



## Case report

# A case of diffuse pulmonary lymphangiomatosis with a venous anomaly presenting with acute respiratory failure and hemoptysis

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## ABSTRACT

Diffuse pulmonary lymphangiomatosis (DPL) is a rare lymphatic disease that can cause diverse respiratory symptoms. A 22-year-old man, whose chest CT had shown an abnormality for years, presented with acute respiratory failure due to the abrupt onset of hemoptysis. The diagnosis of DPL was confirmed by surgical lung biopsy and lymphangiography. Histopathological investigation showed dilated vascular and lymphatic vessels. DPL can cause acute and life-threatening symptoms during its chronic clinical course. A coexisting anomaly in the venous system may be present in DPL patients with hemoptysis.

## 1. Introduction

Diffuse pulmonary lymphangiomatosis (DPL) is an extremely rare lymphatic disease characterized by infiltration of dilated lymphatic vessels into the lungs [1]. The disease usually progresses slowly and causes several chronic respiratory symptoms, such as exertional dyspnea, cough, and hemoptysis [1]. Abnormal findings on imaging studies are sometimes the only manifestation in patients with DPL. However, little is known about the development of acute symptoms and the pathology in DPL because of its rarity. The case of a patient with DPL with a coexisting venous anomaly diagnosed by surgical lung biopsy (SLB) and lymphangiography after presenting with acute respiratory failure and hemoptysis is presented.

## 2. Case report

A 22-year-old man with no significant medical history presented with dyspnea and hemoptysis of sudden onset. He had been once referred to our department for an abnormal shadow on a chest X-ray and computed tomography (CT) two years before this admission. According

to the medical record, intermittent hemoptysis started at the age of 15 years, and a thoracic abnormal shadow had already been noted on a medical check-up in his high school. When he first came to our hospital, the chest X-ray showed bilateral infiltration, in addition to dilation of the mediastinum (Fig. 1A). Chest CT showed abnormally enlarged soft tissue surrounding the mediastinum and pericardial area, as well as peribronchovascular and interstitial septal thickening (Fig. 1B and C). Thoracic magnetic resonance imaging (MRI) showed T2 high-intensity dilated soft tissue in the mediastinum and bilateral hilar areas (Fig. 1D). DPL was suspected, and further diagnostic investigations were planned. However, he was lost to follow-up because he was asymptomatic and was reluctant to obtain a definite diagnosis of such a difficult-to-treat disease.

On the current admission, SpO<sub>2</sub> was 98% while breathing oxygen at 2 L/min, blood pressure was 154/97 mmHg, and other vital signs were normal. On physical examination, coarse crackles were heard on the right side of his chest. Laboratory examination showed no abnormal findings. Chest CT showed ground-glass opacities, reflecting the current alveolar hemorrhage, in addition to enlargement of the mediastinum and the interstitial septal thickening that had already been seen on

**Abbreviations:** DPL, Diffuse pulmonary lymphangiomatosis; SLB, surgical lung biopsy; CT, computed tomography; MRI, magnetic resonance imaging; GLA, generalized lymphatic anomaly; ISSVA, the International Society for the Study of Vascular Anomaly; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

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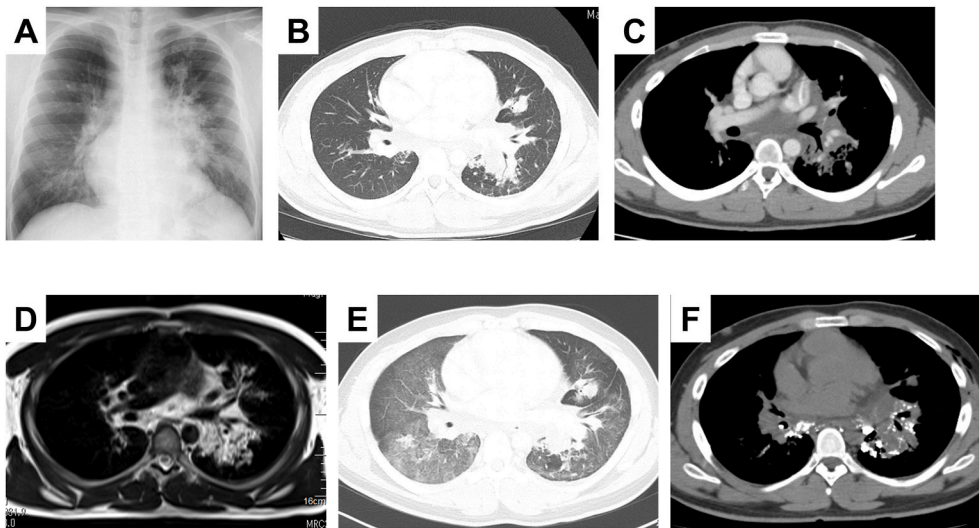
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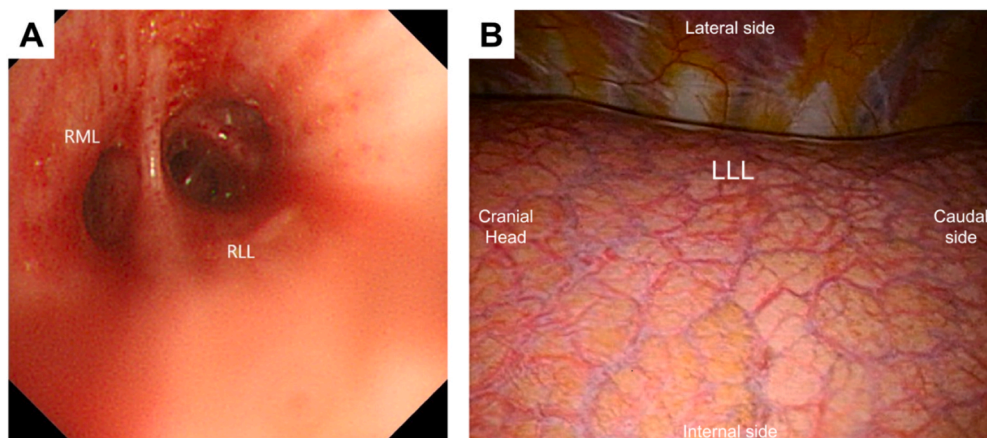
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**Fig. 1.** Imaging studies. (A) A chest X-ray at the time of the first visit showing enlargement of the mediastinum. (B) Chest CT with the lung window at the time of the first visit showing the infiltrations around bilateral hilar areas. (C) Chest CT with the soft-tissue window at the time of the first visit showing the enlarged soft-tissue infiltration in the mediastinum. (D) Thoracic MRI at the time of the first visit showing the T2 high-intensity dilated soft tissue in the mediastinum and bilateral hilar areas. (E) Chest CT with the lung window on admission showing ground-glass opacities in addition to the infiltrations already confirmed on the previous CT. (F) CT taken 24 hours after intranodal lymphangiography. Lipiodol accumulation is confirmed in the mediastinum and bilateral hilar areas.



**Fig. 2.** Gross findings. (A) Bronchoscopic findings. A view of the right bronchus intermedius showing a diffuse erythematous mucosa and clots. RML, right middle lobe; RLL, right lower lobe. (B) Thoracoscopic findings of pleural surface showing yellowish pleura with diffuse telangiectasia. LLL, left lower lobe.

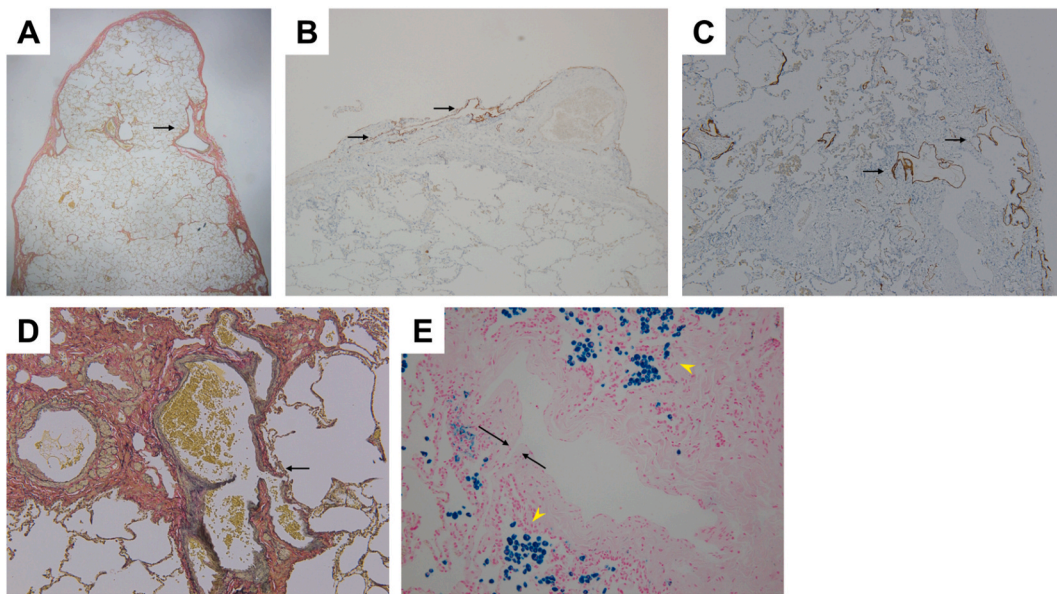
previous CT scans (Fig. 1E). On bronchoscopy, diffuse mucosal erythematous change and uncountable clots were reported (Fig. 2A). Transbronchial lung biopsy showed lung tissue with mild fibrosis and hemorrhage, but it failed to confirm any particular disease. Hemoptysis stopped after the admission without any medication or intervention, and his acute respiratory failure improved accordingly.

Therefore, he underwent SLB to make a definite diagnosis. Thoracoscopy showed yellowish pleura with diffuse telangiectasia (Fig. 2B). Histologically, the SLB samples taken from segments 6 and 10 of the left lung showed dilated lymphatic vessels and veins in the subpleural area and interlobular septa (Fig. 3A–C). Dilated veins showed heterogeneity in wall thickness and a vulnerable area leading to alveoli (Fig. 3D). Prussian blue staining showed hemosiderin-laden macrophages around these dilated vessels, suggesting past alveolar hemorrhage (Fig. 3E). After SLB, he underwent intranodal lymphangiography. CT obtained after lymphangiography with lipiodol showed accumulation of lipiodol in the dilated mediastinal soft tissue, pericardium, and bilateral hilar areas (Fig. 1F). The contrast medium gradually spread into both lungs through the interlobular septa and peribronchovascular bundles. A diagnosis of DPL was confirmed based on these findings. Medical treatment with sirolimus was planned.

### 3. Discussion

The present report described a case of DPL with acute respiratory symptoms for the first time in his life since a thoracic disorder had been suspected due to abnormal imaging studies. Management of the acute symptoms was achieved by supportive therapy, such as oxygen and rest, in this case.

Lymphatic anomaly is a progressive disease, and involvement of the pulmonary system is known to be a risk factor for mortality in generalized lymphatic anomaly (GLA) [2]. However, since standard clinical studies on DPL are scarce, the clinical course and the prognosis can only be approximated based on the previous case reports and case series. Although most of the previously reported cases presented with chronic symptoms such as exertional dyspnea and cough, attention should be paid to the fact that a small number of patients present with acute and intense respiratory failure due to hemoptysis [3–5]. Libby et al. reported a case of GLA involving thoracic lesions who underwent lobectomy due to uncontrollable massive hemoptysis [3]. The underlying mechanism of such acute exacerbation has not been precisely documented in the previous literature. In the present case, histopathological investigation showed dilated veins with heterogeneity in wall thickness, as well as dilated lymphatic vessels. In addition, hemosiderin-laden macrophages were found around the fragile veins. These findings may explain the mechanism of acute alveolar hemorrhage in DPL. Furthermore, this



**Fig. 3.** Histopathological findings of the lung. (A) Elastica van Gieson staining,  $\times 12.5$ , showing dilated venous vessels in the subpleural area (arrow). (B) (C) D2-40, magnification  $\times 100$ , showing dilated lymphatic vessels in the subpleural area (arrows). (D) Elastica van Gieson staining, magnification  $\times 100$ , showing irregularity in vascular wall thickness and a vulnerable area leading to alveoli (arrow). (E) Prussian blue staining, magnification  $\times 200$ , showing hemosiderin-laden alveolar macrophages (arrowheads) around dilated veins (arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

coexisting venous anomaly may bring new insight into clinically diagnosed DPL. Dilated veins formed secondary to the primary lymphatic malformation are sometimes found in imaging studies. On the other hand, the vascular anomalies classification by the International Society for the Study of Vascular Anomaly (ISSVA) defines combined vascular malformations as two or more vascular malformations in one lesion [6]. Such combined anomalies in the lung is extremely rare. To the best of our knowledge, only one case report explained a lymphatic malformation with venous anomalies [7]. Given the diffuse dilation in veins in the specimen, the present case may correspond to one of the combined vascular malformations, lymphatic-venous malformations. In clinical DPL patients with hemorrhage, a combined venous anomaly may be a cause of alveolar hemorrhage.

Recently, reports on the effectiveness of sirolimus for vascular anomaly have emerged [8–10]. The effectiveness of sirolimus is due to dual inhibition of mammalian target of rapamycin (mTOR) and the vascular endothelial growth factor (VEGF) pathway [11]. The shrinkage of target lesions and the improvement of related symptoms by sirolimus has been reported in lymphatic anomalies [9], and the response rate increases with treatment duration [10]. Given this evidence, sirolimus was chosen as the most promising treatment option for this patient who had both lymphatic and venous malformations.

In conclusion, acute respiratory failure due to hemoptysis is a rare but important symptom in patients with DPL. A microscopic venous anomaly may be present in addition to the lymphatic anomaly in patients with hemoptysis.

#### Informed consent

Appropriate consent, permissions and releases were obtained from the patient before submission.

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#### Declaration of interest

Masayuki Hojo reports personal fees (honoraria) from AstraZeneca, Boehringer-Ingelheim, GlaxoSmith Kline, Novartis Pharma, outside the submitted work.

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