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CASE REPORT

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Clinical characteristics and genetic analysis of a patient with diffuse pulmonary lymphangiomatosis: a case report and literature review

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Abstract

Background Diffuse pulmonary lymphangiomatosis (DPL) is a rare pulmonary disorder, which affects the lymphatic channels from the mediastinum to the pleura. DPL is often misdiagnosed or missed due to the lack of clear specificity and definitive medical therapies. In most cases, the disease progresses to chronic morbidity or even death.

Case presentation Here, we have reported a case of DPL in a 17-year-old boy who presented with hemoptysis and progressive breathlessness. The diagnosis was confirmed based on the typical imaging features observed through high-resolution computed tomography, chest magnetic resonance imaging, and lymphangiography. Furthermore, we have presented the genetic characteristics of the patient and his parents and discovered the following heterozygous variants of *BCL6*: NM_001706: exon5: c. A463G (p.M155V) and *ATM*: NM_000051: exon3: c.A107G (p.D36G). The patient underwent treatment with sirolimus for 2 months; his clinical symptoms disappeared completely, and the mediastinum soft mass shrank dramatically.

Conclusions Early diagnosis of DPL is challenging for clinicians, and imaging plays an important role in determining the location and severity of the disease. The gene mutation detected in this study may facilitate the pathogenesis of DPL. Sirolimus can prevent further disease progression in the short term, which may be an effective and safe therapeutic alternative for treating DPL.

Keywords Diffuse pulmonary lymphangiomatosis, Mediastinum mass, Lymphangiography, Sirolimus

Background

Diffuse pulmonary lymphangiomatosis (DPL) is a very uncommon disease characterized by abnormal proliferation and dilatation of lymphatic channels, which often involves soft tissues, mediastinum, lungs, spleen, and bone [1–4]. The precise incidence, etiology and pathogenesis of DPL are lacking because most studies are based on case reports [1, 2, 5–17]. DPL occurs mostly in children and is rare in adults, with no significant difference in sex distribution. Dyspnea, cough, chest pain and hemoptysis are the major symptoms of DPL. However, the disease was often misdiagnosed or missed due to a clear specificity, and the literature on the genetic

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characteristics of DPL is inadequate. Here, we have presented the case of a young man with DPL, who was diagnosed based on typical imaging features. We performed the whole-exome sequencing of the patient and his parents, and we believe that the identified mutation may be the underlying cause of DPL development.

Case presentation

On December 22, 2022, a 17-year-old boy was admitted to our hospital with a history of intermittent hemoptysis and coughing for the past 4 months. His symptoms gradually worsened, and he experienced breathlessness for more than 10 days. Notably, 10 days before his admission, he completed isolation and symptomatic treatment for coronavirus disease (covid)−19 and presented with symptoms of fever and sputum production. At the age of 3 years, he had undergone total splenectomy at Children's Hospital for diffuse splenic hemangioma. He had recovered well and lived a normal daily life. However, 2 years ago, he visited several hospitals to seek clarification regarding the gradually growing mass in his mediastinal, which was discovered during a routine chest X- ray examination, although he did not experience any associated pain or discomfort. In the following 2 years, he felt chest pain occasionally as well as shortness of breath when indulging in some intensive exercises, such as running and playing basketball. On a routine visit to doctors, a mass, suspected to be lymphoma, sarcoidosis, or other malignant tumor, was detected. Positron emission tomography- computed tomography (PET-CT) revealed soft tissue density shadows filling the mediastinum around the pericardium and mixed and local liquid density; the metabolism of the mass was similar to that of the mediastinal blood pool, because of which systemic inflammatory or connective tissue-derived lesions was considered initially. Multiple enlarged lymph nodes and patchy shadows with low metabolism observed around the gastric fundus, cardia, and retroperitoneum were considered to be homologous with the soft tissue of the mediastinum. Accordingly, the patient underwent a mass biopsy twice via fine-needle aspiration (FNA) in the chest a year ago, and the pathological examination revealed small strips of fat, small blood vessels, and chronic inflammation of fibrous connective tissues in the tissue, but no tumor cells or inflammatory cells. Neither a tumor nor any known systemic inflammation or connective tissue disease of the mass was diagnosed; therefore, the boy did not receive any specific treatment for the mass. Cough, sputum, and intermittent hemoptysis were new symptoms that started showing 4 months ago. The patient's chest CT revealed soft tissue infiltration in the mediastinum was significantly larger than that detected earlier before (10 months ago); accordingly, he was prescribed diuretics and hemostatic drugs to alleviate his symptoms. The patient had no history of smoking, alcohol or drug abuse. He had no brothers or sisters, and both his parents were healthy.

The patient was sent into the ward in a wheelchair, and he could not lie down due to serious coughing and worsened dyspnea. His physical examination revealed T 37.0℃ HR122 bpm RR 20 bpm BP 97/65mmHg SpO2 85% (on room air). No enlarged lymph nodes were detected in superficial area (including the bilateral neck, supraclavicular, armpits, and inguinal regions). Thin moist rales were heard in both lower lung fields, but without edema in his lower limbs. His blood test routine showed a higher white blood cell count of 14.04×10^9/L (3.5–9.5) ↑, red blood cell count of 4.39×10^{12}/L (4.3–5.8) and platelet count of 350×10^9/L (125–350). Arterial blood gas showed an oxygen partial pressure of 63 mmHg with inhalation of 33% oxygen concentration. The c-reactive protein level was 41.33 mg/L (0–10) ↑, the brain natriuretic peptide was 130 pg/mL (0–120) ↑, the prothrombin time was 17.9s (11–15) ↑, the prothrombin activity was 54% (80–120) ↓, the activated partial thromboplastin time was 40.9s (28–43.5), the fibrinogen was 2.0 g/L (2.0–4.0) and the D-Dimer was more than 20 mg/L (0–0.5) ↑. No significant abnormality was found in liver and kidney functions, electrolytes, erythrocyte sedimentation rate, procalcitonin, tumor makers, and connective tissue disease makers. The tests for pathogenic microorganisms in phlegm were negative. CT pulmonary angiography did not show filling defects in pulmonary arteries. However, we found significantly enlarged mediastinum with compressed or narrowed pulmonary arteries, veins, trachea and aorta by mediastinum soft mass. The lung window showed thickening of peribronchovascular and interlobular septal, diffused pulmonary interstitial infiltrations, and small amounts of pleural effusion on both sides (Fig. 1A and B). Axial T2-weighted (Fig. 2A) and coronal T2-weighted (Fig. 2B) images from chest magnetic resonance imaging (MRI) demonstrated that diffuse infiltration and thickening of the mediastinum, bilateral hilum, and peribronchovascular bundles, exhibiting high signal intensity on T2. No significant enhancement signal was found in the enhanced scan (The gadopentetate dimeglumine (0.2 mmol/L; Magnevist, Bayer) was infused via the elbow vein in a pellet manner at a rate of 3 mL/s), suggesting diffuse lymphatic vessels of the mediastinum, lungs and retroperitoneum. Therefore, DPL was suspected, and we performed a direct lymphangiography: a total of 19 ml iodinated oil injection (Lipiodol Ultra-Fluide, Guerbet) was administered at a rate of 8 ml/h through the dorsal lymphatic vessel of the patient's right foot, followed by a whole-body dynamically observation on the digital subtraction angiography unit. It showed

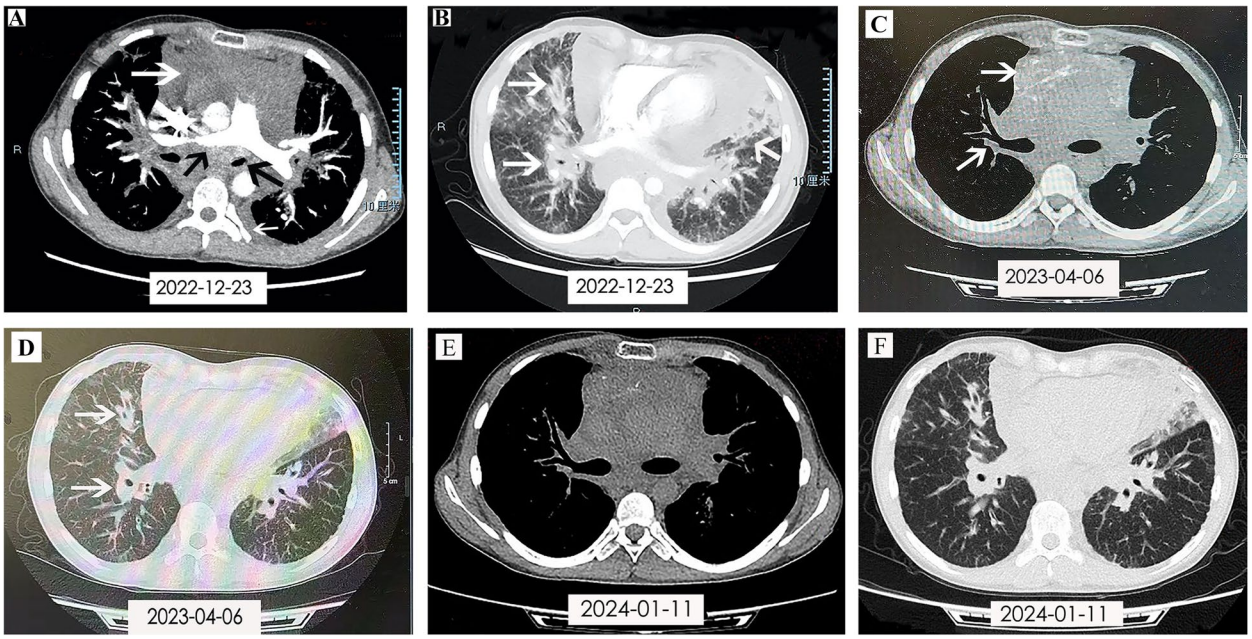

Fig. 1 **A** CT pulmonary angiography with soft-tissue window showing significantly enlarged soft-tissue infiltration in the mediastinum without enhancement (white arrow), but with compressed pulmonary arteries, veins, aorta, and bilateral hilar by mediastinum mess (black arrow), and small amounts of pleural effusion on either side (short arrow). **B** CT pulmonary angiography with lung window showed bilateral thickening of interlobular septal and peribronchovascular bundles (white arrow), diffuse ground-glass opacities in bilateral pulmonary parenchyma, and the presence of mediastinal, pericardial, and pleural effusions. **C** Chest CT scan after 4 months of sirolimus treatment. CT scan with a soft-tissue window displaying decreased soft-tissue infiltration in the mediastinum and accumulated lipiodol in the mediastinal soft tissues, pericardium after lymphangiography (white arrow). **D** Chest CT scan after 4 months of sirolimus treatment. CT scan with a lung window displaying shrunken interlobular septal and peribronchovascula (white arrow). **E** Chest CT scan with a soft-tissue window after 1 year of sirolimus treatment. **F** Chest CT scan with a lung window after 1 year of sirolimus treatment

that lymphatic vessels were tortuous, disordered, and dilated from the right lumbar trunk region to the T12 vertebral level. The thoracic duct was severely expanded throughout the entire course. A contrast medium was found refluxing in the mesentery, which moved up along the left side of the thoracic spine and gradually returned to the mediastinum at the level of bronchial bifurcation. A small amount of contrast agent entered the blood when the patient was breathing calmly. Abdominal CT scan after direct lymphangiography showed that the liver was enlarged and the spleen was not displayed; nodular and patchy low-density shadows were observed within the hepatic-gastric space, retroperitoneal space, and the surrounding mesentery. Unfortunately, a biopsy could not be obtained through video-assisted thoracoscopic surgery or bronchoscopy because of the procedural side-effects, which include fatal chylothorax [11], bloody pleural effusion [1], or even death [18, 19]. Therefore, based on these typical imaging findings, we diagnosed the patient with DPL. During the hospitalization period, the condition of the patient improved following the administration of oxygen supplements, antibiotics, hemostatic agents, and diuretics. The patient was finally discharged on the 12th day.

Genetic analysis

Genomic DNA was isolated from peripheral blood leukocytes of the patient and his parents using the Magbead Blood DNA kit (CWBIO, Taizhou, China). We performed whole-exome sequencing using the NOVOSeq6000 (Illumina, San Diego, CA, USA), with150 bp paired-end sequencing mode. The sequencing reads were aligned to the human reference genome (hg19/GRCh37) using BWA. GATK was used to detect SNVs and indels. Variant annotation and interpretation were conducted by ANNOVAR. Moreover, Sanger sequencing was performed to validate the suspected variant loci using the ABI3730xl sequencer (Applied Biosystems, United States of America). The results were compared with the reference sequence of the Human genome hg19 published on the Ensemble website using the Snap Gene Viewer software.

Whole-exome sequencing (WES) results of the patient and his parents revealed that he had the following heterozygous variants of *BCL6*: NM_001706: exon5: c. A463G (p.M155V), and the following heterozygous variants of *ATM*: NM_000051: exon3: c.A107G (p.D36G) (Fig. 3A and B and Supplementary material). Two heterozygous

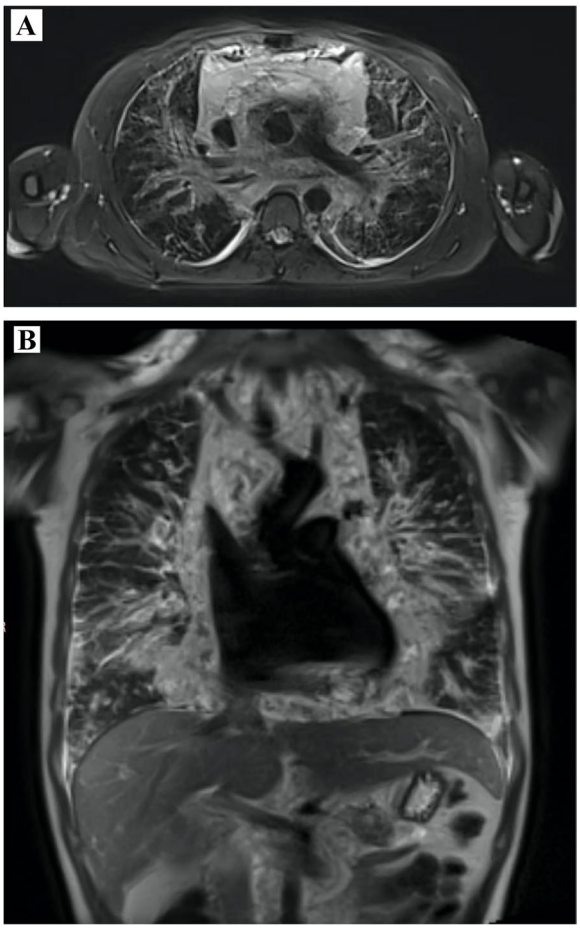

Fig. 2 **A** T2-weighted fast BLADE image showing the T2 high intensity dilated soft tissue in the mediastinum and bilateral hilar areas. (This single-layer scanning time is about 2 min). **B** Mediastinum and bronchovascular bundles were widened, with diffuse long T2-weighted signals, connected from the right cervical trunk to chylous cistern

mutations were detected in the exonic region of *BCL6* c.463 A > G and *ATM* c.107 A > G, resulting in amino acid changes in: p.M155V and p.D36G, respectively. However, the two mutation sites were not reported in the Human Gene Mutation Database (http://www.hgmd.org), and corresponding clinical characteristics were unknown. Genetic analysis of his parents revealed that the mother had the same mutation, but she was healthy and nothing unusual was discovered in her chest CT.

Outcome

The patient was readmitted to our department one month after discharge due to the reoccurrence same symptoms. During this round of treatment, in addition to antibiotics and diuretics, sirolimus was administered orally 2 mg daily, and a low-fat medium-chain triglyceride diet was recommended. The patient was followed up after 2 months. His discomforts had completely disappeared, and his chest CT showed the mass had shrunk by nearly half compared with the mass observed in the previous scan (Fig. 1C and D). His pulse oxygen saturation was 96% on room air, the c-reactive protein level declined to 21.96 mg/L, and brain natriuretic peptide was 102 pg/mL within the normal range. The patient is currently being treated with sirolimus alone and the drug concentration is monitored regularly. However, due to the patient gradually developed an intolerable facial acne-like rash, he reduced the sirolimus dose to 1 mg daily and the sirolimus drug concentration did not meet the level of 10–15 ng/ml, which was 7 ng/ml in the latest test. In the next 9 months of follow-up, the imaging changes of his chest CT were still significant compared to the one at the onset of the disease. (Figure 1E and F), and his symptoms are stable presently.

Discussion

DPL is a rare lymphatic disorder occurring predominantly in children and young adults that may involve the soft tissues, mediastinum, lungs, spleen, and bone [4]. Disorders of the pulmonary lymphatic system occur in a variety of clinical settings, including lymphangiomas, lymphangiectasis, lymphangiomyomatosis, and lymphangiosarcoma [2, 4, 7]. Histopathological examinations are necessary for distinguishing DPL from other diseases, such as multifocal proliferation of abnormal lymphatic vessels and increased number of complex anastomosing channels with positive lymphatic endothelial antigen for D2-40 and CD31 by immunohistochemical staining [1, 5, 20]. However, in the present case, the mediastinal lymphatic vessel of the patient was severely dilated, leading to interstitial pulmonary edema that worsened his dyspnea and cough and declined oxygen saturation. After multidisciplinary discussions (involving the experts from the respiratory department, thoracic surgery, endoscopy center, and imaging operation center) and considering that invasive lung biopsy could lead to fatal chylothorax [11] or other serious complications, we did not perform any invasive examination on the patient. We diagnosed the patient with DPL based on the typical imaging features in high-resolution CT, chest magnetic resonance imaging, and lymphangiography instead of pathological diagnosis.

DPL is generally considered to be congenital, resulting from developmental mutations in the lymphatic system before the 20th week of gestation [14]. Genetic variation may play a crucial role in some disease progression. In a previous study, *TNFRSF13B* mutation (c.431 C > T, p.Ser144Leu) was detected in DPL with thrombocytopenia. However, this mutation was considered to be a candidate for the predisposition to familial or sporadic

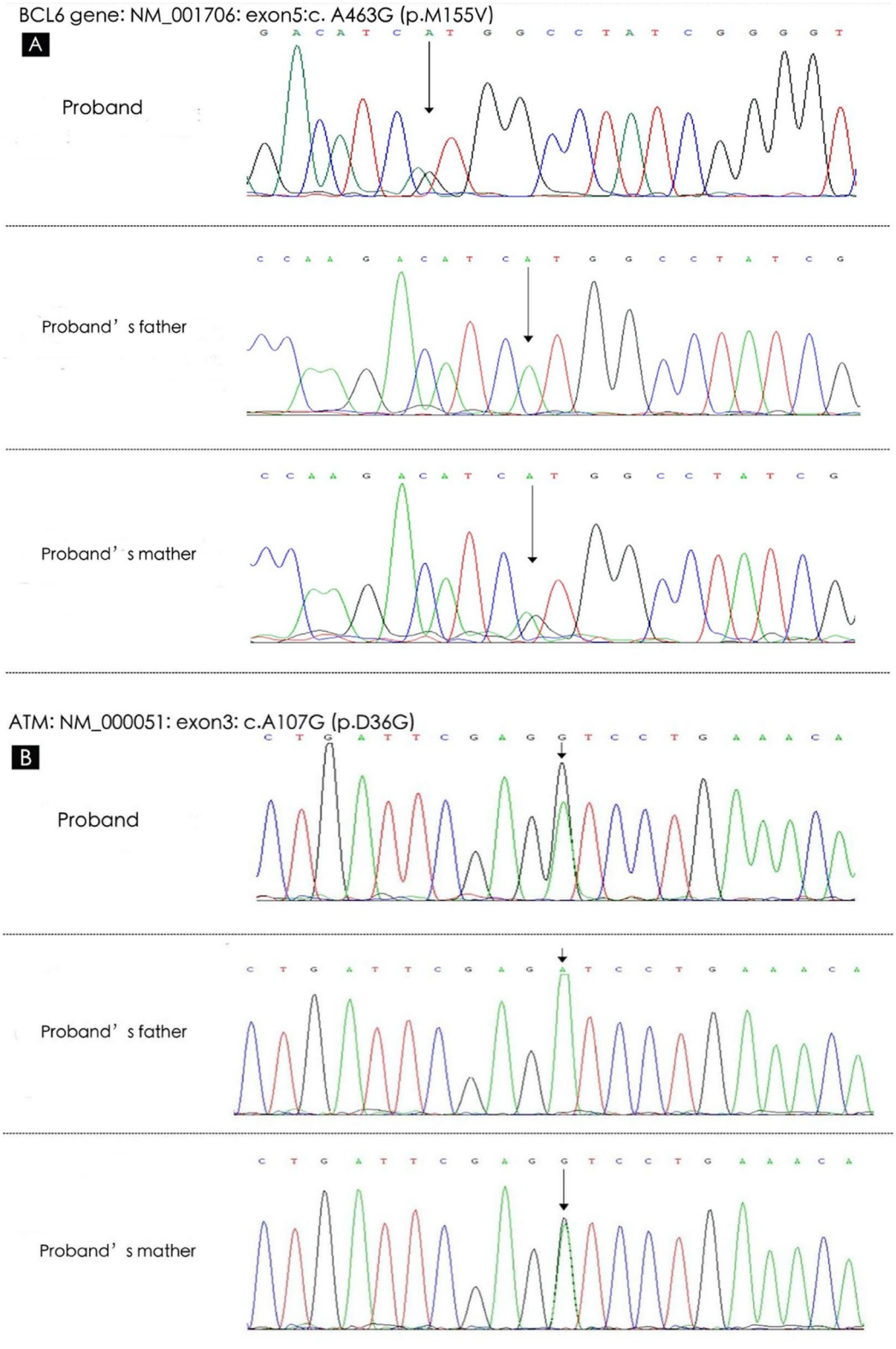

Fig. 3 Whole exom sequencing (WES) results revealed that the patient and his mother had heterozygous variants of *BCL6*: NM_001706: exon5:c. A463G (p.M155V) (**A**) and *ATM*: NM_000051: exon3: c.A107G (p.D36G) (**B**), respectively

immune thrombocytopenia [21]. To the best of our knowledge, our report is the first of its kind in English literature, which describes the genetic characteristics of a patient with DPL. *BCL6* c.463 A > G and *ATM* c.107 A > G variants have never been reported in the Human Gene Mutation Database (http://www.hgmd.org). However, to the best of our knowledge, *BCL6* is located at chromosome 3, which belongs to the anti-apoptotic family and is the main regulatory factor of B cells in the germinal center; it directly regulates target genes to maintain cell activation, differentiation, apoptosis, proliferation and DNA damage response, which appears to be a common oncogene of cancer occurs in lymphoid organs [22]. *ATM* is located at chromosome 11q22-23 bands, and the germline mutations are responsible for ataxis-telangiectasia, a rare autosomal recessive disorder associated with a high incidence of childhood leukemias and lymphomas, suggesting that *ATM* gene alterations may be involved in lymphomagenesis [23]. Moreover, we considered that the participation of the *BCL6* and *ATM* mutation may play a role in the pathogenesis of DPL. The patient and his mother exhibited the same mutations of the disease; however, the clinical phenotype of the mother was negative. As such, people carrying the same genetic mutation without similar external phenotype are not uncommon in genetics. Therefore, more numbers of studies are required to elucidate both genes' roles in the pathogenesis of DPL.

No established treatment is available for DPL to date. In most cases, the disease progresses gradually to chronic morbidity or even life-threatening conditions. Some reports suggested that DPL in adults may show a less aggressive progression and a more favorable prognosis than that in children [9, 10]. Due to a lack of randomized studies, no definitive medical therapies have been recommended for DPL. We searched all reports of DPL in the English language in PubMed and have summarized the treatment approaches in Table 1. Thoracic lymphangiomatosis can be found in a localized or diffuse form. Surgical resection is suggested for localized lung or mediastinal lesions; however, the risk of disease recurrence is high [14]. Other treatments include low-fat medium-chain triglyceride diets [10, 13], therapies including interferon-alpha [2, 4], corticosteroids [7, 8], sirolimus [14], radiation [7], propranolol [1, 17], bevacizumab [12], and even lung transplantation. In this case report, considering the age and hemoptysis comorbidities of the patient, we prescribed sirolimus and altered his diet for the subsequent treatment. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor, which is an immunosuppressive agent generally used for preventing the rejection of renal transplants and treating patients with sporadic lymphangioleiomyomatosis [14]. Lymphatic vessel proliferation is affected by the expression of a signal protein, vascular endothelial growth factor (VEGF), and its subtypes, including VEGF type A (VEGF-A) [12]. In vitro experiments showed that sirolimus can impair downstream signaling of the proliferation and migration driven by VEGF-A and VEGF-C via the mTOR to the p70S6 kinase in lymphatic endothelial cells, thereby inhibiting lymphangiogenesis [24]. A few studies have reported that sirolimus is an effective and safe therapeutic option in improving clinical symptoms, increasing the first second forced expiratory volume (FEV1) and forced vital capacity (FVC) of pulmonary function tests, and reducing the volume of the lymphatic mass for treating

Table 1 Literature review of characteristic features of diffuse pulmonary lymphangiomatosis in English

Ref	Year	Sex	Age	Symptoms	Treatment	Outcome
1	2022	M	27	Cough and sputum	propranolol	alive
2	2004	M	48	Dyspnea and sputum	Interferon and surgical ligation	alive
4	2001	M	22	dyspnea	Interferon	Respiratory failure
6	2005	F	8	Cough, hemoptysis and dyspnea	Radiation therapy	Respiratory failure
8	2012	F	38	dyspnea	corticosteroids	alive
9	2014	F	52	asymptomatic	No treatment	asymptomatic
10	2019	F	24	Severe breathlessness, cough and sputum	Low-fat diet, octretide and propranolol	alive
11	2019	M	51	Breathlessness, dry cough	bevacizumab	alive
12	2019	M	59	Cough and sputum	surgical ligation, Low-fat diet	alive
13	2020	M	27	Dyspnea and hemoptysis	sirolimus	alive
14	2020	M	22	Respiratory failure	sirolimus	Lost to follow-up
16	2023	M	8	Cough, blood phlegm	Prednisone, propranolol, sirolimus	alive
20	2020	M	18	Cough, sputum and dyspnea,	pericardial resection, prednisone	alive
[a]	2023	M	17	Hemoptysis and dyspnea	sirolimus	alive

[a] The patient in this article

DPL [16, 17, 25, 26]. Given this evidence, sirolimus was selected as the most promising treatment option for this patient. Based on the follow-up, the short-term prognosis was encouraging and the side effects were tolerable. The optimal treatment duration for this case is unknown. The current English literature reports that the longest treatment duration with sirolimus was 4 years in a 20-year-old patient with DPL [27]. In rare conditions, such as DPL, case reports are often the only available source of information to help guide treatment decisions. Therefore, we hope to provide important information on the possible management of this condition.

Owing to the limitations imposed by the rules of privacy and data protection, patient data from different hospitals cannot be shared online and we were unable to obtain detailed information on the patient's splenectomy history form 15 years ago (including his chest imaging examination). Both diffuse splenic hemangiomas and lymphangioma should be diagnosed accurately as both two diseases are rare and indeed difficult to distinguish, requiring further immunohistochemical differentiation [28–30]. However, in the absence of the patient's consent, we could not determine whether the splenic lesion was an isolated lesion or an infiltration of DPL in different organs. We therefore believe that advancement in diagnostic technology and the accumulation of clinical experience would facilitate the diagnosis of this rare disease in the future.

Conclusions

To conclude, early diagnosis of DPL is challenging for clinicians; therefore, misdiagnosis and missed diagnosis are very common in patients with DPL having atypical symptoms. The imaging results provided the first diagnostic information, revealing a soft mass in the mediastinum, thickening of interlobular septal and peribronchovascular, infiltration of pulmonary interstitial, and pleural effusion. Although imaging plays an important role in determining the location and severity of the disease, only lymphangiography or pathology results can help confirm the final diagnosis. The gene mutation found in this study may play an underlying role in the pathogenesis of DPL. However, more case studies are required to confirm this hypothesis. Sirolimus can be an effective and safe therapeutic choice for treating DPL, which should be verified in clinical investigation.

Abbreviations

DPL	Diffuse pulmonary lymphangiomatosis
CT	Computed tomography
MRI	Chest magnetic resonance imaging
WES	Whole-exom sequencing
VEGF	Vascular endothelial growth factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03544-w.

Supplementary Material 1.

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Authors' contributions

Dr Yu-Xuan Feng identified the patient case reported here, collected all materials, and was a major contributor in writing the manuscript. Drs Yi-Min Mao, Tong-Sheng Wang, and Shuai Zhang conducted the study and analyzed the clinical data. Drs Wen-Qing Xu and Min Liu performed and analyzed the imaging data. Prof Ying Nong designed the study and wrote the revision of the manuscript. All authors have reviewed the manuscript and approved the final version for submission.

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Data availability

Due to privacy considerations, individual patient data cannot be publicly shared, and because the short storage time of the testing agency, we are unable to trace the raw sequencing data of the patient and his parents. Other datasets or images used during the current study are available from the corresponding author on reasonable requests.

Declarations

Ethics approval and consent to participate

The presented case involves a retrospective analysis of clinical data and medical interventions performed as part of routine patient care. Our study had received approval from the ethics committee of the China-Japan Friendship Hospital. Written informed consent for the publication of clinical details and clinical data was obtained from the patient and his parents.

Consent for publication

Written informed consent was obtained from the patient and his parents for publication of this case report and any accompanying images.

Competing interests

The authors declare no competing interests.

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