Diagnosis and treatment of diffuse pulmonary lymphangioma in children: A case report

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Abstract. The present study aimed to investigate the clinical characteristics of diffuse pulmonary lymphangioma (DPL) in children to improve the diagnosis and treatment of this disease. A case of pediatric DPL was observed for its clinical symptoms, imaging features, lung biopsy pathological characteristics and immunohistochemical phenotypes, and relevant literature was also reviewed. The main clinical manifestations of this pediatric patient were a cough, shortness of breath, hemoptysis, bloody chylothorax and pericardial effusion. Chest computed tomography showed a grid-like shadow and markedly thickened interlobular septa. Pathological examination revealed lymphatic vessel hyperplasia and expansion. Immunohistochemistry showed positive staining of lymphatic endothelial cells CD31 and D2-40. The patient's condition improved after combined treatment with methylprednisone, propranolol, sirolimus and somatostatin, whose bloody chylothorax also achieved good therapeutic effect after conservative treatment. Overall, the clinical and imaging appearances of DPL are lack of characterization, and its clinical manifestations include cough, shortness of breath and chylothorax. Computed tomography may show mesh-like shadows of both lungs and thickened interlobular septa. The definite diagnosis of DPL depends on biopsy pathology. In addition to this case, B-ultrasound-guided puncture biopsy is effective and safe, and propranolol-sirolimus treatment has a certain effect, but the clinical effect may be different. Conservative treatment of pleural effusion can result in better curative effect.

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Introduction

Diffuse pulmonary lymphangiomatosis (DPL) is a rare disease which is insidious, and its pathogenesis is unknown. It usually occurs after birth or in childhood, and can also occur in adults. There is no significant gender difference (1). Diffuse pulmonary lymphangiomatosis (DPL) is a relatively rare congenital lymphoproliferative pulmonary disease characterized by abnormal lymphatic hyperplasia, dilation, and thickening of the soft tissues of the lungs, pleura, and mediastinum (2). The younger the age of onset, the worse the prognosis (3). The main clinical manifestations of DPL patients are cough, sputum, chest tightness, shortness of breath, and dyspnea, and some patients also show repeated intractable chylothorax (4). Lung CT scans may reveal diffuse interstitial changes, ground glass manifestations, multiple nodules and diffuse septal thickening, and diffuse mediastinal and paratracheal soft tissue infiltration (3), with mediastinal lymph node enlargement, perihilar soft tissue shadows, and pleural calcification (5). Bronchoscopy revealed diffuse translucent vesicular changes in the bronchial wall mucosa (3). Respiratory failure and chylous fluid accumulation secondary to infection are the major causes of death in DPL patients (6,7). We retrospectively analyzed the clinical data of a case of DPL in a child admitted to the First Affiliated Hospital of Guangzhou Medical University in order to improve clinicians' understanding of this disease and explore new therapeutic directions.

Case report

An 8-year-old boy with the chief complaint of cough for two weeks, anhelation for one week, and fever for two days was admitted to our hospital on March 24, 2020. The onset of the disease was mainly dry cough, and then cough phlegm appeared gradually, accompanied by blood phlegm once (15 ml). The chest computed tomography (CT) revealed 'Interstitial pneumonia is present in both lungs; Bilateral pleural effusion with local consolidation.' The patient received intravenous anti-infection therapy of cefmetazole, cefoperazone sodium and sulbactam sodium for two days and closed thoracic drainage in a local hospital, and the therapeutic effect was not satisfactory, then the patient went to our hospital for further treatment. The child initially developed a chylous

pericardial effusion at age 1. He underwent partial pericardiectomy, pericardial drainage and thoracic catheter ligation at another hospital for chylous pericardial effusion at the age of 2, during which he also received anti-infection, nutritional support and somatostatin therapy (The exact course of treatment was not known).The patient was regularly followed up for three years after discharge, and reexamination of chest radiographs showed no abnormality.

Upon physical examination, the child looked dyspnoeic and could not keep horizontal. The three concave signs was positive. Respiratory sounds in both lungs were weakened, obvious in the left lung, and wet rales and wheezing were heard. Several lymph nodes with a diameter of 0.5-0.8 cm were found in the neck, armpit, and groin of both sides, which were mobile, without tenderness and adhesion.

Laboratory examinations revealed severe microcytic hypochromic anemia, with hemoglobin value of 80 g/l. T-SPOT showed no abnormality. Blood and pleural effusion cultures were negative. The pleural fluid test suggested chylothorax. Contrast-enhanced chest CT (Figs. 1 and 2) showed multiple lymph nodes in bilateral cervical roots and mediastinum, which were fused into clusters, and the trachea and mediastinal great vessels were surrounded. Furthermore, there was multiple thickening of interlobular septa in the right lung, multiple inflammations in both lungs and atelectasis in the left lung, and massive pleural effusion on the left side. Positron emission tomography (PET)-CT showed soft tissue thickening around the trachea, blood vessels, and thyroid gland in the lower neck and the mediastinum, especially in the anterior and superior mediastinum. The pulmonary interlobular septum was significantly thickened, and the bronchial vascular bundle was thickened, accompanied by multiple patchy shadows of increased density and consolidation. The pleural effusion of the child was chylous (Fig. 3). Biopsy of the mediastinal mass revealed patchy, small lymphocytes with few thymus corpuscles. The tumor tissue was fissured and had a sparse reticular structure (Fig. 4). Immunohistochemistry results revealed the following: D2-40 (+), CD31 (+), Ki67 (1%+), SALL4 (-), SOX-10 (-), SMA (-), TDT (-), CD5 (-), CD117 (-), PLAP (-), AFP (-), HMB45 (-) and tissue changes consistent with the vascular origin of the tumor, inclined to lymphangioma.

After the treatment with prednisone, propranolol, sirolimus and somatostatin, the clinical symptoms of the child were improved. At the same time, the patient underwent a thoracentesis and the drainage tube was removed after laboratory examination of the pleural effusion. In the treatment of pleural effusion, we chose conservative treatment instead of repeated drainage. Afterwards, the pleural fluid in B-mode chest ultrasound was not significantly increased, blood routine hemoglobin concentration was stable, and fibrinogen level was not progressively decreased. Thus, we can consider the treatment was effective. The child was discharged on June 4, 2020. After discharge, he did not have a fever or pale face. Regular blood routine examinations were performed, and hemoglobin level was maintained at 90-110 g/l. He did not have anhelation and could be supine. The child was admitted to the hospital for a second time on July 27, 2020, and planned to receive lymphangiography and occlusion. During hospitalization, the patient's condition worsened due to infection, and hemoptysis occurred. Bronchoscopy showed obvious congestion, erosion, and bleeding of the left bronchial mucosa (Fig. 5), which was considered as the cause of hemoptysis. During the second admission, the patient was treated with oral prednisone for anti-inflammation, propranolol for stabilizing endothelial cells, sirolimus for suppressing the immune response, piperacillin sodium and tazobactam sodium for anti-infection activity, along with somatostatin, and calcium and iron supplements, after which the patient's condition was stable. Lymphangiogram and occlusion were performed on August 20, 2020. The child's condition was continuously followed up and observed, and regular outpatient follow-ups were performed until April 2021. The child's condition is stable, and he has a normal diet, no cough, hemoptysis, anhelation, chest tightness, and other discomforts. Routine blood reexamination revealed a hemoglobin concentration of 110 g/l.

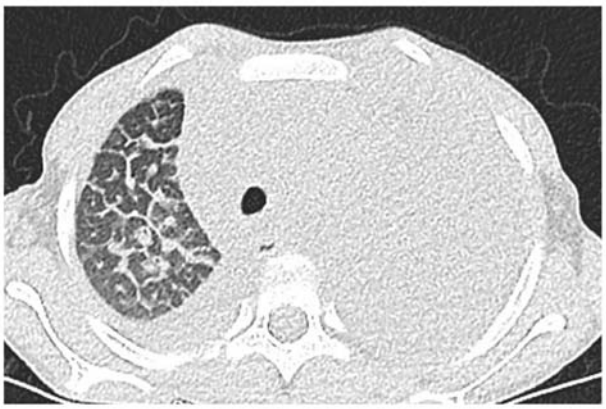

Figure 1. Multiple thickening of interlobular septa in the right lung.

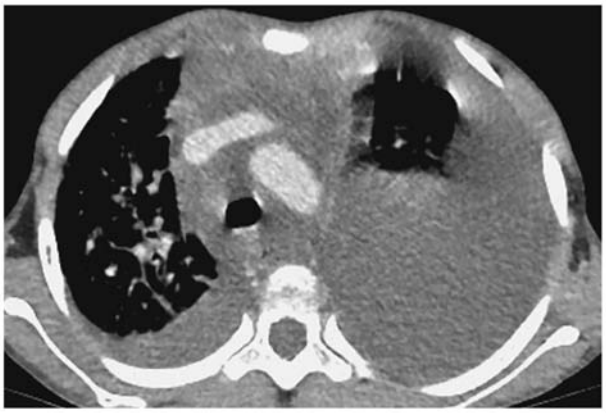

Figure 2. Multiple lymph nodes in bilateral cervical roots and mediastinum, which were fused into clusters, and the trachea and mediastinal great vessels were surrounded.

Discussion

Lymphangioma is when the original lymphatic sac is isolated from the lymphatic system during embryonic development, the remaining lymphoid tissue is hyperplastic, and the lymph fluid gradually accumulates causing the lymphatic vessels to expand like a capsule (3). About 10% of DPL occurs in the mediastinum, and only in the lungs is rare (8).

Figure 3. Pleural effusion of the child was chylous.

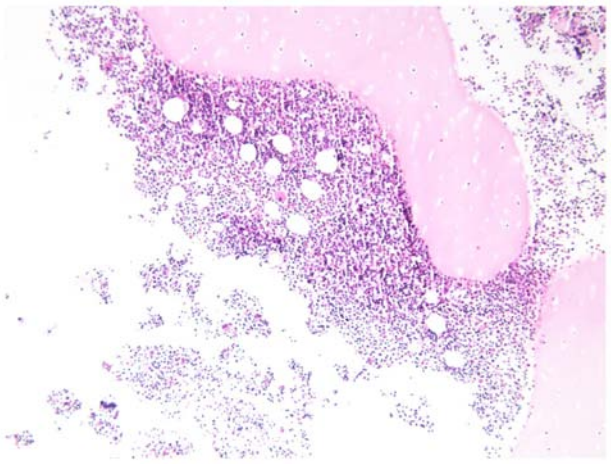

Figure 4. Biopsy of mediastinal mass revealed patchy small lymphocytes with a few thymus corpuscles, which were fissured and had a sparse reticular structure.

DPL needs to be differentiated from diffuse pulmonary lymphangiectasis, pulmonary lymphangiomatosis, pulmonary capillary angiomatosis, sarcoidosis and other diseases. Diffuse lymphangiectasia of lung includes primary and secondary 2 kinds. Primary lymphangiectasia occurs mostly in infants and young children. It is congenital abnormal development of interstitial connective tissue of the lung, manifested as lymphangiectasia of the pulmonary capillary. Secondary lymphangiectasia is mainly due to surgical operations, radiation, infection, tumors, trauma and other factors caused by lymphatic circulation disorders (9). Pulmonary capillary

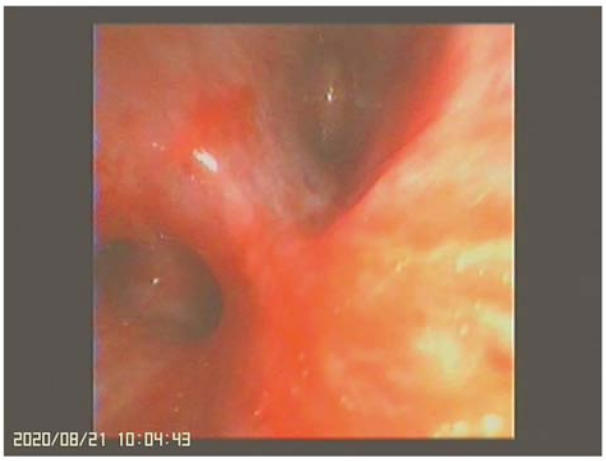

Figure 5. Bronchoscopy showed obvious congestion, erosion and bleeding of the left bronchial mucosa.

angiomatosis is a pulmonary capillary abnormal hyperplasia disease, its clinical symptoms are similar to pulmonary hypertension, common pleural effusion and hemoptysis, can be diagnosed by pulmonary angiography (10).

The case reported in this paper began to show clinical symptoms at the age of 1, and was diagnosed as DPL at the age of 8 according to pathological findings in our hospital. Among the DPL patients reported in China, this case has the youngest onset age and the longest diagnosis time span. The disease was not diagnosed at the beginning, and clinical symptoms appeared again six years after surgical treatment, indicating that the disease progressed relatively slowly. Finally, the diagnosis was confirmed by pathological examination. Because of the lack of clinical understanding of DPL, which is prone to misdiagnosis, the patient was not considered for the disease despite the surgical treatment of chylothorax and pericardial effusion. To define the diagnosis based on clinical and radiographic features alone is not enough; most patients need confirmation by bronchoscopy, lung biopsy, or open lung biopsy, but the risk is huge. Shen (11). reported a case of DPL in children through bronchoscopy biopsy of the lung hemorrhage and death after TBLB chylothorax. In our case, the mediastinal puncture was a safe and effective method under B-ultrasound localization, which can be confirmed by pathological manifestations and immunohistochemistry. D2-40 staining was positive, and it can specifically identify lymphatic endothelium.

There is no universally accepted specific drug for the treatment of DPL, and treatment is mostly supportive and aimed at alleviating clinical symptoms. Drug therapy included propranolol (12), glucocorticoids, and bevacizumab (13,14). Surgical treatment included thoracic duct ligation and heart and lung transplantation (15). There have been reports of no recurrence of the disease after 4 months to 3 years of follow-up following complete surgical resection of the pulmonary lymphangioma (16,17,18). Kandi *et al*. reported that radiotherapy was used in the treatment of lymphangioma, and no recurrence was observed during a follow-up period of 20 months to 8 years (19). In our case, the child was treated with oral propranolol, as reported by Ozeki *et al* (12), but there was no considerable improvement. A review of relevant

literature (20). shows that sirolimus is currently considered to have a considerable effect in hemangioma, lymphangioma, and other diseases that respond poorly to propranolol. Gurskyte *et al* (21). studied the case of a 27-year-old male patient with DPL and found that sirolimus could effectively improve the condition and prevent disease progression. Combined treatment with propranolol and sirolimus showed clinical efficacy. Sirolimus combined with propranolol may be effective in improving the condition of children with DPL, which opens up new treatment options for such children. At present, the treatment of DPL pleural effusion is still controversial. In the case reported in this paper, conservative treatment has also achieved good results, which also provides a new idea for the treatment of pleural effusion.

In summary, children who have difficulty breathing, unexplained interlobular septal thickening, interstitial pneumonia combined with hemorrhagic chylothorax, or pericardial effusion, especially with the diagnosis of diffuse mediastinal soft tissue infiltration, should be considered for DPL. The diagnosis of DPL has certain difficulties, mainly based on the pathological examination, and diagnosis by ultrasound-guided biopsy is effective and safe. Sirolimus may be an alternative treatment option for pediatric DPL. Conservative treatment of pleural effusion can result in better curative effect.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XPS and CYL wrote the manuscript and contributed to the data analysis and interpretation. HYZ collected data. JXX, ZHH, SY and DHC contributed to the data interpretation and manuscript revision. DHC designed research and approved the final version of manuscript. All authors read and approved the final manuscript. XPS and CYL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Consent for publication was obtained from the patient's parents.

Competing interests

The authors declare they have no competing interests.

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