

# Pulmonary lymphangiectasia

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## Abstract

*Congenital pulmonary lymphangiectasia (PL) is a rare developmental disorder involving the lung and characterized by pulmonary subpleural, interlobar, perivascular, and peribronchial lymphatic dilatation. Both frequency and etiology are unknown. PL presents at birth with severe respiratory distress, tachypnea, and cyanosis, with a very high mortality rate at or within a few hours of birth.*

*At birth, mechanical ventilation and pleural drainage are nearly always necessary to obtain a favorable outcome of respiratory distress. Home supplemental oxygen therapy and symptomatic treatment of recurrent cough and wheeze are often necessary during childhood, sometimes associated to prolonged pleural drainage. Recent advances in intensive neonatal care have changed the previously nearly fatal outcome of PL at birth. Patients affected by PL who survive infancy, present medical problems which are characteristic of chronic lung disease.*

## Keywords

Pulmonary Lymphangiectasia

## Disease name/Synonyms

Pulmonary Lymphangiectasia is also called:

- Pulmonary Cystic Lymphangiectasis
- Pulmonary Lymphangiomatosis

## Definition/Diagnostic criteria

Congenital pulmonary lymphangiectasis (PL) is a rare developmental disorder involving the lung and characterized by pulmonary subpleural, interlobar, perivascular, and peribronchial lymphatic dilatation. On the basis of improved

characterization of the clinical presentation and recent noteworthy advances in intensive neonatal care, the original classification [1] has been modified and PL has been sub-divided into two major categories, defined as primary and secondary PL [2, 3].

When presenting as a primary pulmonary developmental defect, PL may be caused by a congenital defect in the primary development of the lung, or may represent the localized expression of more generalized lymphatic involvement. When it is part of generalized

lymphatic dysplasia, PL presents with dilated pulmonary lymphatics as part of a generalized form of lymphangiectasia, i.e., truncal lymphangiectasia, which is usually associated with lymphedema. Hemihypertrophy may also be observed, although only rarely in infants and young children.

Cardiovascular and lymphatic obstructive forms constitute the secondary PL group. Hypoplastic left heart syndrome, pulmonary vein atresia, congenital mitral stenosis, cor triatum, and thoracic duct agenesis are the main possible causes of secondary PL.

### Etiology

The etiology of PL is not known. It has been suggested that PL lymphatic channels of the fetal lung do not undergo the normal regression process at 20 week's gestation, and thus large lymphatic vessels persist, that are normal in the 9-16 week gestation maturation developmental process [4]. Obstruction of pulmonary lymphatics or veins, or the action of infectious agents have also been taken into consideration [2].

Secondary PL may be caused by a cardiac lesion. Pulmonary lymphatics dilatation develops *in utero* because of obstructed pulmonary venous flow, or it can be caused by a cardiac lesion which has been hypothesized to interfere with the normal regression of the lymphatic tissue elements after the 16<sup>th</sup> week of fetal life [3].

### Clinical description

PL may present at birth as a stillbirth or with severe respiratory distress, tachypnea, and cyanosis, with a very high mortality rate at or within a few hours of birth [2]. Clinical diagnosis of PL can be strongly suspected in full-term neonates who present severe respiratory distress with pleural effusion (especially if chylous) at birth, with or without generalized or localized lymphedema.

As reported in the early studies on this topic, before effective mechanical ventilation became available, most children did not survive. Mechanical ventilation has almost always been required in the most recently reported cases [2, 3]. In the post-neonatal period, children with PL present with respiratory difficulties of varying degree, associated with a relapsing course. During both the neonatal and post-neonatal period PL may be associated with chylothorax, chylopericardium, and chylous ascites. In older children it is frequently associated with recurrent cough, wheeze, increased respiratory effort with inspiratory crackle, and even congestive heart failure. The disease is characterized by frequent respiratory exacerbations [3, 5].

Contradictory data have been reported with reference to outcome. A recently reported series [5, 6] stated that respiratory symptoms improved over time in most of their study patients (8/9), including those who presented in the neonatal period (3/9). These data are in contrast with a previously reported, 11 patient series [6], in which all the patients who had been diagnosed during the neonatal period died (6/11). It must be pointed out that in this latter study, 2/11 patients were born at < 30 weeks' gestation, and that another 4/11 subjects had complex cardiac abnormalities. In the former study the occurrence of cardiac involvement was less severe, and included pulmonary stenosis in 2/9 patients, and mild tricuspid regurgitation in 3/9, including one patient who also presented pulmonary hypertension. When diagnosis is made in childhood or adult age, the outcome is more likely to be favorable *quoad vitam* [5].

Other small series and single case reports do not consent to establish a consistent prognosis [2, 3, 6-15].

Recent advances in intensive neonatal care have changed the previously nearly fatal outcome of PL at birth. Patients affected by PL who survive infancy often present medical problems that are characteristic of chronic lung disease. Gastroesophageal reflux and poor growth are also not uncommon during the first year of life, especially between six and twelve months of age, and are closely related to chronic lung disease. If chylothorax occurs, a number of components are lost, including fats (mainly phospholipids, cholesterol, and triglycerides), proteins (mainly albumin, immunoglobulins, and fibrinogen), electrolytes, and fat-soluble vitamins in concentrations similar to what is found in plasma, causing severe cadential manifestations.

### Diagnostic methods

As previously reported, during the prenatal period all the causes leading to hydrops fetalis (HF) have to be taken into consideration in the diagnosis of PL. The diagnostic approach includes the following: complete family and obstetric history; ultrasound examination and magnetic resonance studies searching for twin gestation, anatomic abnormalities, heart fetal echo, and doppler blood flow assessment; maternal evaluation including blood type, Rh, antibody screening, Kleihauer-Betke stain, TORCHES-CLAP titer (TOxoplasma gondii; Rubella virus; Cytomegalovirus; Herpes simplex virus; Enterovirus; Syphilis; Chickenpox [varicella-zoster] virus; Lyme disease [Borrelia burgdoferi]; AIDS; Parvovirus B19), metabolic studies, and Hb electrophoresis; invasive fetal

assessment includes amniocentesis (karyotype, cultures, TORCHES-CLAP, and restriction endonuclease, fetal blood sampling (blood type, Hb electrophoresis, blood gas, cultures, TORCHES-CLAP, and DNA analysis), and fetal effusion sampling (TORCHES-CLAP, protein content, and cell count).

The postnatal diagnostic approach includes the laboratory and instrumental evaluation that is needed to rule out various conditions possibly related to PL, and to establish whether PL is primitive or secondary.

Hematologic causes can be ruled out by blood cell count, Kleihauer-Betke stain, Hb electrophoresis, CBC and smear; cardiovascular causes can be excluded by echocardiogram and ECG; congenital infections by TORCHES-CLAP; genitourinary causes by kidney sonography, BUN, and plasma-urine creatine; chromosomal, syndromic, and metabolic diseases by usual diagnostic protocols.

Diagnostic methods that can be useful in diagnosing PL include conventional radiologic studies, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [2, 5, 6, 10, 12, 14-19], lymphoscintigraphy [2, 15, 20, 21], lung functionality tests [5], lung biopsy [5, 16], bronchoscopy [5, 16], and pleural effusion examination [22, 23].

Chest X-rays usually show hyperinflation with interstitial markings. Longitudinal follow-up indicates the possible progression of hazy infiltrates, that are usually seen during the neonatal period, to a more perihilar interstitial pattern with varying degrees of lung inflation. Generally speaking, it may be affirmed that, like the clinical features, the radiological findings in PL improve over time.

High-Resolution CT demonstrates diffuse thickening of the interstitium, both of the peribronchovascular interstitium and the septa surrounding the lobules. Helical chest CT usually highlights eventual diffuse interstitial change involving thickening of the interlobular septa, which is very often associated with the presence of pleural fluid effusion and atelectasia. Findings from CT scan studies have also shown improvement over time, although the regional pattern of parenchymal inhomogeneity persisted in several studies.

Coronal MRI T1 may permit to show thickening of the interstitium, pleural fluid effusion, and atelectasia, if present. Axial MRI T2 usually shows high-signal material within the pulmonary interstitium, which is very often associated with pleural effusion.

It has been demonstrated that, despite the greater dose of radiation that is given during CT as compared to chest radiography, CT is

preferable for the diagnosis of PL and, more in general, for the diagnosis of pediatric interstitial lung disease.

Lymphoscintigraphy is a mildly invasive technique that provides valuable morpho-functional information regarding the lymphatic system. It highlights the accumulation of lymphatic fluid in the interstitial tissue that causes swelling, which is most evident in the limbs. Lymphoscintigraphy is useful for evaluating lung lymph vessel involvement by proving there is an accumulation of radiotracer in the lung and by providing evidence of back-flow within the thoracic duct.

It is also useful for evaluating possible, generalized, associated lymph vessel dysfunction by identifying delay, asymmetric or absent visualization of regional lymph nodes, "dermal back-flow", asymmetric visualization of lymphatic channels, collateral lymphatic channels, interrupted lymphatic structures, and lymph nodes of the deep lymphatic system.

Borderline disease may occur in the newborn. In these cases, quantitative analysis, obtained by determining the transport index, may increase the sensitivity and specificity of lymphoscintigraphy in the very early diagnosis of lymphatic disorders of the newborn.

Evaluation of pleural effusion: chylothorax is usually diagnosed in the presence of pleural effusion with a triglyceride level > 1.1 mmol/L and a cell count > 1,000 cells/ $\mu$ L, with a predominance of lymphocytes (approx. 80%), according to the criteria drawn up in previous reports. However, this is an unreliable diagnostic test in malnourished patients and in patients not receiving enteral nutrition, including the fetus and occasionally the neonate. Without enteral feeding, not enough chylomicron (the main triglyceride carrier) is produced to raise chyle triglyceride levels. In these patients, a diagnosis of chylothorax may easily be made by detecting lymphocytes in the pleural fluid.

In the few cases in which lung function tests were performed, they showed various patterns including restrictive, obstructive, and normal values. It is noteworthy that, pulmonary function tests were stable over time in the patients who obtained multiple values. Bronchoscopic evaluation, while not specifically indicated in PL, may be useful for ruling out other pulmonary pathologies, and for performing bronchial lavage to identify and isolate respiratory pathogenic organisms. No tracheo-bronchial anatomical abnormalities were reported in PL patients who were evaluated by bronchoscopy. Signs of bronchitis are often reported.

Lung biopsy may be useful to demonstrate the presence of dilated lymphatic spaces in the sub-

pleural connective tissue, along the thickened interlobar septa, and around the bronchovascular axes.

Great care must be taken when interpreting lung biopsies. In fact, the pathological findings in PL patients may change a great deal over time, especially in case of viral infection, and, more in general, may span from initial recognition of minimal evidence of lymphatic dilatation, possibly related to a technical artifact (cross-clamping of the lung), to proof of severe lymphangiectasia. In this case, the lymphatic vessels are characterized by a thin wall, devoid of smooth muscle, and with slightly dilated lumen, lined by flattened endothelial cells. Note that severe clinical conditions frequently do not permit to perform lung biopsies, especially in newborns.

Post-mortem examinations of the lung may be difficult and sometimes not very informative. Lung removal during autopsies causes the lymphatics to collapse, thus preventing the network of intercommunicating channels from being evidenced.

PL has also been associated with multiple congenital anomaly syndromes, among which we can mention [Noonan syndrome](#), [Turner syndrome](#), [Down syndrome](#) [11, 24, 25], [Fryns syndrome](#) [14], [Hennekam syndrome](#) [26], Milroy syndrome [14], and Urioste syndrome [24, 25, 27]. A syndromic classification of hereditary lymphedema was recently proposed [28].

### Differential diagnosis

PL may be diagnosed during the prenatal and /or neonatal period, or in older children or adults when it presents with a milder course [2, 3, 5]. During the prenatal period, all causes leading to hydrops fetalis have to be taken into consideration. Any condition that may possibly be related to respiratory distress syndrome of the neonate has to be evaluated (pulmonary aspiration syndrome, interstitial lung disease, pulmonary infection). Furthermore, PL should be taken into consideration in the differential diagnosis of children with chronic respiratory symptoms and with rare pediatric interstitial lung disease, which is a heterogeneous group of disorders characterized by the presence of inflammation of the pulmonary interstitium [29]. Several conditions may present with clinical and radiologic signs similar to disorders involving lung interstitium. Therefore, in differential diagnosis, it must be considered idiopathic interstitial pneumonitis, follicular bronchiolitis, alveolar proteinosis, lymphocytic interstitial pneumonitis, idiopathic pulmonary hemosiderosis, and lymphangiomatosis.

Finally, it must be suggested both paying careful attention to all cases of peripheral lymphatic involvement, with or without clinical pulmonary signs, as well as searching for generalized lymphatic dysplasia.

### Epidemiology

The incidence of PL is unknown. Any attempt to provide precise statistics regarding the incidence of PL would be misleading considering that to date only few isolated cases or small series have been reported. Autopsy studies suggest that approximately 0.5-1% of infants who are stillborn or die in the neonatal period have PL, and in two reported stillborn series, 5 out of 451 cases and 11 out of 2,514 cases, respectively were identified [3]. Congenital PL may be associated with NIHF (non-immune hydrops fetalis) and with congenital chylothorax [15]. Although the incidence of these conditions is not directly correlated to the possible incidence of PL, it may be useful to keep in mind that the incidence of hydrops fetalis in obstetric-neonatal referral centers may be as high as 1:800 [30]. Furthermore, this condition carries a dreadful prognosis with a mortality rate ranging from 50% to 98%, and that the incidence of congenital chylothorax is about 1:10,000-15,000 pregnancies, with a male-female ratio of 2:1 [30].

### Genetic counselling

The low number of reported cases does not permit to perform consistent genetic counseling. Most cases are sporadic. Affected siblings have been described both in cases of the isolated primary form, and occasionally in various genetic multiple congenital anomalies (see above in "Diagnostic methods"). A male predominance in the primary form is reported, but data are not entirely convincing.

In a recent review [28] pulmonary lymphatic dysplasia was described in autosomal dominant syndromes (yellow nail syndrome - OMIM #153300-, Noonan - #OMIM 163950-, Intestinal lymphangiectasia - OMIM #152800, lymphedema/cerebral arterio-venous anomaly - OMIM 152900-) autosomal recessive syndromes (PEHO syndrome - OMIM #260565-, German syndrome - OMIM 231080-, Hennekam lymphangiectasia- OMIM #235510-, Campomelia, Cumming type - OMIM #211890-, Idiopathic hydrops fetalis - OMIM #236750-, hypotrichosis lymphedema teleangiectasia - OMIM #607823-, Knobloch syndrome - OMIM #267750-, and Urioste syndrome -OMIM #235255-), and X-linked syndromes (lymphedema hypoparathyroidism -OMIM 247410- and mandibulofacial dysostosis, lymphedema syndrome [31]).

The occurrence of PL in siblings, and the association with a wide number of autosomic recessive syndromes would make a recessive mode of inheritance a reasonable hypothesis, although to date, one that has certainly not been proved. When PL occurs as part of other known syndromes, such as Down syndrome, Noonan syndrome, or other previously mentioned ones, genetic counselling should refer to the common recommendations that are usually made for each known syndrome [11, 13, 24-27, 32].

### Antenatal diagnosis

Obstetric fetal ultrasound evaluation plays a key role in antenatal diagnosis of PL.

The conditions leading to the pathologic increase in interstitial and total fetal body water may be correlated to congenital PL, and, more in general, should be correlated to conditions that cause hydrops fetalis. Hydrops fetalis must be taken into consideration in the presence of generalized skin thickening of > 5 mm, and two or more of the following signs: placental enlargement, pericardial effusion, pleural effusion, or ascites [30].

Any of these conditions may occur in cases of congenital PL. Most studies on fetal hydrops, however, include cases in which fluid accumulation is not present in all compartments. It is generally assumed, in fact, that the etiology is the same and that these cases represent an earlier stage of the same pathological conditions. Although this is true for some pathologies, others lead to an accumulation of fluid only in some compartments (i.e., isolated ascites, isolated hydrothorax, or other isolated conditions), without clear progression to generalized hydrops. Very early ultrasound recognition of abnormal fluid accumulation often ends in premature birth, thus generalized hydrops cannot fully develop. This may generate considerable overlapping in the literature among hydrops, nuchal cystic hygroma, and accumulations of lymph fluid in body cavities caused by dysplasia and/or obstruction of lymphatic vessels [30].

### Management including treatment

Treatment is generally supportive. At birth, in the presence of severe respiratory distress associated with pleural effusion, delivery room management could be a challenge and multiple procedures might be required. Tracheal intubation and assisted ventilation are usually necessary. When effective gas exchange is not reached, sterile thoracentesis and/or paracentesis must be taken into consideration. Fluid replacement, inotropic support and, in case of persistent pulmonary hypertension, ventilatory

management with high frequency oscillatory ventilation and/or nitric oxide may be necessary. Airway, chest wall, and pulmonary edema, pleural effusion, pulmonary hypoplasia with associated respiratory distress syndrome, perinatal depression, hypoxia, and acidosis are the main problems that occur during delivery room resuscitation and then during at birth stabilization.

The immediate at birth evacuation of the pleural effusion with assisted ventilation may lead to favorable outcome of respiratory distress.

Respiratory problems that occur in the post-neonatal age, and that can continue over the next years of life often need home supplemental oxygen and symptomatic treatment for recurrent cough and wheeze. A great deal of attention must be paid to avoid bronchitis since common respiratory pathogens are usually involved. Cultures from bronchoalveolar lavage should be done in order to start selective antibiotic treatment.

In patients with rapidly expanding pleural effusion that requires placing unilateral or bilateral chest tube(s), the large amount of fluid that is drained over days and weeks leads to the loss of great quantities of albumin, immunoglobulin, and many other plasma factors that must be replaced, in some cases even on a daily basis. Gastroesophageal reflux requires standard treatment.

Nutrition plays an important role in reducing lymphatic production. Enteral nutrition with medium-chain triglycerides and total parenteral nutrition were successfully employed [2, 3].

Octreotide and antiplasmin have been used in PL and in intestinal lymphangiectasia. Non-univocal data are available regarding the effectiveness of these drugs [33-37].

When the chyle leakage persists (intractable chylothorax), pleurodesis by instillation of sclerosing agents (talc, fibrin glue, povidone-iodine) or parietal pleurectomy appear to be effective. Pleurodesis may be associated to thoracic duct ligation or suture of leaking collaterals [38-40].

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