Lymphology 38 (2005) 111-121

PULMONARY LYMPHANGIECTASIA

C. Bellini, F. Boccardo, C, Campisi, P. Toma, G. Taddei, G. Villa, P. Nozza, G. Serra, E. Bonioli

Servizio di Patologia Neonatale (CB,GS), Dipartimento di Pediatria (DIPE), Università di Genova, Istituto G. Gaslini; Dipartimento di Scienze (FB,CC) Chirurgiche Specialistiche Anestesiologiche e Trapianti d'Organi (DISCAT), Università di Genova; Servizio di Radiologia (PT), Istituto G. Gaslini; Servizio di Medicina Nucleare (GT,GV), Università di Genova; Unità Operativa di Anatomia Patologica (PN), Istituto G. Gaslini; and Dipartimento di Pediatria (DIPE) (EB), Università di Genova, Istituto G. Gaslini, Genova, Italia

ABSTRACT

Congenital pulmonary lymphangiectasia (PL) is a rare developmental disorder involving the lung and is 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.

Congenital pulmonary lymphangiectasia (PL) is a rare developmental disorder involving the lung and characterized by pulmonary subpleural, interlobar, perivascular, and peribronchial lymphatic dilatation. Pulmonary Lymphangiectasia is also called Pulmonary Cystic Lymphangiectasis and Pulmonary Lymphangiomatosis.

INCIDENCE AND CLASSIFICATION

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 (1). Congenital PL may be associated with non-immune hydrops fetalis and with congenital chylothorax (2). 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 obstetricneonatal referral centers may be as high as 1:800 (3). Furthermore, this condition carries a dreadful prognosis with a mortality rate ranging from 50% to 98%, and the incidence of congenital chylothorax is about 1:10,000-15,000 pregnancies, with a male-female ratio of 2:1 (3).

TABLE 1
Classification of Pulmonary Lymphangiectasia

Primary Pulmonary Lymphangiectasia	• Failure of normal regression process of lymphatic channels of the fetal lung (20 weeks gestation) • Part of a generalized form of lymphangiectasia • Syndromic (See Table 4)
Secondary Pulmonary Lymphangiectasia	• Cardiovascular • Thoracic duct agenesis • Infections

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 weeks gestation, and thus large lymphatic vessels persist, which 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 suggested (5). Secondary PL may be caused by a cardiac lesion. Pulmonary lymphatic 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 16th week of fetal life (1).

On the basis of improved characterization of the clinical presentation and recent noteworthy advances in intensive neonatal care, the original classification (6) has been modified and PL has been sub-divided into two major categories, defined as primary and secondary PL (*Table 1*) (1,5).

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. 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.

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 (5). 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 (1,5).

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 crackles, and even congestive heart failure. The disease is characterized by frequent respiratory exacerbations (1,7).

Contradictory data have been reported with reference to outcome. A recently reported series (7,8) 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 (8), 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 (7).

Other small series and single case reports do not permit a consistent description (1,2,5,8-16).

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 chemical 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 that found in plasma.

DIAGNOSTIC METHODS

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 (> 5 mm), and two or more of the following signs: placental enlargement, pericardial effusion, pleural effusion, or ascites (3).

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 condition. Although this may be true in some cases, other disorders lead to an accumulation of fluid only in some compartments (i.e., isolated ascites, isolated hydrothorax), without clear progression to generalized hydrops. Very early ultrasound recognition of abnormal fluid accumulation often ends in premature birth, before the development of generalized hydrops. This may generate considerable overlapping in the literature among hydrops, nuchal cystic hygroma, and accumulations of lymph in body cavities caused by dysplasia and/or obstruction of lymphatic vessels (3).

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 (*Table 2*): 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;

TABLE 2
Prenatal Diagnostic Approach to Pulmonary Lymphangiectasia

History	US Studies	Maternal Laboratory Evaluation	Invasive Fetal Assessment		
			Amniocentesis	Fetal blood sampling	Fetal effusion sampling
Family history (genetic disease or congenital anomalies) Infections/Trauma	Twin gestation Anatomic abnormalities Heart fetal echo Doppler blood flow assessment	Blood type, Rh, antibody screen, Kleihauer-Betke stain TORCHES-CLAP Metabolic studies Hb electrophoresis	Karyotype Cultures TORCHES-CLAP Restriction endonuclease	Karyotype CBC and smear Blood type Hb electrophoresis Blood gas TORCHES-CLAP DNA analysis	Cultures TORCHES-CLAP Protein content Cell count Cultures

TABLE 3
Postnatal Diagnostic Approach to Pulmonary Lymphangiectasia

Laboratory and instrumental evaluations	Ruled out causes
Blood cell count, Kleihauer-Betke stain, Hb electrophoresis, and CBC and smear	Hematologic causes
Echocardiogram, ECG	Cardiovascular causes
TORCHES-CLAP	Congenital infections
Karyotype, genetic consultation	Chromosomal, syndromic, and metabolic disease
Kidney sonography, creatinine	Genitourinary causes
Lymphoscintigraphy, MR – CT scans	Congenital lymphatic dysplasia

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

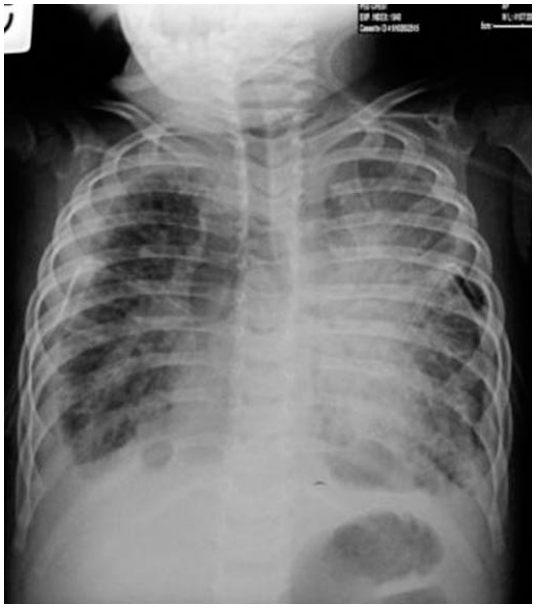

Fig. 1. Congenital Pulmonary Lymphangiectasia. Chest radiograph; antero-posterior view. Thoracic radiographs show increased interstitial markings, coarse reticulonodular appearance of the lungs, and bilateral pleural effusion. The diffuse thickening of the peribronchovascular interstitium and septa surrounding the lobules are evident. Overaeration is also present. This image is of a female patient, who presented with progressively worsening respiratory distress at 18 months of age and eventually required bilateral pleural drainage and left pleurodesis. The patient is currently awaiting evaluation of partial surgical correction and, at the time of submitting this paper, is still an in-patient in our Pediatrics Department. To date no lymphoscintigraphy has been performed due to the patient's critical condition.

fetal effusion sampling (TORCHES-CLAP, protein content, and cell count).

The postnatal diagnostic approach (*Table 3*) includes the laboratory and instrumental evaluation that is needed to rule out various conditions possibly related to PL, and to establish whether PL is primary or secondary.

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

Diagnostic methods that can be useful in diagnosing PL include conventional radiologic studies, CT and MR imaging (2,5,7,8,12,14,16-20), lymphoscintigraphy (2,5,21,22), lung functionality tests (7), lung biopsy (7,17), and pleural effusion examination (23,24).

Chest x-rays usually show hyperinflation with increased interstitial markings, and pleural effusion *(Fig. 1)*.

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 Computed Tomography demonstrates smooth thickening of the interlobular septa, peribronchial thickening which is very often associated with the presence of pleural fluid effusion and atelectasis, patchy ground glass opacity and increased attenuation of the mediastinal fat with bilateral pleural effusion and pleural thickening (*Fig. 2*). 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 show thickening of the interstitium, pleural fluid effusion, and atelectasias, if present. Axial MRI T2 usually shows high-signal material within the pulmonary interstitium, which is very often associated with pleural effusion.

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 minimally invasive technique that provides valuable

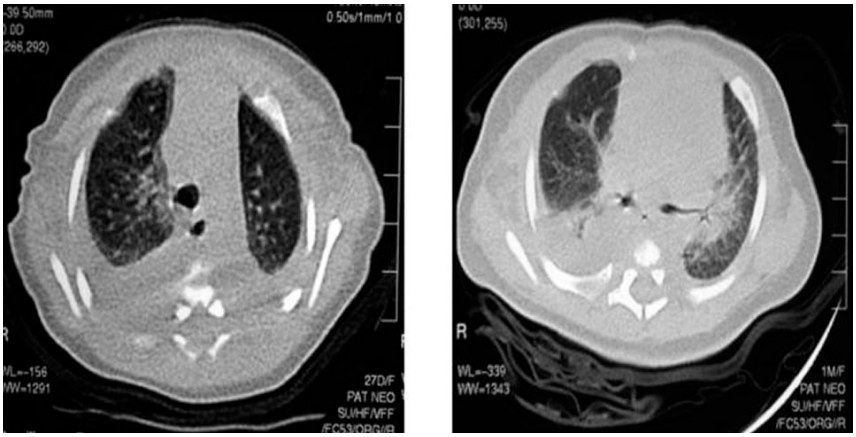

Fig. 2. Congenital Pulmonary Lymphangiectasia. High-resolution CT images (2.0 mm thick sections at 10-mm intervals) demonstrate thickening of the interlobular septa and pleural effusion. This image is of a female patient, who presented with severe respiratory distress at birth requiring artificial ventilation and bilateral pleural drainage. Generalized lymphedema was evident, especially in the lower right leg and foot, and in the genitalia. Intestinal lymphangiectasia was suspected. No pulmonary biopsy was performed, however lymphoscintigraphy showed abnormal drainage of the lower limbs (right more than left), and demonstrated back-flow within the thoracic duct. The CT picture, together with clinical evidence and the lymphoscintigraphic study, strongly suggests a diagnosis of pulmonary lymphangiectasia.

morpho-functional information regarding the lymphatic system *(Fig. 3)*. 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 demonstrating 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 associated generalized lymph vessel dysfunction by identifying delay, asymmetric or absent visualization of regional lymph nodes, "dermal backflow," 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/ml, with a predominance of lymphocytes (~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, insufficient chylomicra (the main triglyceride carrier) are produced to raise chyle triglyceride levels. In these patients, a diagnosis of chylothorax is suggested by detecting lymphocytes in the pleural fluid.

In the few cases in which lung function tests have been 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

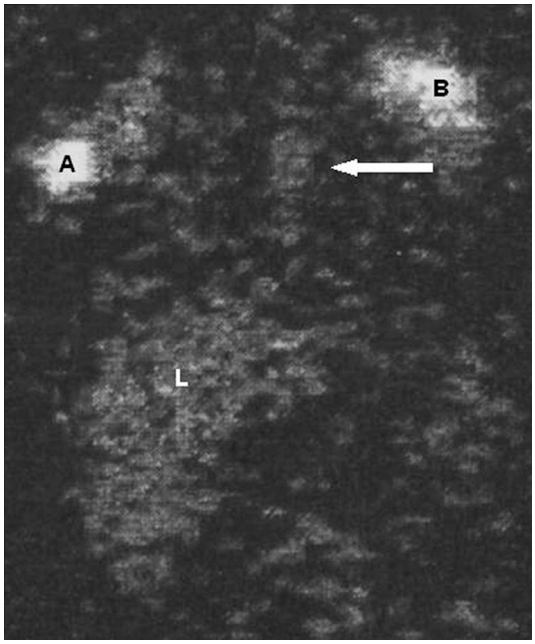

Fig. 3. Lymphoscintigraphy in a newborn affected by pulmonary lymphangiectasia and generalized lymphedema. A, B, and L indicate the right axillary lymph nodes, left axillary lymph nodes, and liver, respectively. The arrow indicates the thoracic duct. Signs of backflow were evident in the thoracic duct with accumulation of the radiocolloid. Diffusion of the tracer in the abdomen and the thorax is also evident, although to a lesser degree. This image is of a male patient, who presented with severe respiratory distress at birth. Respiratory problems mandated transportation to the intensive care unit where immediate intubation, artificial ventilation, and bilateral surgical drainage were performed. After initiation of enteral feeding on the third day, chylothorax was diagnosed. Thoracic radiographs showed increased interstitial markings, and High Resolution Computed Tomography confirmed the diffuse thickening of the interstitium, both of the peribronchovascular interstitium, and the septa surrounding the lobules.

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. Pleural histologic studies are also useful (*Fig. 4*). The pathological findings in PL patients may change a great deal over time, especially in case of viral infection, and, more generally, may range 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 allow lung biopsies to be performed, 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 documented.

PL has also been associated with multiple congenital anomaly syndromes, among which are Noonan syndrome, Turner syndrome, Down syndrome (13,25,26), Frijns syndrome (16), and Urioste syndrome (25,26,28). A syndromic classification of hereditary lymphedema was recently proposed (29).

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 (1,5,7). 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

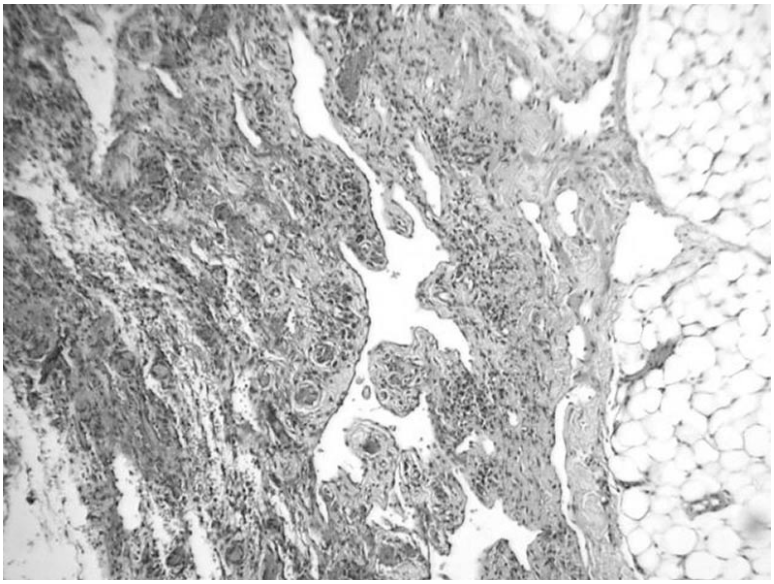

Fig. 4. Pleural histological study. Histological examination shows dense connective tissue with conspicuous fibrosis and patchy chronic (lymphocyte-plasma cell) inflammation, which is consistent with pleural thickening; dilated irregular lymphatic spaces are positioned within the pleura; the lymphatic vessels have thin walls that are devoid of muscle fibers. Some of the lymphatics are cystically dilated. This image is of a female patient, who presented with respiratory distress and pleural effusion at age 18 months. Radiological evaluation and the pleural effusion study pointed to a diagnosis of pulmonary lymphangiectasia. The histological material was obtained after surgical intervention for left pleurodesis. Currently, the patient is in follow-up without any significant pleural effusion, and respiratory function seems to have improved.

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 (30). Several conditions may present with clinical and radiologic signs similar to disorders involving lung interstitium. Therefore, in differential diagnosis, we must take into consideration interstitial pneumonitis, connective tissue disorders, follicular bronchiolitis, alveolar proteinosis, lymphocytic interstitial pneumonitis, idiopathic pulmonary hemosiderosis, and lymphangiomatosis. Sarcoidosis, extrinsic allergic alveolitis, Langherhans cell histiocytosis, aspiration pneumonitis, and lipid storage diseases must also be evaluated.

Finally, it is highly recommended that careful attention should be paid to all cases of peripheral lymphatic involvement, with or without clinical pulmonary signs, and evidence of generalized lymphatic dysplasia should be sought.

GENETIC COUNSELING

The low number of reported cases does not allow consistent genetic counseling to be performed. 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 (29), pulmonary lymphatic dysplasia was described in autosomal dominant syndromes, autosomal recessive syndromes, and in X-linked syndromes (31) (*Table 4*).

TABLE 4
Hereditary Pulmonary Lymphangiectasia Syndromes

Autosomal dominant syndromes	OMIM catalog	Autosomal recessive syndromes	OMIM catalog	X-linked syndromes	OMIM catalog
Yellow nail syndrome	#153300	PEHO syndrome	#260565	Lymphedema hypoparathyroidism	#247410
Noonan	#163950	German syndrome	#231080	Mandibulofacial dysostosis	
Intestinal lymphangiectasia	#152800	Hennekam lymphangiectasia	#235510		
Lymphedema/cerebral arteriovenous anomaly	#152900	Campomelia, Cumming type	#211890		
		Idiopathic hydrops fetalis	#236750		
		Hypotrichosis lymphedema teleangectasia	#607823		
		Knobloch syndrome	#267750		
		Urioste syndrome	#235255		

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 counseling should refer to the common recommendations that are usually made for each designated syndrome (13,15,25-28,32).

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 stabilization at birth. 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 performed in order to start selective antibiotic treatment.

In patients with rapidly expanding pleural effusion requiring placement of 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 lymph production. Enteral nutrition with medium-chain triglycerides and total parenteral nutrition have been successfully employed (1,5).

Octreotide and antiplasmin have been used in PL and in intestinal lymphangiectasia. Inconsistent 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 combined with thoracic duct ligation or suture of leaking collaterals (38-40).

REFERENCES

1. Esther, CR, Jr, PM Barker: Pulmonary lymphangiectasia: Diagnosis and clinical course. Pediatr. Pulmonol. 38 (2004), 308-13.
2. Bellini, C, M Mazzella, C Arioni, et al: Hennekam syndrome presenting as nonimmune hydrops fetalis, congenital chylothorax, and congenital pulmonary lymphangiectasia. Am J Med. Genet. 120A (2003), 92-96.
3. Bukowski, R,GR Saade: Hydrops fetalis. Clin. Perinatol. 27 (2000), 1007-1031.
4. Moore, KL,TVN Persaud: *The Developing Human: Clinically Oriented Embryology*. 7th ed. Philadelphia, Pa.: Saunders, 2003.
5. Bellini, C, M Mazzella, C Campisi, et al: Multimodal imaging in the congenital pulmonary lymphangiectasia-congenital chylothorax-hydrops fetalis continuum. Lymphology 37 (2004), 22-30.
6. Noonan, JA, LR Walters, JT Reeves: Congenital pulmonary lymphangiectasis. Am. J. Dis. Child. 120 (1970), 314-319.
7. Barker, PM, CR Esther, Jr., LA Fordham, et al: Primary pulmonary lymphangiectasia in infancy and childhood. Eur. Respir. J. 24 (2004), 413-419.
8. Bouchard, S, M Di Lorenzo, S Youssef, et al: Pulmonary lymphangiectasia revisited. J Pediatr Surg. 35 (2000), 796-800.
9. Felman, AH, RM Rhatigan, KK Pierson: Pulmonary lymphangiectasia. Observation in 17 patients and proposed classification. Am. J. Roentgenol. Radium Ther. Nucl. Med. 116 (1972), 548-558.
10. Gardner, TW, AC Domm, CE Brock, et al: Congenital pulmonary lymphangiectasis. A case complicated by chylothorax. Clin. Pediatr. (Phila). 22 (1983), 75-78.
11. Wagenaar, SS, J Swierenga, CA Wagenvoort: Late presentation of primary pulmonary lymphangiectasis. Thorax. 33 (1978), 791-795.
12. Nobre, LF, NL Muller, AS de Souza Junior, et al: Congenital pulmonary lymphangiectasia: CT and pathologic findings. J. Thorac. Imaging 19 (2004), 56-59.
13. Moerman, P, K Vandenberghe, H Devlieger, et al: Congenital pulmonary lymphangiectasis with chylothorax: A heterogeneous lymphatic vessel abnormality. Am. J. Med. Genet. 47 (1993), 54-58.
14. Huber, A, D Schranz, I Blaha, et al: Congenital pulmonary lymphangiectasia. Pediatr. Pulmonol. 10 (1991), 310-313.
15. Gilewski, MK, CC Statler, G Kohut, et al: Congenital pulmonary lymphangiectasia and other anomalies in a child: provisionally unique syndrome? Am. J. Med. Genet. 66 (1996), 438-440.
16. Chung, CJ, LA Fordham, P Barker, et al: Children with congenital pulmonary lymphangiectasia: after infancy. Am. J. Roentgenol. 173 (1999), 1583-1588.
17. Copley, SJ, M Coren, AG Nicholson, et al: Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease. Am. J. Roentgenol. 174 (2000), 549-554.
18. Njolstad, PR, H Reigstad, J Westby, et al: Familial non-immune hydrops fetalis and congenital pulmonary lymphangiectasia. Eur. J. Pediatr. 157 (1998), 498-501.
19. Scott, C, C Wallis, R Dinwiddie, et al: Primary pulmonary lymphangiectasis in a premature infant: Resolution following intensive care. Pediatr. Pulmonol. 35 (2003), 405-406.
20. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 13-1992. A full-term newborn boy with chronic respiratory distress. N. Engl. J. Med. 326 (1992), 875-884.
21. Bellini, C, C Arioni, M Mazzella, et al: Lymphoscintigraphic evaluation of congenital lymphedema of the newborn. Clin. Nucl. Med. 27 (2002), 383-384.
22. Bellini, C, F Boccardo, G Taddei, et al: Diagnostic protocol for lymphoscintigraphy in newborns. Lymphology 38 (2005), 9-15.

23. van Straaten, HL, LJ Gerards, TG Krediet: Chylothorax in the neonatal period. Eur. J. Pediatr. 152 (1993), 2-5.
24. Staats, BA, RD Ellefson, LL Budahn, et al: The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin. Proc. 55 (1980), 700-704.
25. Urioste, M, JI Rodriguez, JM Barcia, et al: Persistence of mullerian derivatives, lymphangiectasis, hepatic failure, postaxial polydactyly, renal and craniofacial anomalies. Am. J. Med. Genet. 47 (1993), 494-503.
26. Bellini, C, E Bonioli, N Josso, et al: Persistence of Mullerian derivatives and intestinal lymphangiectasis in two newborn brothers: confirmation of the Urioste syndrome. Am. J. Med. Genet. 104 (2001), 69-74.
27. Van Balkom, ID, M Alders, J Allanson, et al: Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome: a review. Am. J. Med. Genet. 112 (2002), 412-421.
28. van Haelst, MM, J Hoogeboom, RJ Galjaard, et al: Lymphangiectasia with persistent Mullerian derivatives: Confirmation of autosomal recessive Urioste syndrome. Am. J. Med. Genet. 104 (2001), 65-68.
29. Northup, KA, MH Witte, CL Witte: Syndromic classification of hereditary lymphedema. Lymphology 36 (2003), 162-189.
30. Bokulic, RE, BC Hilman: Interstitial lung disease in children. Pediatr. Clin. North Am. 41 (1994), 543-567.
31. Opitz, JM, JF Reynolds, JM FitzGerald: Mandibulofacial dysostosis or bilateral hemifacial microsomia with hearing loss, telecanthus, tetramelic postaxial hexadactyly, congenital hypotonia and lymphedema with joint hypermobility, and pigmentary dysplasia: A new syndrome? Am. J. Med. Genet. 33 (1989), 433-435.
32. Scott-Emuakpor, AB, ST Warren, S Kapur, et al: Familial occurrence of congenital pulmonary lymphangiectasis. Genetic implications. Am. J. Dis. Child. 135 (1981), 532-534.
33. Makrilakis, K, S Pavlatos, G Giannikopoulos, et al.: Successful octreotide treatment of chylous pleural effusion and lymphedema in the yellow nail syndrome. Ann Intern. Med. 141 (2004), 246-247.
34. Widjaja, A, KF Gratz, J Ockenga, et al: Octreotide for therapy of chylous ascites in yellow nail syndrome. Gastroenterology 116 (1999), 1017-1018.
35. Rimensberger, PC, B Muller-Schenker, A Kalangos, et al: Treatment of a persistent postoperative chylothorax with somatostatin. Ann. Thorac. Surg. 66 (1998), 253-254.
36. Lamberts, SW, AJ van der Lely, WW de Herder, et al: Octreotide. N Engl J Med. 334 (1996), 246-254.
37. MacLean, JE, E Cohen, M Weinstein: Primary intestinal and thoracic lymphangiectasia: a response to antiplasmin therapy. Pediatrics 109 (2002), 1177-1180.
38. Riquet, M,A Badia: [Surgery for chylothorax]. Rev. Pneumol. Clin. 60 (2004), 104-108.
39. Brissaud, O, L Desfrere, R Mohsen, et al.: Congenital idiopathic chylothorax in neonates: chemical pleurodesis with povidone-iodine (Betadine). Arch. Dis. Child Fetal Neonatal Ed. 88 (2003), F531-F533.
40. Ryu, JH, CH Doerr, SD Fisher, et al.: Chylothorax in lymphangioleiomyomatosis. Chest. 123 (2003), 623-627.

Carlo Bellini, MD, PhD
Dipartimento di Pediatria
Università di Genova
Istituto G. Gaslini,
Largo G. Gaslini, 5
16147 Genova, Italy
Tel: +39 10 5636762
Fax: +39 10 3770675
Email: carlobellini@ospedale-gaslini.ge.it