

# Lymphangiomatosis involving the pulmonary and extrapulmonary lymph nodes and surrounding soft tissue

## A rare case report

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### Abstract

**Background:** Diffuse pulmonary lymphangiomatosis (DPL) mainly affects the lung and pleura. There are very few pathological reports of lung damage accompanied by diffuse involvement of the extrapulmonary lymph nodes and surrounding soft tissue. The clinicopathological significance of coexistence of pulmonary and extrapulmonary lesions is unknown.

**Methods:** Here, we report a 16-year-old male patient. The pathological specimens of the supraclavicular lymph node and soft tissue together with the lung biopsy were analyzed by pathological observation and immunohistochemical staining. Literatures were reviewed and clinical and imaging findings were discussed.

**Results:** The patient presented with coughing and expectoration for 1 year and intermittent hemoptysis for 4 months. Ultrasound revealed swollen lymph nodes in bilateral neck, left armpit, and pubic symphysis. Chest CT scan showed diffuse grid and linear shadows, bilateral pleural thickening, and nodule formation. Multiple enlarged lymph nodes were mainly investigated in bilateral hilar, mediastinal, para-aortic, lesser curvature, and retroperitoneal. Supraclavicular lymph node biopsy confirmed the lymphatic hyperplasia and expansion in the capsule and surrounding soft tissue. The thoracoscopic examination found bloody chylothorax on the left chest. And lung biopsy showed the lymphatic vessel hyperplasia and expansion on the pleura and adjacent lung tissue. Immunohistochemical stains showed that the lymphatic endothelial cells were positive for D2-40 and CD31. Lymphangiomatosis involving the pulmonary and extrapulmonary lymph nodes and surrounding soft tissue was diagnosed based on the aforementioned histological findings.

**Conclusion:** Lymphangiomatosis of superficial lymph node mainly involves the capsule of lymph nodes and its surrounding soft tissue. The information obtained from the lymph node biopsy can prompt and assist the diagnosis of DPL.

**Abbreviation:** DPL = diffuse pulmonary lymphangiomatosis.

**Keywords:** diagnosis, diffuse pulmonary lymphangiomatosis, lymph node lymphangiomatosis, lymphangiomatosis

## 1. Introduction

Lymphangiomatosis is a rare disease characterized by abnormal proliferation of lymphatic vessels. It can be single organ involvement or multiple organ involvement, and single organ involvement is common. The lung is a relatively common involved organ, which is commonly involved alone. Lymphan-

giomatosis with pulmonary and extrapulmonary lymph nodes and surrounding soft tissue involvement is rare. Diffuse pulmonary lymphangiomatosis (DPL) is a rarely aggressive and progressive lung disease that is characterized by diffuse proliferation of abnormal lymphatic vessels.<sup>[1-3]</sup> Because its etiology remains unknown and the clinical manifestations are not typical, it is easy to be misdiagnosed.<sup>[4,5]</sup>

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Clinically, the specimens of punctured lung biopsy are too small to obtain valuable diagnostic material. To provide enough pathological materials, small incision or video-assisted thoracoscopic (VATS) lung biopsy is often required, but this method easily induces and even aggravates existing chylothorax. DPL mainly results in infiltration of the lung and pleura, while the morphological changes in combination with diffuse involvement of the extrapulmonary lymph nodes and surrounding soft tissue is rarely reported. The clinicopathological significance of coexistence of the both lesions remains unclear. Lymph node involvement often manifested as the hyperplasia of lymphoid tissues and its surrounding soft tissue, in addition to lymphatic hyperplasia and varying degrees of expansion in the capsule. It is not easy to distinguish lymph node lymphangiomatosis (LNL) from chronic nonspecific inflammation of lymph nodes. In addition, LNL biopsy is rarely reported, and pathologists lack understanding of it. The above reasons often lead to the misdiagnosis and missed diagnosis of LNL.

We have here reported a case of DPL with superficial lymphadenopathy.<sup>[6]</sup> At first, the biopsy of supraclavicular lymph node failed to obtain a pathological diagnosis of LNL. Through surgical lung biopsy, we were able to obtain a pathological diagnosis of DPL. Later, we reviewed the sections of the lymph node and found the presence of LNL. This paper reports the rare difficult case to improve the diagnostic level of pathologists, and to explore the clinical significances of coexistence of pulmonary and extrapulmonary lesions.

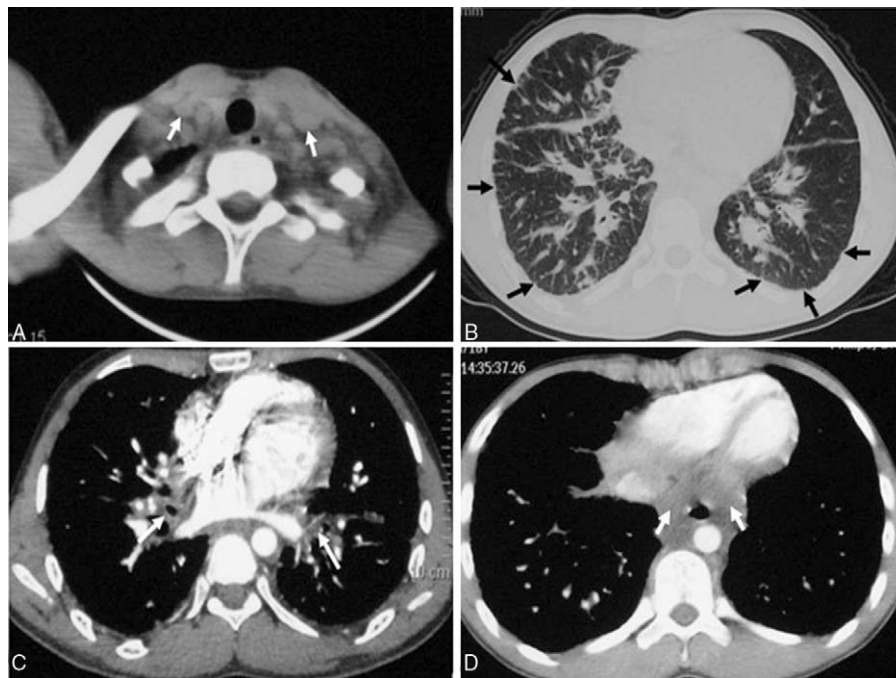
## 2. Case report

A 16-year-old boy was admitted to our hospital with 1-year history of cough and sputum, and 4-month history of intermittent

hemoptysis. A month ago, the patient presented with cough, expectoration, and bloody sputum without obvious causes. The patient had no specific history or history of contact. This study was performed in accordance with the ethical guidelines of the Tongji University School of Medicine.

On admission, ultrasound showed swollen lymph nodes in bilateral neck, left armpit, and pubic symphysis. Rough respiratory sounds were identified in 2 sides of lung without dry rales. Laboratory examination revealed a hemoglobin level of 161 g/L, a red blood cell count of  $5.33 \times 10^{12} \text{ L}^{-1}$ , a white blood cell count of  $4.4 \times 10^9 \text{ L}^{-1}$  (60.1% neutrophils, 27.8% lymphocytes), a platelet count of  $255 \times 10^9 \text{ L}^{-1}$ , and an erythrocyte sedimentation rate (ESR) cutoff value of 8 mm/h. Serum antibody test revealed an IL-1 level of 45 ng/L, interferon- $\gamma$  level of 26 ng/L, ECP level of 62.40  $\mu\text{g/L}$  and other data was normal. Pulmonary function tests revealed a mild obstructive ventilatory defect. Bronchoscope showed congestion and edema of bronchial mucosa.

A chest computed tomography (CT) scan showed an *irregular soft tissue density* mass located in the left clavicle (Fig. 1A), with diffuse grid and linear shadows, bilateral pleural thickening, pleural adhesion, and nodule formation. Multiple enlarged lymph nodes were mainly investigated in bilateral hilar, mediastinal, para-aortic, lesser curvature, and retroperitoneal (Fig. 1B–D). PET-CT examination revealed bilateral pulmonary interstitial changes with mediastinal, bilateral hilar, gastric and retroperitoneal multiple fusion lymph nodes, slightly increased FDG uptake, the highest SUV value 1.87, sphenoid sinus and right maxillary sinus inflammation, and the skull had no obvious abnormalities. Clinical diagnosis included double lung infection, tuberculous pleurisy, sarcoidosis, or tumor. The initial clinical diagnosis was double lung infection, pleurisy, sarcoidosis or tumors and so on.



**Figure 1.** (A) CT scans showed irregular soft tissue density (arrowheads) on both sides of the clavicle. (B) Chest CT scan at lung window demonstrated diffuse mesh shadow of bilateral lungs, line shadow, uneven thickening of both side lobes, bilateral pleural thickening and adhesion, accompanied by nodule formation (arrowheads). (C) Mediastinal window image showed bilateral pulmonary hilum thickening and disorder, thickening of bronchial tube wall, irregular soft tissue density around here (arrowheads). (D) CT scanning also revealed irregular patchy soft tissue density around the lower esophageal wall (arrowheads).

The biopsy of the right supraclavicular lymph node showed chronic inflammatory changes, but anti-inflammatory treatment was not effective. VATS lung biopsy of the left lung was performed for definitive diagnosis. Surgical exploration revealed the pleural thickening and adhesion, the texture of subpleural lung tissue hardens, left chest bloody chylothorax. Partial resection of the left lung was performed. After surgery, thoracic drainage from hemorrhagic chylothorax was 200 mL, which showed positive for the chylous test.

The resected surgery specimens were fixed in 10% neutral formalin and embedded in paraffin. The thickness of the slice was 4 to 5  $\mu\text{m}$ . Sections with HE staining was observed under light microscope. Immunohistochemical staining technique were performed for detecting D2-40 (1:200, DAKO, Denmark), CD31 (1:40, DAKO, Denmark), CD34 (1:50, DAKO, Denmark), SMA (1:100, DAKO, Denmark), CK, CD3, CD20, CD79a, and HMB-45 (1:50, DAKO, Denmark) by EnVision.

Pathologically, diffuse proliferation and dilated lymphatic vessels were seen in the pleura, along the interlobular septa and surrounding lung tissue, and the proliferation of lymphatic endothelial cells was well differentiated without atypia. The smooth muscle cells around lymph vessels presented hyperplasia, and its wall thickening, ranging in size. The adjacent lung tissue was approximately normal, with mild emphysema in some areas (Fig. 2A and B).

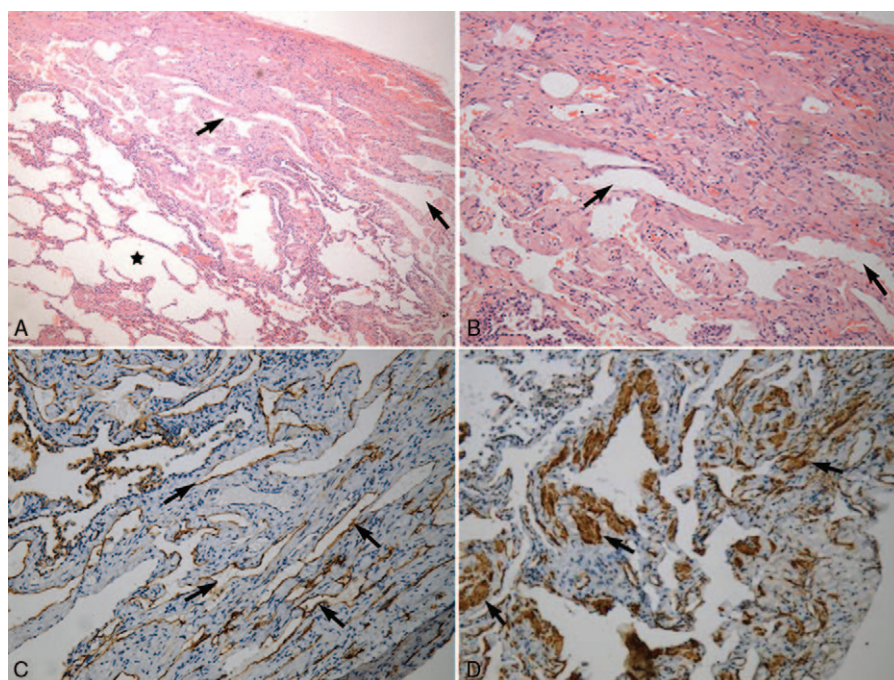
Immunohistochemical staining showed that the proliferating lymphatic endothelial cells were positive for D2-40 (Fig. 2C) and CD31, the vascular endothelial cells were positive for CD34, and the peripheral lymphatic smooth muscle showed positive for SMA (Fig. 2D), pan-CK, and HBM45 staining were negative.

The initial pathological diagnosis of right supraclavicular lymph node was "chronic inflammation of lymph node." After

the pathological diagnosis DPL was established, the sections of lymph node biopsy were reviewed. Under light microscopy, hyperplastic and dilated lymphatic vessels were seen in the hyperplastic capsule and surrounding soft tissue. And the wall of lymphatic vessels demonstrated hyperplasia of the smooth muscle, uneven, deformed, and varied in size (Fig. 3). And to better distinguish the lymphatics from veins, we have used some additional stain to confirm our results (Fig. 4). The final pathological diagnosis was DPL with involvement of the extrapulmonary lymph node (right supraclavicular) and surrounding soft tissue. Based on the aforementioned histological findings, a clinical diagnosis of lymphangiomatosis involving the pulmonary and extrapulmonary lymph nodes and its surrounding soft tissue was established. Symptomatic treatments were given and the patient was subjected to routine follow-up.

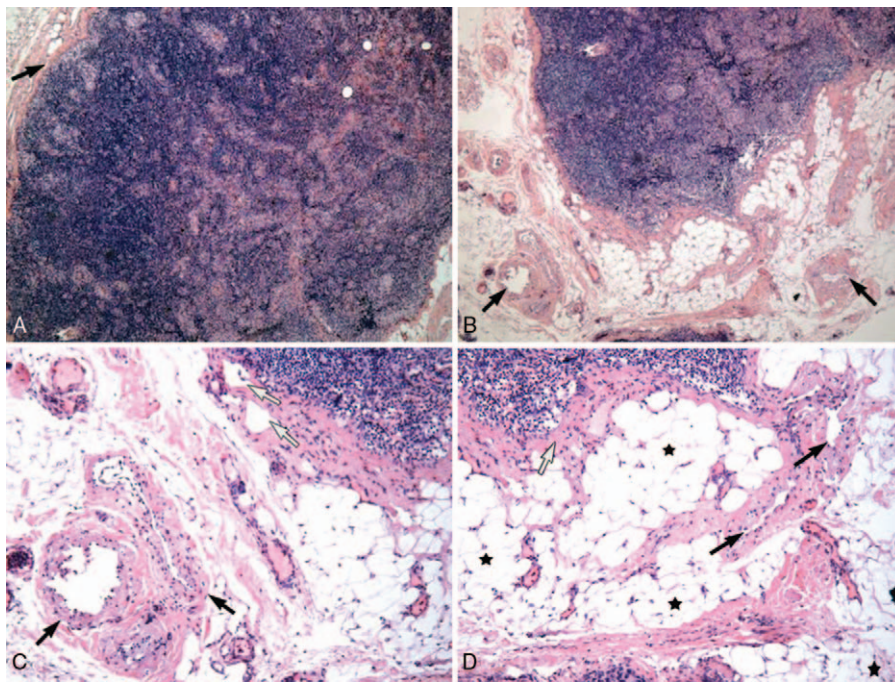
### 3. Discussion

Lymphangiomatosis is a rare disease characterized by abnormal development, malformation, and hyperplasia of the lymphatic vessels, mainly involving lung, bone, and other organs. It can be a single organ involvement (such as DPL) or multiple organ involvement.<sup>[7,8]</sup> Because it is rare, it is difficult to study large numbers of cases. Clinical, imaging, and pathological features are often observed in the form of case reports.<sup>[9-12]</sup> Lung involvement is the leading cause of death and is therefore of particular interest to the clinic. The pathogenesis of DPL is slow and the clinical manifestation is nonspecific. The most common clinical manifestations were unexplained cough, expectoration, hemoptysis, dyspnea, and chylothorax, followed by recurrent episodes of fever and pneumonia. Because of the lack of characteristic clinical and imaging features of DPL, it is easily misdiagnosed as other

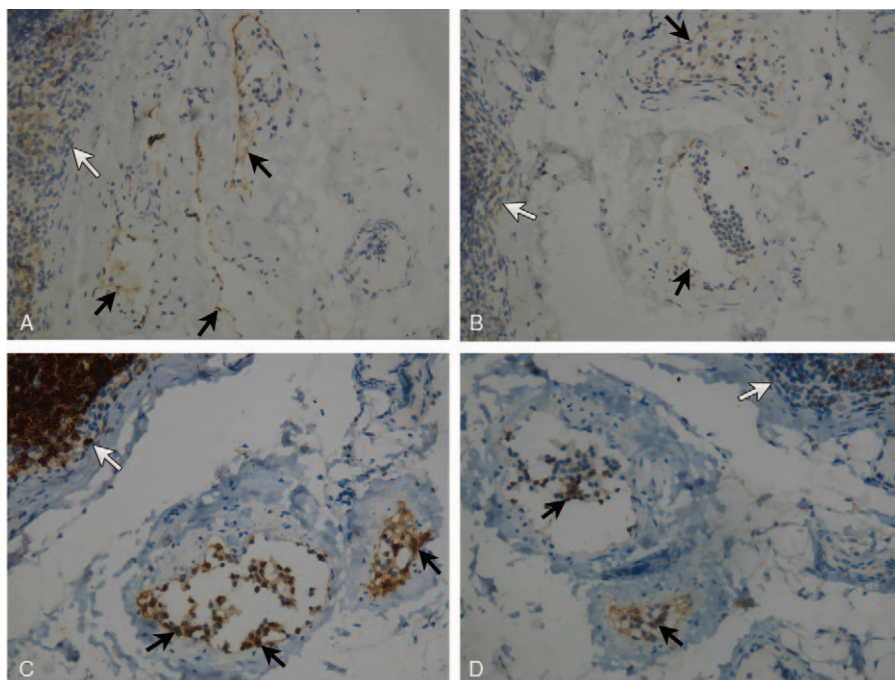


**Figure 2.** (A) Lung biopsy verified diffuse proliferation and dilated lymphatic vessels (arrowheads) under the pleura, with mild emphysema in adjacent lung tissue (★, H&E,  $\times 40$ ). (B) Enlargement of (A). The wall of the lymphatic vessels was thickened and the lumen was slit (arrowheads). The lower left corner was adjacent to the normal lung tissue (H&E,  $\times 100$ ). (C) Immunohistochemical staining for D2-40 in (B) showed the lymphatic endothelial cells were positive (arrowheads, EnVision,  $\times 100$ ). (D) Immunohistochemical staining for smooth muscle actin (SMA) in (B) revealed a brownish yellow positive staining of the smooth muscle around the lymphatics (arrowheads, EnVision,  $\times 100$ ).





**Figure 3.** (A) Lymph node biopsy showed the thickening of the lymph node capsule (arrowhead), the proliferation of lymphoid tissue in the capsule, and it was difficult to distinguish the lesions from chronic inflammation of lymph node (H&E,  $\times 100$ ). (B) The lesions of the lymph node and surrounding soft tissue demonstrated hyperplasia of fibers and adipose tissue as soon as lymphatic vessels (arrowheads) in the soft tissue, including hyperplastic vascular tissue (H&E,  $\times 40$ ). (C) At high magnification of (B) we found hyperplasia and dilatation of the lymphatic vessels (hollow arrowheads) in the thickening capsule of lymph node. The hyperplasia, dilation and deformity of lymphatic vessels and smooth muscle hyperplasia of the tube wall were shown in soft tissue (arrowheads, H&E,  $\times 200$ ). (D) Another field of view revealed the thickened lymph node capsule (hollow arrowhead) and the hyperplasia, malformed lymphatics (arrowheads) and hyperplastic adipose tissue (★) in surrounding soft tissue (H&E,  $\times 200$ ).



**Figure 4.** D2-40 immunohistochemical staining (A) showed that the lymphatic endothelial cells in the soft tissues surrounding the lymph node were brownish yellow positive staining (arrowheads, EnVision,  $\times 40$ ). Another field of view with D2-40 immunohistochemical staining (B) showed that the lymphatic endothelial cells were brownish yellow positive staining (arrowheads), and there were clusters of lymphocytes in the cavity (EnVision,  $\times 40$ ). Most of these lymphocytes showed CD79a positive staining (C, arrowheads), and a few showed CD3 positive staining (D, arrowheads). Hollow arrowheads showed lymph node tissue (EnVision,  $\times 200$ ).

diseases.<sup>[12,13]</sup> In this article, we report a 16-year-old male with cough, expectoration, and hydrothorax. Before lung biopsy, the clinical diagnosis was tuberculous pleurisy or sarcoidosis and so on. Because of the lack of clinical knowledge of the disease, it was not even suspected during the operation.

DPL is difficult to be diagnosed on the basis of clinical manifestations and imaging.<sup>[9–12]</sup> Definite diagnosis requires small incision open chest or VATS lung biopsy. The main points of pathological diagnosis are: the focus of the lesion is multifocal (which can be shown by imaging), usually distributed along the pleura, interlobular septa, and alveolar septa, and the lesions are diffusely filled with hyperplastic and dilated lymphatics vessels. The lymphatic endothelial cells with proliferation are well differentiated without atypia; immunohistochemical staining shows that the cells were positive for D2–40 and CD31, and negative for CD34. Milky chest water and multiple nodular and diffuse mesh images on chest CT are helpful for the diagnosis of DPL.<sup>[9–12]</sup> It is necessary to point out that if the specimens of puncture lung biopsy are too small, or surgical lung biopsy is not satisfactory (such as extrusion and tissue lesions block too small), pathologists' lack of experience may be misdiagnosed, because the lesions are mistaken for the blood vessels and fibrous connective tissue. The reported case was considered as a chronic inflammation of the pleura during rapid pathological diagnosis of operation.

DPL mainly affects the lungs and pleura, and can also cause diffuse involvement of extrapulmonary tissue (such as lymph nodes and their surrounding soft tissue), which is lacking in pathological reports.<sup>[14]</sup> The manifestations of lymph nodes involvement are mainly lymphoid hyperplasia and fibrous thickening capsule in which there are different degrees of proliferation, expansion, and deformity of the lymphatic vessels. Soft tissue around lymph nodes is often involved, and its pathological findings include hyperplasia, dilatation, and deformity of lymph vessels with different degrees besides the hyperplasia of fibrous adipose tissue and smooth muscle cells of the tube wall. In addition, vascular proliferation and deformity are also common. These findings are not easily distinguished LNL from chronic nonspecific inflammation. Also, LNL biopsy is rarely reported,<sup>[4]</sup> and pathologists lack knowledge of it. The aforementioned reasons often lead to the misdiagnosis and missed diagnosis of LNL. In our case, the lymph node was diagnosed as chronic lymphadenitis at first visit. After DPL diagnosis, the sections of lymph node biopsy were re-examined. We found that the lymph node and its surrounding soft tissue were also involved.

Small incisions open chest or VAST lung biopsy are often required for pathological diagnosis of DPL. However, the injury is relatively large, often leading to or exacerbating preexisting chylothorax. Therefore, if the extrapulmonary lymph nodes and surrounding soft tissue are simultaneously involved, they should be biopsied for pathological diagnosis. As it is a minimally invasive biopsy, patients would accept it easily. If we can get the definite pathological diagnosis of LNL, it will be a hint and

reference for the diagnosis of DPL. Combined with clinical and imaging, clinical diagnosis of DPL can be made, and surgical lung biopsy may be avoided or replaced by aspiration lung biopsy. After all, surgical lung biopsy is very traumatic, complicated, and sometimes difficult to operate.

In conclusion, we reported a rare case of lymphangiomatosis involving the pulmonary and extrapulmonary lymph node and its surrounding soft tissue, and demonstrated their pathological features. The final diagnosis was not confirmed until the DPL diagnosis and a review of the sections of lymph node biopsy had been done. It shows that the pathological changes of LNL relatively lack characteristics, and the pathological doctors who lack experience easily miss diagnosis and misdiagnose. The significance of this paper is that the biopsies of lymph nodes and their surrounding soft tissue should be selected first. The acquisition of pathological diagnosis can be used as a reference for the diagnosis of DPL, and may also relieve the patient from suffering from lung biopsy.

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