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An Autopsy Case of Congenital Pulmonary Lymphangiectasis Masquerading as Pulmonary Interstitial Emphysema

Sohsuke Yamada and Yasuyuki Sasaguri
University of Occupational and Environmental Health
Kitakyushu

1. Introduction

Congenital pulmonary lymphangiectasis (CPL) is a rare and poorly documented disease of neonates, and is characterized by prominent and diffuse microcystic lymphatic dilation in the septal, subpleural and peribronchial tissue throughout both lungs. Although an accurate incidence of CPL is elusive, a previous autopsy study has suggested that approximately 1% of all infants stillborn or dead in the neonatal period have CPL (Laurence KM, 1955), and at least 30 and 130 cases of CPL have been reported in Japan and in the world, respectively. According to previous CPL reports, males are affected more than females, and there is no familial predisposition in most cases. However, a few cases have described an association with genetic disorders, such as Noonan, Down, Turner, and Fryns syndromes (Fryns JP & Moerman P, 1993; Jacquemont S et al., 2000). CPL is generally divided into two groups: primary (congenital) and secondary. In addition, Noonan classified CPL into three groups (Noonan JA et al., 1970): group 1 is characterized by generalized lymphangiectasis (lymphedema with intestinal lymphangiectasis) (Bellini C et al., 2001; Maclean JE et al, 2002); in group 2, CPL is caused by pulmonary venous hypertention or obstruction associated with surgery, radiation, infection, tumor, or cardiovascular anomalies including anomalous pulmonary venous drainage or cor triatriatum (Gilewski MK et al., 1996; Verlaat CWM et al., 1994); group 3 is due to a primary developmental defect of the pulmonary lymphatics (Huber A et al., 1991; Moerman P et al., 1993). Therefore, groups 1 and 3 of CPL are primary (congenital), and group 2 is secondary. In particular, group 3 CPL is characterized by severely disturbed pulmonary gas exchange and a poor prognosis (Hoehn T et al., 2006), and some reports have shown that neonates with group 3 CPL have lymphatic dilation in the lungs and multiple other organs, and pursue an adverse clinical course (Frank J et al., 1955; Hirano H et al., 2004; Mckendry JBJ et al., 1957). Because of the clinicopathological similarities between group 3 CPL and pulmonary interstitial emphysema (PIE), CPL tends to be misdiagnosed as PIE (Finder J & Steinfeld J, 2004; Xiao ZY et al., 2009). Although a conclusive diagnosis of CPL can only be made pathologically or by autopsy, CPL should be distinguished from PIE because of their distinct treatments and prognoses (Laurence KM, 1955; Finder J & Steinfeld J, 2004; Xiao ZY et al., 2009).

2. Case report

An autopsy case of CPL group 3 is described with a special reference to distinction from PIE.

2.1 Clinical summary

A male Japanese neonate was born at 34 weeks of gestation after the pregestational treatment for infertility and medication for mild amniorrhexis, and was the second child born to non-consanguineous parents. The parents' first baby weighed 3,276 g and was born at 40 weeks of spontaneous gestation 5 years before this case. The patient weighed about 2,300 g at birth, and his Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. The amniotic fluid was clear, and the amount was approximately 400 mL. The placenta, weighing 460 g, had no remarkable features. However, he developed a severe moaning sound and dyspnea about 10 minutes after birth, in spite of artificial oxygenation. A chest X-ray film showed bilateral frosted glass-like infiltrates with an air bronchogram and an air leak (arrows) around the cardiac shadow, suggesting pneumomediastinum (Fig. 1).

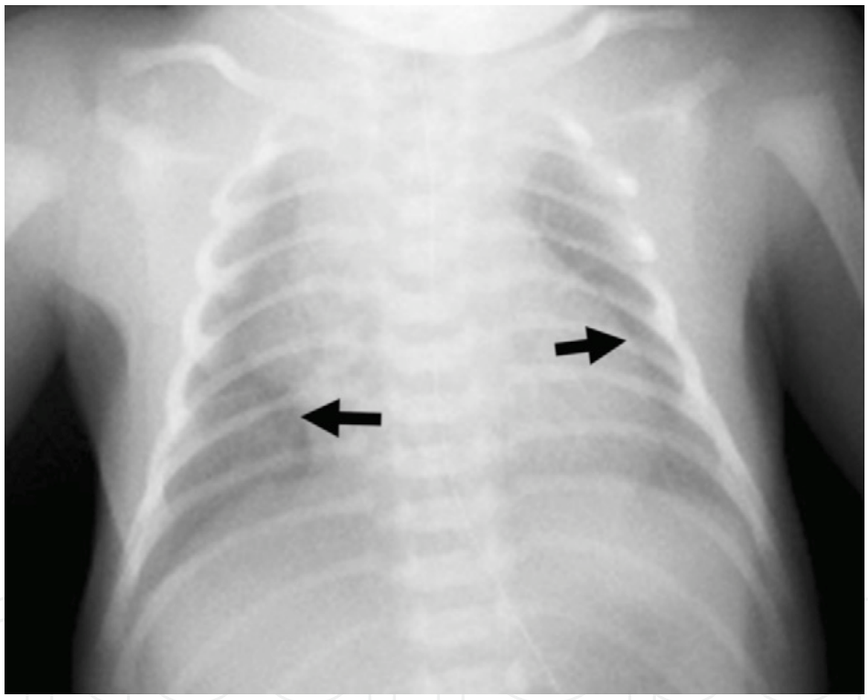


Fig. 1. Plain chest X-ray.

Despite artificial ventilation after intubation and surfactant substitution therapy, he died of hypoxemic respiratory failure 13 hours after birth due to persistent pneumomediastinum and bilateral pneumothorax, which were resistant to the puncture by thoracostomy tubes and the intravenous administration of dopamine and bicarbonate. The blood cell counts and values of blood biochemistry were within normal limits, except for a venous blood sample when breathing at 30% oxygen concentration in the incubator showing elevated partial pressure of carbon dioxide ($PaCO_2$) (70.7 mmHg), and decreased base excess (–7.4 mEq/L) and pH (7.145), indicating marked respiratory acidosis. An autopsy was performed approximately 3 hours after death.

2.2 Gross findings

At autopsy, the baby measured 45cm in height and weighed 2,328 g. An external examination showed no detectable anomalies or abnormalities except for several needle marks on the chest wall and the extremities. In an internal examination of the thoracic cavity (Fig. 2) there was a bilateral clear yellow pleural fluid (20 mL; 20 mL) without hemorrhage or chylothorax, and one cystic lesion was noted in the anterior mediastinum.

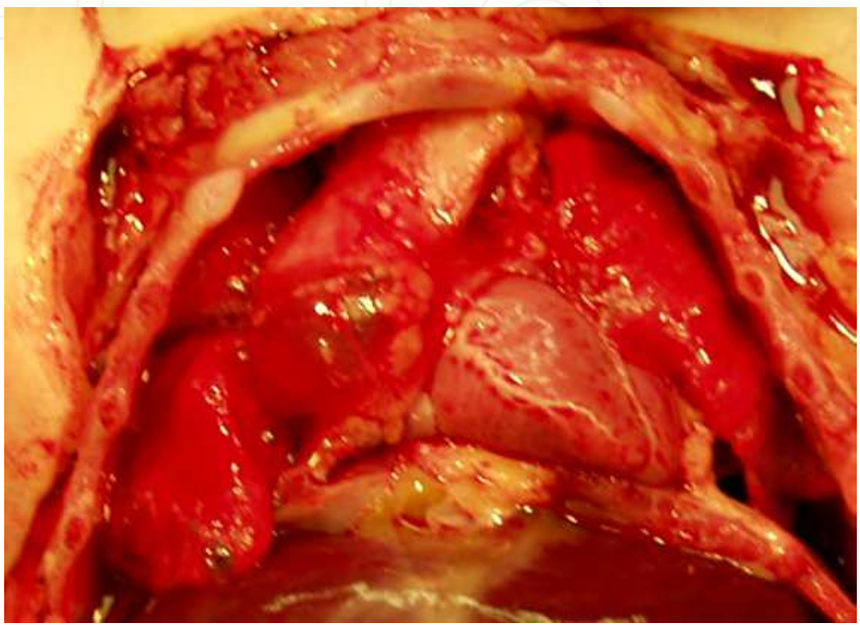


Fig. 2. An internal examination of the thoracic cavity.

In addition to the visceral pleura, both lungs demonstrated a network of dilated cystic spaces. The left and right lungs weighed 21 g and 23 g, respectively, and were firm in consistency. The cut surfaces of the congestive lungs also showed numerous cystic spaces ranging from about 1 to 2 mm in size in the surface visceral pleura as well as in the thickened interlobular septum and hilum, although the cystic changes were inconspicuous after formalin fixation. These findings were well recognized in a hematoxylin-eosin-stained scanning magnification of the lungs (Fig. 3).

The heart, weighing 18 g, showed no gross abnormalities. No specific findings were identified in the other internal organs or the brain, except for a clear yellow peritoneal fluid (150 mL).

2.3 Pathological findings

A histological examination of the lungs showed diffuse and marked lymphatic dilation in the peribronchial (Fig. 4A), subpleural, interlobular (Fig. 4B) and hilar areas.

The dilated lymphatic channels were invariably lined with flattened endothelium, which was immunohistochemically positive for D2-40 (Nichirei Bioscience Co., Tokyo, Japan, 1:1) (Fig. 5), CD31 (Dako Cytomation Co., Kyoto, Japan, 1:20) and CD34 (IMMUNOTECH, Marseille, France, 1:50).

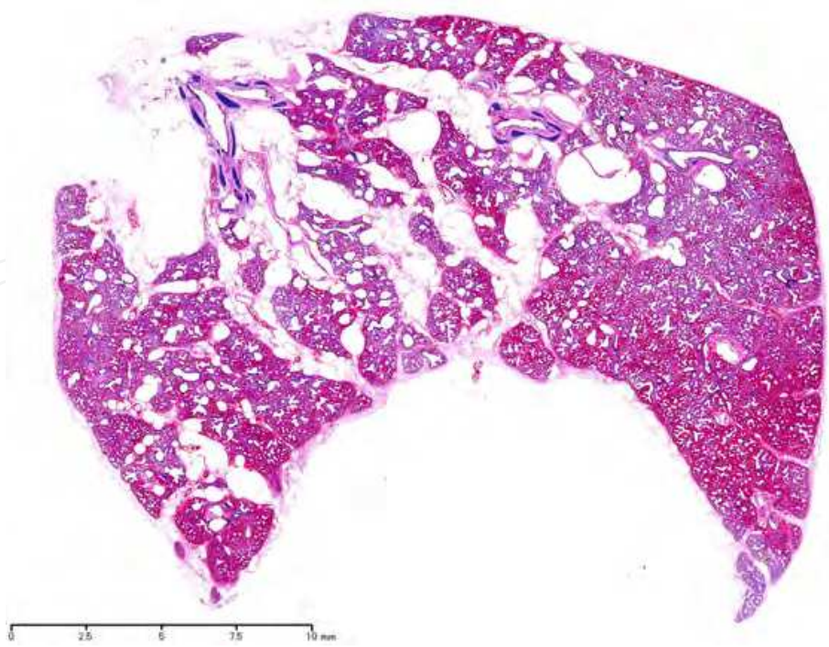


Fig. 3. Scanning magnification of the lung, right lower lobe.

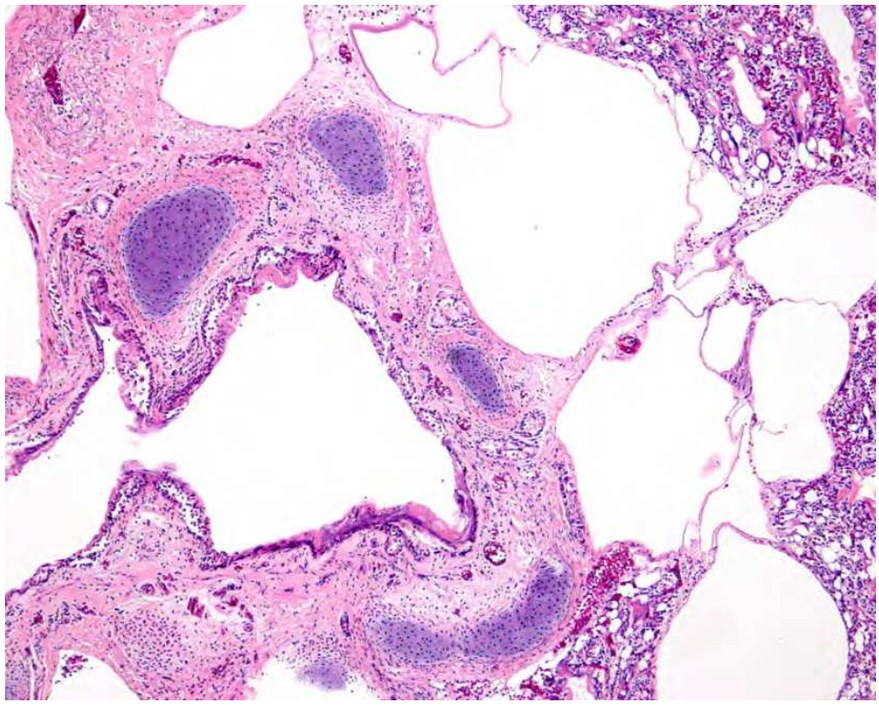


Fig. 4A. Histological finding of CPL (peribronchial).

No CD68-positive (Dako, 1:100) foreign-body type histiocytes were seen in these cystically-dilated lesions. Most of the mature-looking alveolar spaces were collapsed, and the alveolar walls were close to each other with frequent deposits of hyaline membrane along the bronchioli or alveolar ducts, accompanied by accumulated basophilic amorphous materials

(Fig. 6), which were negative for Kossa staining and probably derived from the necrotic bronchioloalveolar epithelium (Wigglesworth JS, eds., 1984).

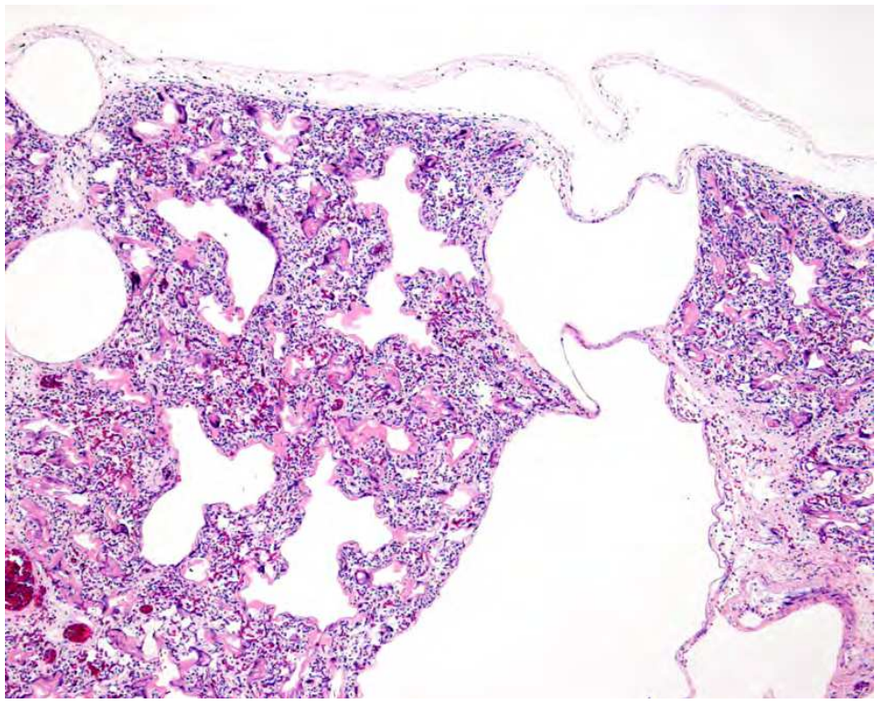


Fig. 4B. Histological finding of CPL (subpleural and interlobular).

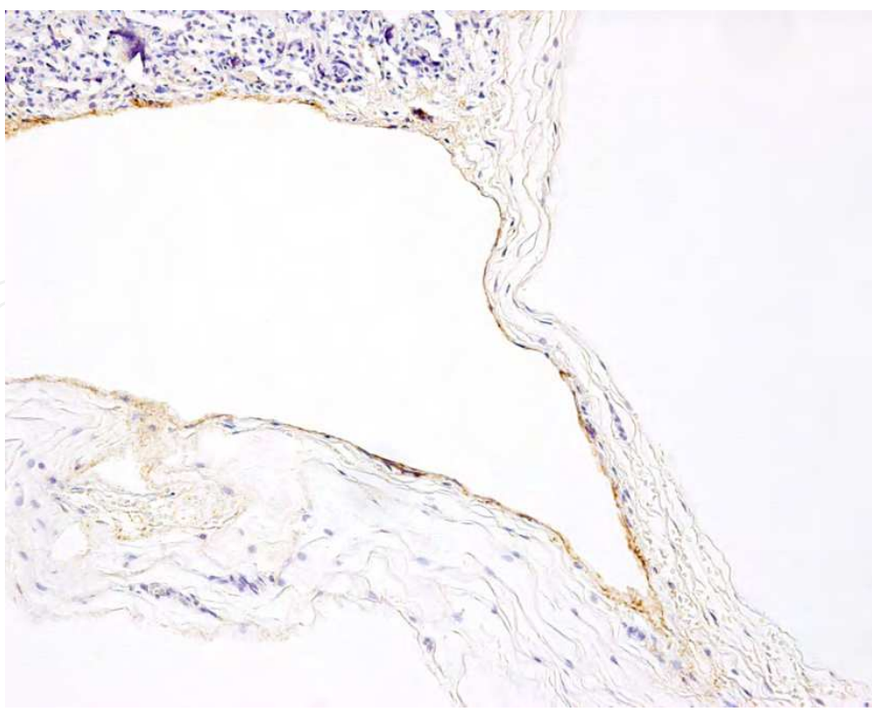


Fig. 5. Immunohistochemical finding of the dilated lymphatic channels.

Additionally, mild lymphangiectasis was found around the mediastinum including the thymus and the intra-abdominal organs such as the adrenal gland, kidney, pancreas, spleen, sigmoid colon, and abdominal aorta, all of which also lacked any foreign-body reaction. Pseudofollicular cysts were present in the definitive adrenal cortex (Fig. 7).

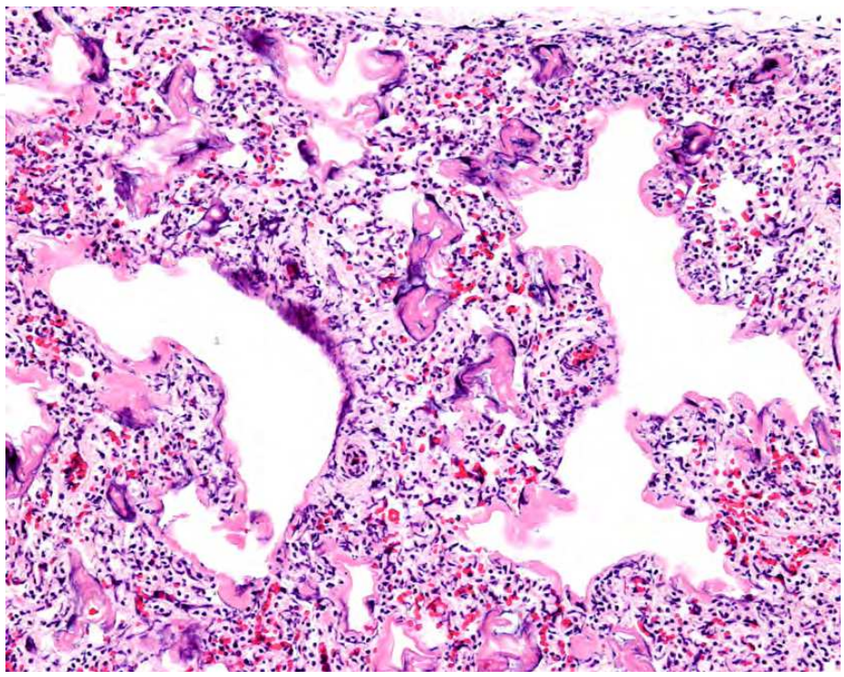


Fig. 6. Histological finding of the bronchioli to alveolar spaces.

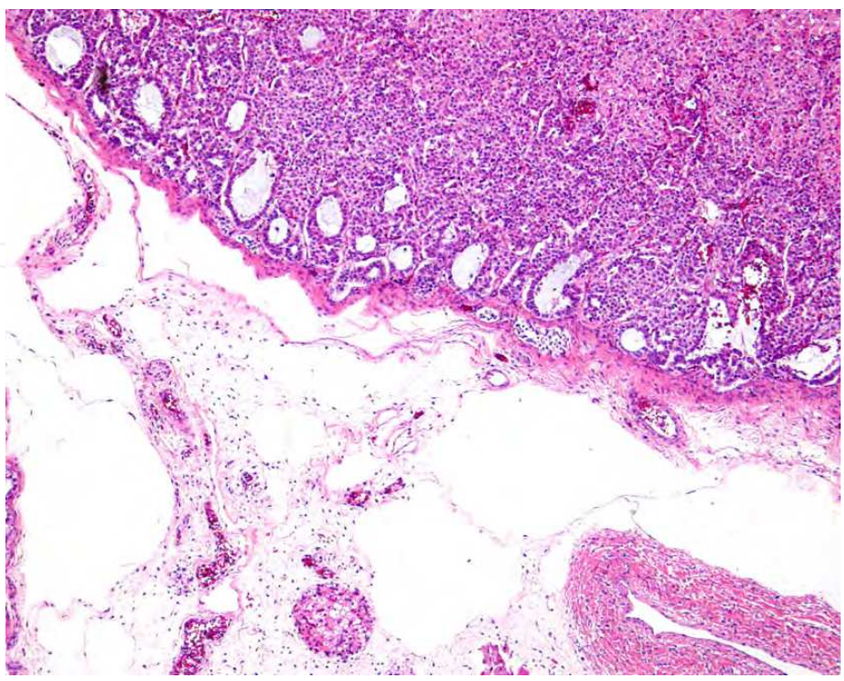


Fig. 7. Histological finding of the adrenal gland.

The diagnosis of CPL, a primary form, Noonan Group 3, was established based on these features.

2.4 Discussion

Congenital pulmonary lymphangiectasis (CPL) was first described by Virchow (Virchow R, 1856), demonstrating clinical manifestations of aggressive dyspnea after birth, cyanosis and death. The lungs of CPL show grossly dilated lymph channels beneath the pleura and in the variably thickened interlobular septa, and these dilated lymph vessels are also recognized in the subpleura, interlobular septa, and peribronchial tissue throughout both lungs microscopically. The mortality rate of neonatal CPL was considered to be nearly 100% more than 30 years ago. However, because neonatal care has advanced significantly since then, the outcome of the patients has improved, especially for those who present the symptoms after the neonatal period or for those belonging to Noonan classification group 1 or 2 (Hirano H et al., 2004; Moerman P et al., 1993). Nevertheless, Noonan group 3 CPL is usually associated with an adverse clinical course and high mortality. It is well known that group 3 CPL is due to a developmental error, probably resulting from a failure of pulmonary interstitial connective tissue to regress and leading to the dilation of pulmonary lymphatic vessels (Xiao ZY et al., 2009). This usually occurs after the 16th week of fetal life (Faul JL et al., 2000; Laurence KM, 1995), followed by insufficient dilatation of alveolar structures. These pathological changes might result in severe pulmonary symptoms (Janett SN et al., 1963), probably including those due to respiratory distress syndrome (RDS).

CPL is often difficult to differentiate from pulmonary interstitial emphysema (PIE) because of the clinicopathological similarities between these two diseases (Laurence KM, 1955; Finder J & Steinfeld J, 2004; Xiao ZY et al., 2009). PIE in the newborn is a frequent complication of RDS or hyaline membrane disease. The typical chest X-ray findings of PIE include multiple large cysts (0.8-3.0 cm) in a background of smaller cysts (0.2-0.4 cm) with uniform minute reticulogranular densities and abnormal airbronchograms caused by RDS (Stocker JT & Madewell JE, 1977). The X-ray in the current case showed bilateral frosted glass-like or cotton-like infiltrates with an air bronchogram and an air leak around the cardiac shadow due to RDS and pneumomediastinum, partly resembling the findings of PIE complicated by pneumomediastinum. Moreover, the patient suffered an uncontrollable bilateral pneumothorax after artificial ventilation was started. Therefore, a clinical distinction between these entities is not straightforward, and a definitive diagnosis of CPL can be made only by pathological examinations (Laurence KM, 1955; Finder J & Steinfeld J, 2004; Xiao ZY et al., 2009). The small cysts of PIE are invariably lined by mono- and multinucleated giant histiocytes displaying a foreign-body type reaction (Keeling JW, eds., 1993). In contrast, cysts in CPL are lined with flattened endothelium without evidence of aggregated histiocytes. Although this case demonstrated pneumothorax and pneumomediastinum, their etiological mechanisms are not easy to explain. However, the bilateral pneumothorax might have been caused by the artificial ventilation, which often results in air leak to the extra-airspaces, rather than by RDS itself. As to the pneumomediastinum prior to the ventilation and pneumothorax, a dilated lymphatic vessel might have been misunderstood as air leakage forming the persistent cystic lesion in the anterior mediastinum, in which, not only the immunohistochemical result of D2-40 showed

positive-stainings, but also no giant cell reaction was identified. Furthermore, it is certain that RDS is sometimes accompanied by pulmonary lymphangiectasis, which might or might not lead to mediastinal lymphangiectasis, to a degree that renders its distinction from CPL difficult (Keeling JW, eds., 1993). However, in RDS, distended lymphatics are primarily interlobular in location, while in CPL they are also found in the subpleural and peribronchial areas and are wider in size, as in the present case. From these viewpoints, it is suggested that this pulmonary to mediastinal lymphangiectasis is caused by not only CPL, but also by RDS, although to a lesser degree.

Besides PIE, CPL should be distinguished from diffuse pulmonary lymphangiomatosis (DPL) (Hirano H et al., 2004; Bush JK et al., 1969; Brown M et al., 1999), because of their similar clinical manifestations and histological features. In addition, an immunohistochemical approach cannot differentiate between CPL and DPL, both of which share positive stainings for vimentin, CD31, CD34, factor VIII-related antigen, and D2-40. Histologically, DPL is characterized by an increased number of complex anastomosing lymphatic channels, in which variable dilation or expansion is a secondary phenomenon within the lungs and mediastinum, whereas in CPL the lymphatics are not increased in number and are relatively more regular in size and shape (Bush JK et al., 1969; Brown M et al., 1999; Hirano H et al., 2004; Moerman P et al., 1993). Based on these features, DPL could also be excluded in our case.

3. Conclusion

Herein was reported a neonate case of group 3 CPL with pathological findings of lymphangiectasis in or around multiple organs, including both lungs, the mediastinum, and those in the intra-abdominal cavity. Although PIE was considered an important differential diagnosis because of the overlapping clinicopathological features, a giant cell reaction surrounding the interstitial cystic lesions, a histological hallmark of PIE, was absent in the present case.

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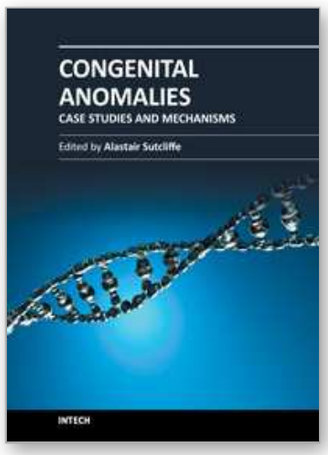
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This book is in essence a collection of essays which are state of the art in their respective areas of knowledge. They inform the reader of all sorts of mechanistic considerations when developing understanding of issues surrounding the origins of congenital abnormalities. These chapters are written by world renown authorities in this area of science and represent a wide range of expertise from a clinician perspective, through to genetic mechanisms. Unlike some books which take a formal textual, somewhat plodding way through pathophysiology here instead we have cut through chapters in which the student , or scientist or medic is lead to understand just how complex the origins can be via examples from different parts of the body. With the erudite chapters are relevant tables and other diagrams to help clarify the text . These chapters represent a starter text for the stimulus for further knowledge of what is an increasingly important area of human health.

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