospital for the further examination of abnormal shadows revealed by chest X-ray. He had mild shortness of breath. Chest computed tomography revealed a fine-grained dendritic shadow with diffuse calcification in both lungs and as well as emphysematous changes in the upper lung lobes. A surgical lung biopsy histology revealed diffuse pulmonary ossification complicated with lung laceration, vascular disruption, hemosiderosis, and emphysema, suggesting vascular Ehlers-Danlos syndrome (vEDS). However, the patient had no external physical signs or family history of vEDS and no COL3A1 gene mutations. We are closely monitoring this patient in the clinic.

Key words: diffuse pulmonary ossification, vascular Ehlers-Danlos syndrome, ectopic bone formation, diffuse lung disease, emphysematous changes

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Introduction

Diffuse pulmonary ossification (DPO) is a rare disease characterized by widespread ectopic bone formation in the lung (1, 2). Because patients with DPO are usually asymptomatic and cannot be identified by simple chest X-ray, the diagnosis is often based on surgical pathology or post-mortem specimens (1, 3). DPO is classified into either nodular or dendriform types, each of which can be further categorized as idiopathic or secondary (1, 3). Although secondary DPO is usually associated with underlying pulmonary or heart disease, some cases are associated with vascular Ehlers-Danlos syndrome (vEDS), which can be caused by mutations in the type III collagen gene COL3A1 (4).

We herein report a case of DPO associated with pathological evidence of weak connective tissue, suggestive of vEDS.

Case Report

A 30-year-old man who had never smoked underwent a general medical examination for the first time in December

2017. Abnormal shadows on chest X-ray were found at this time. In January 2019, he was referred to our hospital for a further examination. He stated that he had not experienced coughing or produced sputum, but he had mild shortness of breath (mMRC grade 1). The patient's medical history was generally unremarkable but did include keratosis pilaris and a history of allergies. There was no significant family history of specific illness, including genetic disease or any disease resulting from consanguineous marriage. The patient was not taking any commonly used medicines or supplements. He had worked in a company cleaning restaurants and hospital drainpipes for about two years prior to the first examination.

The patient's height was 171 cm, weight 90 kg, body temperature 36.7 °C, pulse rate 97 bpm, and percutaneous oxygen saturation (SpO₂) 99 % (in room air). His conjunctiva were neither anemic nor icteric. A physical examination revealed no respiratory or cardiovascular abnormalities, and no crackles or murmurs were heard on chest auscultation. He did have spiny papules on the arms but did not exhibit clubbed fingers, leg edema, or superficial lymphadenopathy.

A peripheral blood test showed no inflammatory findings but a slight elevation of lactate dehydrogenase, creatine

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Table. Laboratory Findings.

Hematology		Serology		Pulmonary function tests	
WBC	9,280 / μ L	CRP	0.31 mg/dL	VC	3.34 L
Nt	65.7 %	ESR1h	2 mm	%VC	73.9 %
Ly	25.1 %	ESR2h	4 mm	FVC	3.31 L
Mo	6.6 %	KL-6	163 U/mL	%FVC	72.1 %
Eo	1.7 %	SP-D	475 ng/mL	FEV1	2.39 L
RBC	568 \times 10 ⁴ / μ L	CH50	\geq 60 U/mL	%FEV1	58.8 %
Hb	17.2 g/dL	C3	153 mg/dL	FEV1/FVC	72.2 %
Hct	50.6 %	C4	29 mg/dL	DLCO	16.4 mL/min/Torr
Plt	32.2 \times 10 ⁴ / μ L	IgG	975 mg/dL	%DLCO	53.4 %
Biochemistry		IgA	207 mg/dL	DLCO/VA	4.21 mL/min/Torr/L
TP	7.8 g/dL	IgM	48 mg/dL	%DLCO/VA	75.2 %
Alb	5.24 g/dL	IgE	55 mg/dL	6-min walking test	
AST	26 IU/L	ANA	< \times 40	Distance	645 m
ALT	37 IU/L	Anti-ARS Ab	<5.0 index	Borg Scale	
γ GT	24 IU/L	RF	<4 IU/mL	Min	0
LD	232 IU/L	ACE	18.4 U/L	Max	8
CK	377 IU/L	sIL-2R	286 U/mL	Pulse rate	
T-Bil	1.5 mg/dL	T-SPOT®	(-)	117	bpm
ALP	194 U/L	ESAT-6	0 Min	169	bpm
Na	144 mEq/L	CFP10	2 Max	SpO ₂	
K	3.9 mEq/L	intact PTH	57 pg/mL	Min	97 %
Ca	9.8 mg/dL	1,25-dihydroxyvitamin D ₃	45.6 pg/mL	Max	88 %
BUN	11 mg/dL				
Cr	0.94 mg/dL				



Figure 1. Chest X-ray showing diffuse reticulogranular shadows in the bilateral lung fields from the middle to the bottom and volume loss in the lungs.

kinase, and total bilirubin. However, these parameters normalized spontaneously. Intact parathyroid hormone and 1,25-dihydroxyvitamin D₃ levels were within the normal range (Table). Pulmonary function tests showed moderately restrictive changes with a reduced diffusion capacity (Table). A 6-minute walking test showed desaturation (minimum SpO₂ of 88% while walking) (Table). Neither an electrocardiogram nor an echocardiogram revealed any abnormalities. Chest radiography revealed diffuse reticulogranular shadows in the bilateral lung fields from the middle to the bottom

and volume loss within the lungs (Fig. 1). Chest high-resolution computed tomography (HRCT) demonstrated fine-grained dendritic shadows and small nodules with diffuse calcification throughout the lungs but mainly in the lower lobes, and as well as emphysematous changes in the upper lobes (Fig. 2). Bone scanning with Tc-99 m hydroxymethylene diphosphate did not clearly show any uptake of tracer in the bilateral lung fields. Based on the chest HRCT findings, we suspected DPO and performed a surgical lung biopsy from the right S3 and S5 for the diagnosis. Thoracoscopy showed macroscopically ragged visceral pleura (Fig. 3). Both specimens had almost identical pathological features.

The essential features were the presence of irregular-shaped ossifications with bone marrow formation and surrounding fibrosis as well as compression of the normal lung structure (Fig. 4b). Laceration of the lung tissue, including the interlobular septum, at the central area (Fig. 4c), mild hemosiderosis (Fig. 4d), and irregular-shaped emphysema were also visible. Disruption of the pulmonary artery was confirmed by Elastica Van Gieson staining (Fig. 4c). These pathological features suggested that DPO might also be accompanied by diseases of weak connective tissue, such as vEDS, in this patient.

With the patient's consent, we conducted genetic testing for COL3A1 gene mutations, but none were found. The patient also had no external physical signs of vEDS, such as skin hyperextensibility and hemoptysis, and there was no family history of the disease. Therefore, we are carefully

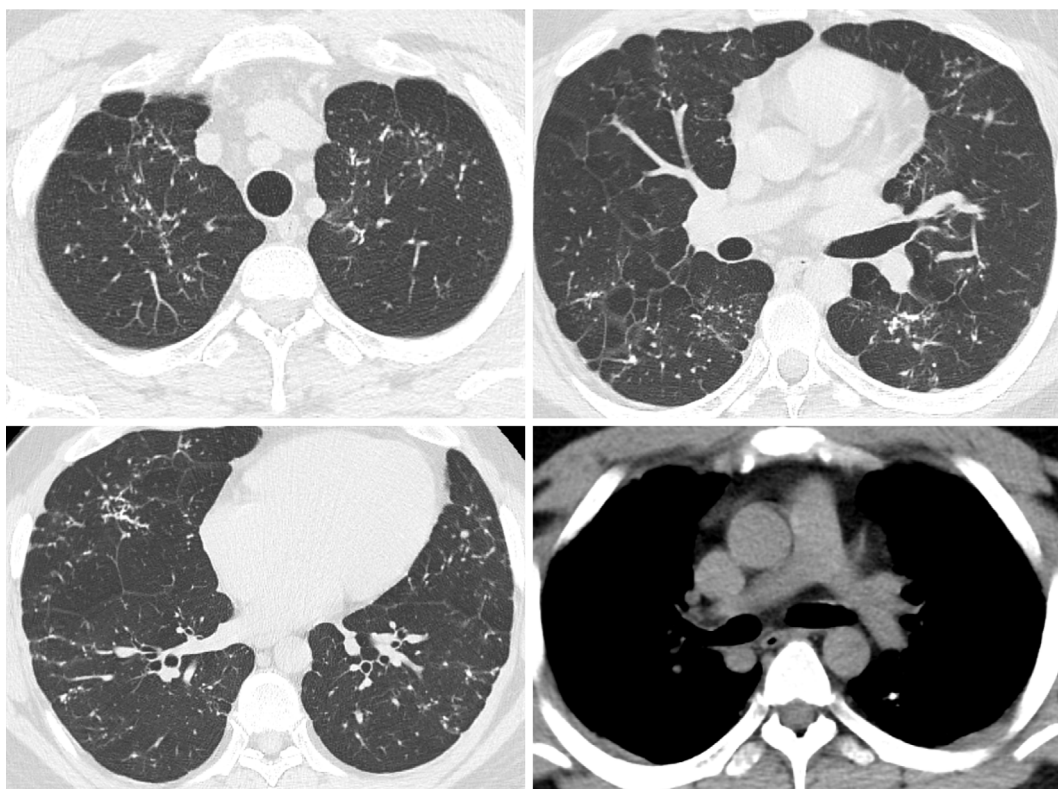


Figure 2. Chest HRCT images depicting fine-grained dendritic shadows and small nodules with diffuse calcification throughout the lungs, mainly in the lower lobes, and emphysematous changes in the upper lobes.

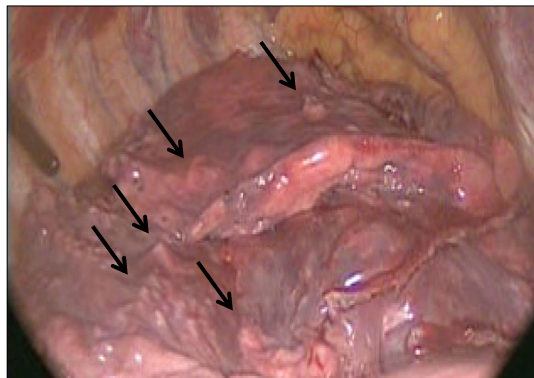


Figure 3. Thorascopic findings showing macroscopically ragged visceral pleura (arrows).

monitoring this patient and have not observed any marked changes in chest imaging results or his pulmonary function over the past two years.

Discussion

This is a case report of a patient who was diagnosed with DPO following a routine general medical examination and then underwent a surgical lung biopsy. DPO is a rare disease that was first reported by Luschka in 1856 (5). In general, individuals with DPO are asymptomatic, and are usually diagnosed indirectly during an autopsy (1-3). Tseung et al. reported that the frequency of DPO was 0.16% and that

the median patient age was 72 (range 32-91) years old, with 88% of affected individuals being men (2). Recently, cases of DPO in younger people have been identified during unrelated medical examinations and thus are diagnosed while the individuals are still alive (6, 7).

DPO is classified into either nodular or dendriform types, each of which can be further categorized as idiopathic or secondary (1, 3). Nodular ossification is characterized by the presence of rounded intra-alveolar bone fragments within the alveolar spaces, which are usually devoid of marrow elements. In contrast, dendriform ossification is characterized by branching osseous structures of mature lamellar bone, often containing marrow, and usually arising within the alveolar septa (2). Nodular ossification is frequently associated with chronic congestion caused by preexisting cardiac disease, such as mitral stenosis. Dendriform ossification is frequently associated with acute and chronic inflammatory lung injury caused by preexisting pulmonary disease, such as idiopathic pulmonary fibrosis, pulmonary amyloidosis, acute respiratory distress syndrome, chronic obstructive pulmonary disease, or asbestosis, and idiopathic cases are also common (8, 9).

The present patient had a case of dendriform pulmonary ossification with widespread formation of ectopic bone containing fatty marrow in the lungs. We initially concluded that this case was idiopathic because the patient had no particular medical history, such as cardiac or pulmonary disease. However, the patient had additional findings that sug-

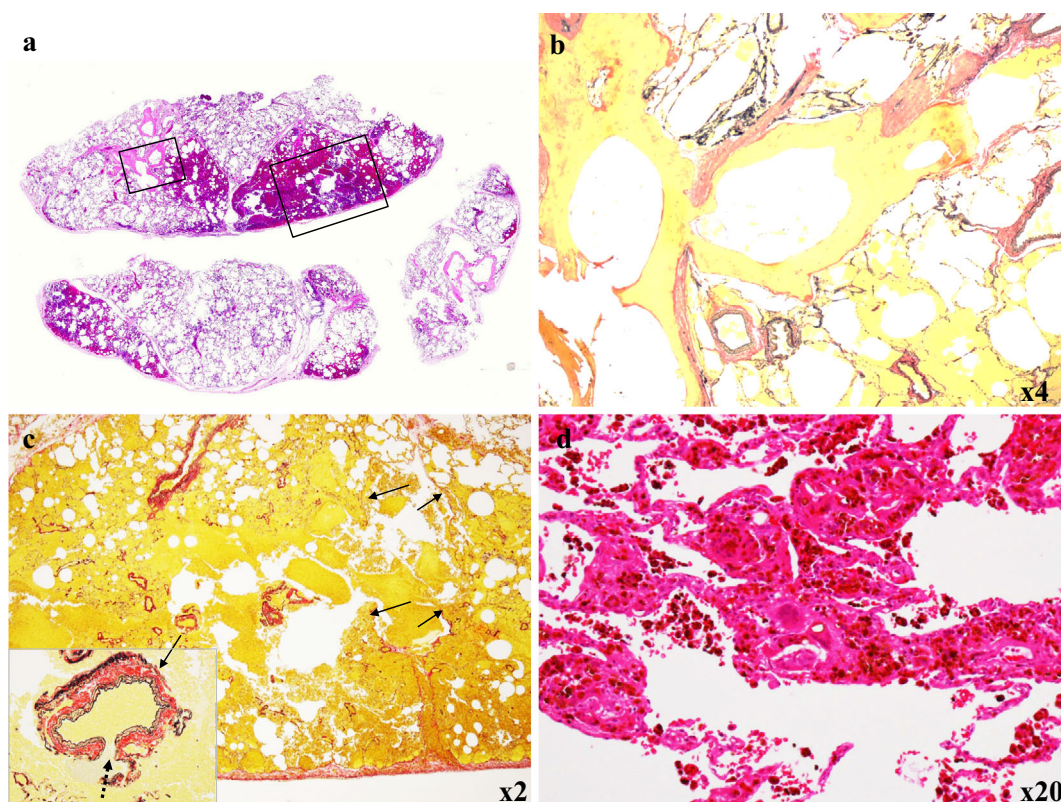


Figure 4. Histological features of surgical lung biopsies. (a) Panoramic view showing hemorrhaging and ossification with bone marrow formation (box). Hematoxylin and Eosin (H&E) staining. (b) Histological features of ossification with bone marrow formation, compression of the normal lung structure, and signs of collagenosis (brown band). Elastica Van Gieson staining (EvG), $\times 40$. Box of (a). (c) Laceration of the interlobular septum (arrows) and the surrounding lung and laceration of the pulmonary artery (inset, dotted arrow). EvG, $\times 20$. Box of (a). (d) Hemosiderosis mainly located in the alveolar lumina or lumens. H&E staining, $\times 200$.

gested a more complex diagnosis. These included emphysematous changes on HRCT with physiologically obstructive ventilatory impairment despite being a non-smoker as well as histological evidence of weak connective tissue, such as laceration of the lung tissue and vascular disruption, hemosiderosis, and irregular-shaped emphysema. Given the compression of the lung tissue in the absence of elastic tissue in the ossifications, the latter might have resulted from hematoma formation followed by organization and ossification (4). These clinical and pathological features suggest that DPO is not primary but secondarily related to weak connective tissue diseases, including vEDS.

EDS refers to a group of genetic disorders of connective tissue resulting from a deficiency in synthesizing normal collagen. EDS used to be classified into 6 major types, but 13 subtypes are now recognized and are described in the international classification of 2017. These are caused by genetic mutations of specific collagen-encoding genes or enzymes that process collagen (10, 11). Most cases of EDS in which the lungs are affected are of the vascular type and associated with bloody sputum, hemoptysis, and pneumothorax (11, 12). vEDS can also cause secondary DPO because of chronic repetition of hemorrhaging and hemostasis in the lung (4). We tested the present patient for mutations of the

COL3A1 gene, as these mutations cause vEDS (10) and are detected in over 95% of vEDS patients (12), but none were found.

We suspected secondary DPO due to vEDS based on the pathological findings. However, we were unable to confirm this because of the negative genetic test results and lack of characteristic physical signs or a family history of the disease. The possibility remained that genetic mutations might be undetected by a sequence analysis. Respiratory findings were the initial symptoms, but systemic findings, such as asymptomatic aneurysm and arterial dissection, may have been the underlying causes. Of note, about 50% of vEDS patients have a *de novo* pathogenic variant (12). Because it causes blood vessel fragility, vEDS can result in life-threatening complications, such as arterial rupture and trauma, or intestinal or uterine rupture (10). Given these possibilities, individuals such as the patient described in this case report must be placed under close observation.

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

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References

1. Kanne JP, Godwin JD, Takasugi JE, Schmidt RA, Stern EJ. Diffuse pulmonary ossification. *J Thorac Imaging* **19**: 98-102, 2004.
2. Tseung J, Duflou J. Diffuse pulmonary ossification: an uncommon incidental autopsy finding. *Pathology* **38**: 45-48, 2006.
3. Peroš-Golubičić T, Tekavec-Trkanjec J. Diffuse pulmonary ossification: an unusual interstitial lung disease. *Curr Opin Pulm Med* **14**: 488-492, 2008.
4. Kawabata Y, Watanabe A, Yamaguchi S, et al. Pleuropulmonary pathology of vascular Ehlers-Danlos syndrome: spontaneous laceration, haematoma and fibrous nodules. *Histopathology* **56**: 944-950, 2010.
5. Luschka H. Verästigte Knochenbildung im Parenchym der Lungen. *Virchow Arch* **10**: 500-505, 1856 (in German).
6. Mizushima Y, Bando M, Mato N, et al. A rare case asymptomatic diffuse pulmonary ossification detected during a routine health examination. *Intern Med* **51**: 2923-2927, 2012.
7. Anan K, Hisanaga J, Kawamura K, Ichikado K. Dendriform pulmonary ossification. *Intern Med* **58**: 1043-1044, 2019.
8. Lara JF, Catroppo JF, Kim DU, da Costa D. Dendriform pulmonary ossification, a form of diffuse pulmonary ossification: report of a 26-year autopsy experience. *Arch Pathol Lab Med* **129**: 348-353, 2005.
9. Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI. Calcium deposition with or without bone formation in the lung. *Am J Respir Crit Care Med* **15**: 1654-1669, 2002.
10. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* **342**: 673-680, 2000.
11. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* **175**: 8-26, 2017.
12. Peter HB. Vascular Ehlers-Danlos syndrome In: *GeneReviews at GeneTests: Medical Genetics Information Resource (database online)*. University of Washington, Seattle, 1997-2015 [Internet]. [cited 2021 Jan 18]. Available from: <http://www.genetests.org>.

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