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CONGENITAL PULMONARY LYMPHANGIECTASIA AND CHYLOTHORAX – A CASE SERIES

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ABSTRACT

Congenital pulmonary lymphangiectasia (CPL) and chylothorax (CC) are rare lymphatic developmental disorders. We report six clinical cases of CPL and CC that were admitted to our level III neonatal intensive care unit over the last 20 years. One case of unilateral CC was successfully treated with pleuro-amniotic shunt; three cases of bilateral CC were associated to lung hypoplasia, hydrops fetalis, and generalized lymphangiectasias; one case of CPL was associated with obstructive congenital heart defect; one case of unilateral CC was successfully treated with thoracocentesis and medium-chain triglyceride diet. Mortality was high (66.6%).

Keywords: Congenital pulmonary lymphangiectasia, chylothorax, lymphangiectasia, lung hypoplasia, hydrops fetalis, congenital heart defect

Congenital pulmonary lymphangiectasia (CPL) and congenital chylothorax (CC) are rare lymphatic developmental disorders (1). CPL is associated with dilation of the pulmonary lymphatics that drain the subpleural and interstitial spaces of the lung (1,2) and CC is a pleural effusion associated to anomalies of the thoracic duct or multiple lymphatic vessels (3). CPL can be divided into primary and secondary forms (3). The primary congenital form presents in neonates and is usually fatal. Secondary forms result from a variety of processes that impair lymphatic drainage, frequently related to lymphatic obstruction, cardiovascular obstruction, or associated with increased lymph production (3). Whereas most cases are sporadic, there have been familial cases reported and associations with congenital anomalies and Noonan, Ulrich-Turner, Down as well as other syndromes (2,4-7). CPL may occur isolated or in a generalized form associated to intestinal lymphangiectasia, hemihypertrophy, and angiomatosis (7). Although the exact incidence of CPL is unknown, autopsy studies suggest that 0.5-1% of infants who are stillborn or die in the neonatal period have CPL (8).

We report on the six clinical cases of CPL and CC that were admitted to our level III neonatal intensive care unit over the last 20 years. Our unit admits about 400 newborns per year and is a referral center for cardiac, thoracic, and neonatal surgery.

CASE REPORTS

Case 1

A 37 week gestational age, birth weight 2990g male was born by C-section and admitted for CC. During pregnancy, a voluminous right pleural effusion was diagnosed on obstetrical echography at 25 weeks of gestation, and a pleuro-amniotic shunt was placed at 30 weeks of gestation. The Apgar score at birth was 9/10 ($1^{st}/5^{th}$ minutes) and the drain was clamped and removed by five minutes of life, after collecting a sample of fluid for analysis, which confirmed the diagnosis of chylothorax (1,100 white blood cells per ml with 94% lymphocytes). The chest x-ray revealed a small right pleural effusion that resolved spontaneously by day (D) seven of life. The child did not need ventilatory support nor oxygen. On D2 he was started on a diet containing medium chain triglycerides. The echocardiographical evaluation revealed a functionally and structurally normal heart and no other congenital anomalies were detected. The blood karyotype was 46,XY. He was discharged on D7 of life and the subsequent outcome was good.

Case 2

A 32 week gestational age, birth weight 2010g female was born by C-section after an echographical diagnosis of hydrops fetalis was made. She needed resuscitation at birth with intravenous adrenaline and was started on mechanical ventilation. The Apgar score was 2/5/6 ($1^{st}/5^{th}/10^{th}$ minutes). A bilateral thoracocentesis was performed and 30 ml of pleural fluid were aspirated from each side of the thorax. The analysis of the fluid was compatible with a chylothorax (1,573 white blood cells per ml with 99% lymphocytes), and a bilateral drain was placed on. Because of a significant bilateral drainage, octreotide was started (1 mcg/kg/day, with daily increase of 1 mcg/kg to a maximum of 10 mcg/kg/day). Infectious, metabolic and genetic studies did not reveal the cause of hydrops; the blood karyotype was 46,XX. Inotropic support with dopamine was needed until D5. A central venous catheter was inserted on D10 in the internal jugular vein. She died on D11 after a sudden pulmonary hemorrhage. The autopsy revealed cardiac tamponade as a complication of the central venous catheter and as the cause of death, and the presence of lung lymphangiectasias complicated by chylothorax, as well as small areas of mediastinal, pancreatic, and mesenteric lymphangiectasias.

Case 3

A 30 week gestational age, 1530g birth weight male newborn, delivered by C-section was admitted for prematurity and hydrops fetalis. Infectious, genetic, and metabolic studies collected by amniocentesis were not revealing; the karyotype was 46,XY. He needed resuscitation with intravenous adrenaline and thoracocentesis that revealed a bilateral CC (1,051 white blood cells per ml with 88.5% lymphocytes). The Apgar score was 1/1/2 ($1^{st}/5^{th}/10^{th}$ minutes). Bilateral pleural drains were inserted and octreotide was started (1 mcg/kg/day, with daily increase of 1 mcg/kg to a maximum of 10 mcg/kg/day). He needed dopamine perfusion during the first 12 hr of life for hypotension. Two doses of surfactant were given and rescue high frequency oscillatory ventilation was needed for hypercapnia. An intraventricular and parenchymal cerebral haemorrhage was detected at 24 hr of life on cranial ultrasound. He died on D2. The autopsy revealed pulmonary hypoplasia, bilateral chylothorax, dilation of lymphatic vessels of the neck, mediastinum, lungs, but also in the skin, kidneys, and mesentery, compatible with congenital lymphatic dysplasia.

Case 4

A female singleton of 3200 grams was delivered at 39 weeks gestation by vaginal delivery. She evolved with sustained refractory hypoxemia not responsive to high frequency oscillatory ventilation, administration of

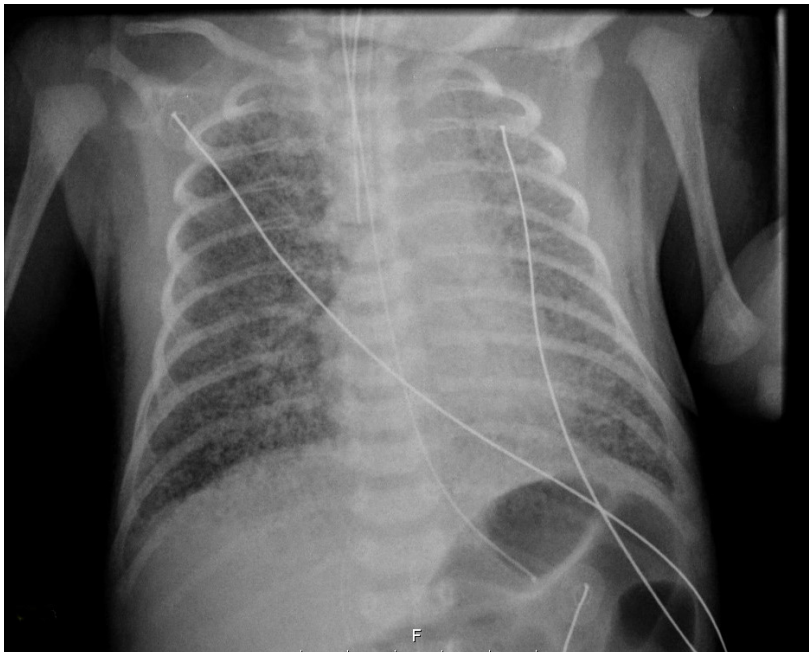

Fig. 1. X-ray of diffuse congenital lymphangiectasia (clinical case number 4).

surfactant, inhaled nitric oxide and vasopressor therapy. The chest X-ray revealed a severe diffuse homogeneous bilateral reticular image (*Fig. 1*). A complete echocardiographic evaluation did not allow the exclusion of a total anomalous pulmonary venous return and a cardiac catheterization was performed, which identified a probable pulmonary vascular malformation associated with a persistence of the fetal circulation. She died on D2. The autopsy of the newborn described findings of diffuse congenital pulmonary lymphangiectasia (*Figs. 2,3*) and pulmonary venous drainage to the left atrium through two ostia, one right and one left (variant of normal), but with small-caliber pulmonary veins. The blood karyotype was 46,XX.

Case 5

A 36 weeks preterm female phenotypically normal newborn, birthweight 2630 g, born by C-section of a 27 year old primigravida was transferred on D1 to our center because of a moderate volume right pleural effusion on thorax x-ray and echography. The Apgar score at birth was 9/10 (1^{st} and 5^{th} minutes, respectively) and the baby was breathing normally in room air. A thoracocentesis was performed with aspiration of 20.5 ml of a citrine fluid, analysis of which confirmed a CC (1,530 white blood cells per ml with 98.8% lymphocytes). He was started on octreotide (1 mcg/kg/day, with daily increase of 1 mcg/kg to a maximum of 10 mcg/kg/day), parenteral nutrition (six days), and a diet with medium-chain triglycerides. The pleural effusion totally regressed, and the baby was discharged home on D13 of life with follow up in the outpatient department for nutritional support. The study was negative for Noonan syndrome and the karyotype was 46,XX. Cranial, cardiac, kidney, and abdominal echographical evaluations were normal.

Case 6

A 34 weeks gestational age male preterm

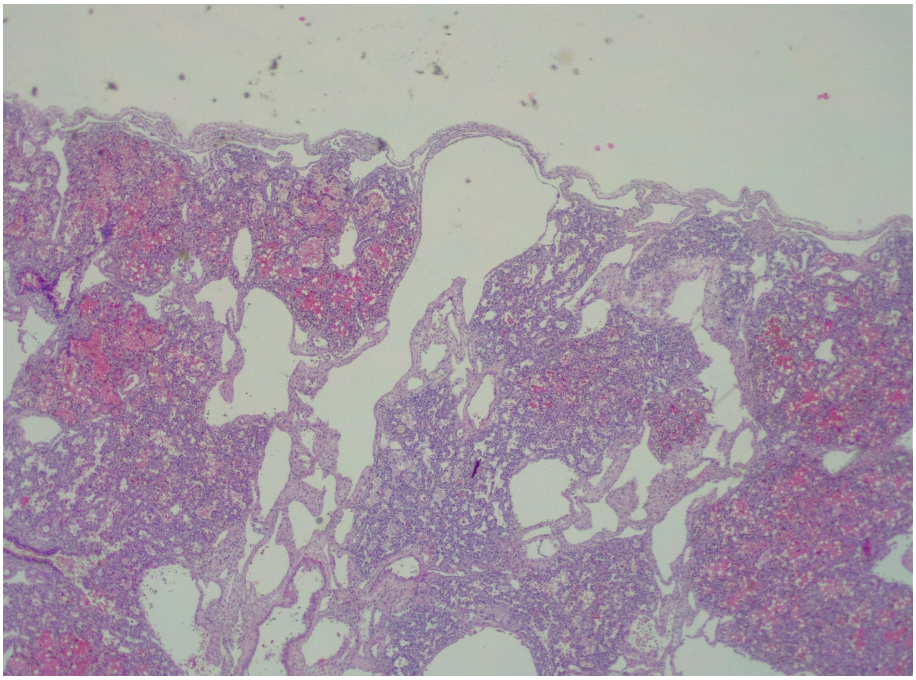

Fig. 2. Hematoxylin-eosin stained lung parenchyma tissue demonstrating marked cystic dilatation of pulmonary lymphatics in interlobular septa (clinical case number 4).

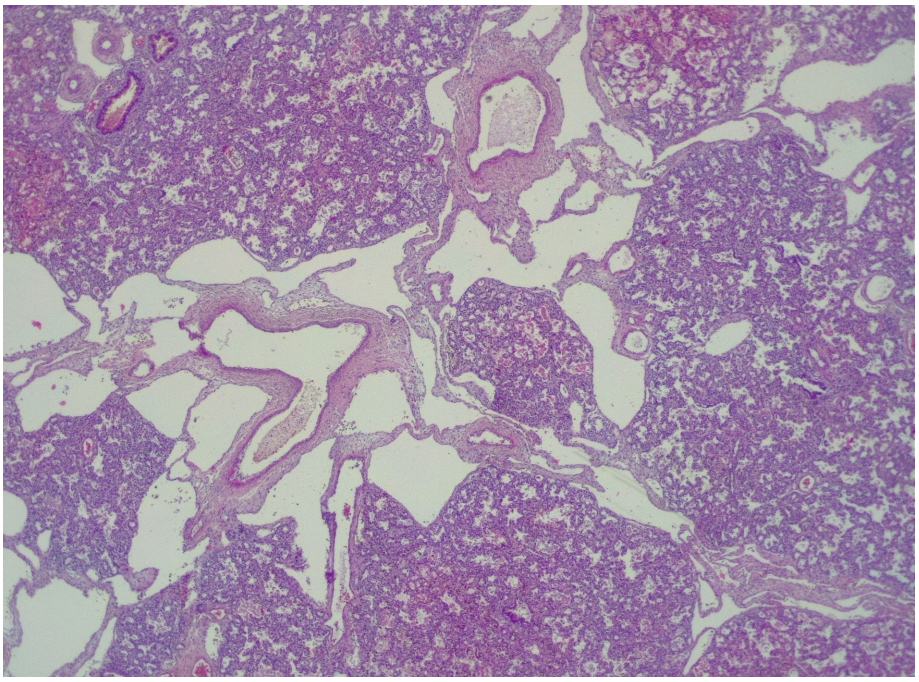

Fig. 3. Hematoxylin-eosin stained lung parenchyma tissue displaying marked cystic dilatation of pulmonary lymphatics beneath the pleura, within interlobular septa, and in peribronchiolar regions (clinical case number 4).

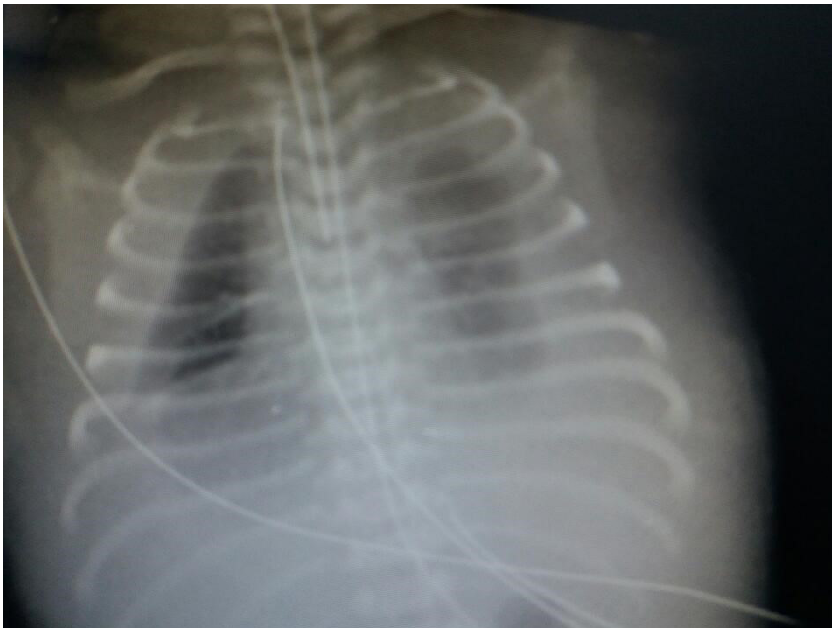

Fig. 4. X-ray image demonstrating bilateral pleural effusions from congenital bilateral chylothorax before drain placement (clinical case number 6).

was born by elective C-section to a 36 years old primigravida because of hydrops fetalis with voluminous bilateral pleural effusions associated with lung hypoplasia (*Fig. 4*). Pregnancy was normally followed with unremarkable obstetrical echographical evaluations until 30 weeks of gestation. At birth, the baby weight was 3760g (over 97th percentile) and generalized oedema was evident. He needed resuscitation with positive pressure, 100% oxygen, tracheal intubation and mechanical ventilation. The Apgar score was 4/7/8 (1st, 5th, 10th minutes). A bilateral thoracocentesis revealed a voluminous CC (1,230 white blood cells per ml with 95% lymphocytes). Bilateral thorax drainage, octreotide infusion (1 mcg/kg/day, with daily increase of 1 mcg/kg to a maximum of 10 mcg/kg/day), and parenteral nutrition were started. Daily drainage was voluminous, almost 100 ml/kg per day, predominantly on the right side, with a very slow improvement over several days. A lymphscintigram was normal, and an angio-tomographic study of the thorax performed to exclude a lymphangiomatous lesion in the thorax was also unremarkable except for bilateral pleural effusions. Because of the voluminous drainage the child needed several albumin infusions, plasma and human immunoglobulin. Acid-base equilibrium was consistently in the normal range. On D43, he underwent thoracic duct surgical ligation with abrasion of the right pleura. A lung biopsy was performed at this time and the lung histological study did not reveal lymphangiectasias nor any other changes. The bilateral pleural effusion drainage did not reduce significantly after the surgical ligation and became more significant on left side. On D70, a second surgical intervention with ligation of several thoracic collateral vessels and abrasion of left pleura was performed with a significant reduction of the pleural drainage. On D76, the child died due to fulminant septic shock caused by Klebsiella pneumonia and Haemophilus influenzae. Blood karyotype was 46,XY, Noonan syndrome study was negative, and CGH-arrays were normal. Cranial,

abdominal and renal ultrasound evaluation and 2D-echoardiogram did not show congenital malformations. Autopsy revealed a severe form of lymphatic dysplasia affecting the lungs, spleen, mesentery, colon, pancreas and portal spaces of the liver, as well as dilation of lymphatic vessels around lymphatic nodes in general.

DISCUSSION

In this series the authors report their experience with the rare cases of CPL and CC in the neonatal period (summarized in *Table 1*). The identification of lymphatic vessels at autopsies was based on the morphology and, in the case of doubt, using an immunocytochemical study with D2-40. The etiology of CPL may be related to failure of regression of the large lymphatic vessels that are normal during the maturation development process at 9-16 weeks of gestation (7). In some cases, CPL may occur in association to chylothorax, and non-immune fetal hydrops may develop during the fetal period as in the reported cases 2,4 and 7 (7). CPL should be distinguished from diffuse pulmonary lymphangiomatosis which is characterized by an increased number of complex anastomosing lymphatic channels with secondary variable dilation or expansion within the lungs and mediastinum. In contrast, the lymphatic vessels in CPL are normal in number and are relatively more regular in size and shape (7).

The prevention of tissue edema is considered a universal role of lymphatic vessels in all tissues except the central nervous system although even there the lymphatics probably function similarly. Also, lymphatics play specialized roles in coordinating adaptive immune responses in secondary lymphoid organs and in transport of dietary lipids from the intestine (9).

Animal studies have shown that lymphatic function is required prenatally for lung inflation at birth (10) and lymphatic-deficient animals are susceptible to die immediately after birth due to respiratory failure. Respiratory failure is due to loss of lymphatic fluid drainage associated with decreased lung compliance and failure of lung inflation at the time of birth (10). The mechanical role of lymphatics in a developing lung is likely to overlap both temporally and functionally with that of pulmonary surfactant, and inadequate lymphatic function may contribute significantly to the respiratory distress syndrome experienced by premature infants (10).

Treatment of CPL is mostly supportive including ventilatory support, drainage of pleural effusions, metabolic and nutritional correction, inhaled nitric oxide and vasopressor support for pulmonary hypertension, extracorporeal membrane oxygenation for selected cases, and surgical resection may be curative in some cases (2-4,7).

CC was the commonest lymphatic anomaly reported in this series in cases 1,2,3,5, and 6. In three cases it occurred associated to hydrops fetalis, generalized lymphangiectasias, and mortality (cases 2,3, and 6).

The favorable evolution of the clinical case 1 with MCT diet could be explained by the natural tendency for spontaneous remission of congenital chylothorax as the thoracic duct matures. In this particular case, the diagnosis of fetal pleural effusion was noted by 25 weeks of gestation, i.e., twelve weeks before birth (at 37 weeks). This long period may have provided enough time for a spontaneous cure.

CC results from multiple lymphatic vessel anomalies or thoracic cavity defects and may accompany other congenital anomalies and genetic syndromes. Fetal chylothorax occurs in 1:15,000 pregnancies and has a male: female ratio of 2:1 and occurs more frequently on the right side (11). Fetal chylothorax may increase the risk of death as it compromises lung development, pulmonary, and cardiovascular function and also is complicated by the loss of drained lymphatic contents. Prenatal interventions such as pleuroamniotic shunting might improve

TABLE 1
Summary of the Seven Clinical Cases of Congenital Pulmonary Lymphangiectasia and Chylothorax

Cases	Demographics	Antenatal	Pathology	Study	Treatment	Outcome	Autopsy study
1	Male GA 37 weeks BW 2990g	Right voluminous pleural effusion on obstetrical echography at 25 weeks of gestation	Unilateral congenital chylothorax	Normal cardiac, cranial, abdominal, kidney echographic evaluation; blood karyotype 46,XY	Pleuro-amniotic shunt placed at 30 weeks of gestation and removed at birth; MCT diet	Discharged on D7	-
2	Female GA 32 weeks BW 2010g	Hydrops fetalis	Bilateral congenital chylothorax	Infectious, metabolic genetic studies not relevant for the cause of hydrops; karyotype 46,XX	Mechanical ventilation; thoracocentesis; drainage; octreotide; dopamine	Deceased on D11	Lung lymphangiectasias, small areas of mediastinum, pancreatic and mesenteric lymphangiectasias
3	Male GA 30 weeks BW 1530g	Hydrops fetalis	Bilateral chylothorax	Infectious, genetic and metabolic studies not relevant; karyotype 46,XY	Mechanical ventilation; drainage; octreotide; dopamine	Deceased on D2	Pulmonary hypoplasia, dilation of lymphatic vessels of the neck, mediastinum, lungs, skin, kidneys and mesenterium compatible with congenital lymphatic dysplasia
4	Female GA 39 weeks BW 3200g	Uneventful	Congenital pulmonary lymphangiectasia associated to obstructive congenital heart disease with sustained refractory hypoxemia	Chest X-ray- severe diffuse homogeneous bilateral reticular image; cardiac catheterization - total anomalous pulmonary venous return; blood karyotype 46,XX	HFOV; surfactant; iNO; vasopressors	Deceased on D2	Diffuse congenital pulmonary lymphangiectasia and pulmonary venous drainage to the left atrium through two ostia, one right and one left (variant of normal), but with small-caliber obstructive pulmonary veins
5	Female GA 36 weeks BW 2630g	Uneventful	Right moderate volume congenital chylothorax	Cranial, cardiac, kidney and abdominal echographical evaluations were normal; negative for Noonan syndrome; blood karyotype 46,XX	Thoracocenthesis; octreotide, parenteral nutrition; MCT diet	Discharged on D13	-
6	Male GA 34 weeks BW 3760g	Hydrops fetalis	Bilateral congenital chylothorax	Lymphoscintigram-normal; angio-CT-bilateral pleural effusion; blood karyotype was 46,XY, Noonan syndrome study negative¸ CGH-arrays were normal; cranial, abdominal and kidney ultrasound evaluation and 2D-echocardiogram did not show congenital malformations; lung biopsy unremarkable	Mechanical ventilation; thoracocentesis; drainage; octreotide; parenteral nutrition; ligation of thoracic duct and collateral lymphatic vessels; bilateral pleural abrasion; albumin; human immunoglobulin; plasma	Deceased on D76	Severe form of lymphatic dysplasia affecting the lungs, spleen, mesenterium, colon, pancreas and portal spaces of the liver, as well as dilation of lymphatic vessels around lymphatic gangliae in general

BW- birth weight; CT – computerized tomography; D – day of life; GA – gestational age; HFOV – high frequency Oscillatory ventilation; iNO – inhaled nitric oxide; MCT – medium chain triglycerides

survival in severe cases of fetal chylothorax. The neonatal treatment strategy is generally supportive with interventions that include thoracostomy drainage and attempts to decrease chyle flow using a stepwise approach that begins with the least invasive means as octreotide or somatostatin administration, parenteral nutrition and a diet containing medium-chain triglycerides. Administration of albumin, coagulation factors and immunoglobulins may be needed in volumous chyle losses. Surgical interventions are reserved for severe prolonged cases and include thoracic duct ligation or embolization, pleurodesis and pleuroperitoneal shunting. Evidence-based treatment choices are lacking and are much needed (11). Most cases of congenital chylothoraces resolve with time. Prognosis depends on the etiology, presence of other congenital anomalies, gestational age, complications arising during the neonatal period, and the degree of pulmonary hypoplasia, with an overall survival ranging from 30% to 70% (11). In our series including five CC, three (60%) died. Expertise in performing lymphatic studies is not universally available, and data on both efficacy and safety of the various therapeutic options are needed to determine the best approach to the treatment of CC (11).

Secondary CPL may be caused by cardiac lesions as the result of obstruction to pulmonary venous flow, or cardiac lesions which have been hypothesized to interfere with the normal regression of the lymphatic tissue elements after the 16th week of fetal life (7). Left-sided obstructive congenital malformations of the heart have been reported in 60% of neonates with CPL at autopsy (7). In this series, one case of CPL was associated with obstructive congenital cardiac anomaly (case 4), although in this case the lymphatic dilation was considered by the pathologist as an anomaly not related to the obstructive cardiac malformation since the pulmonary veins were not enlarged.

Hypoplastic left heart syndrome, pulmonary vein atresia, congenital mitral stenosis, and cor triatum have already been described in association with CPL (7).

Previously, CPL has been almost uniformly fatal (3). Although with this poor prognosis, improved outcomes, possibly as the result of advances in neonatal and pediatric intensive care medicine have been reported (12). The rarity of CPL makes it difficult to ascertain specific figures for mortality and survival but although optimism regarding survival cannot be justified in the face of manifestations of CPL, such as hydrops fetalis, chylothorax and severe neonatal respiratory distress, the outcome of CPL need no longer be viewed as pessimistically as it once was, particularly in the absence of co-morbidities, such as congenital heart disease (13).

Our mortality was high (66.6%) compared to literature and one case associated with congenital heart disease died.

CONCLUSION

In this series, CC was the most prevalent lymphatic anomaly and was associated with generalized lymphatic dysplasia and hydrops fetalis in three cases. Hydrops fetalis and generalized lymphatic dysplasia were associated to a poor outcome of congenital chylothorax. The association of CPL with an obstructive cardiac defect was also noted to have a poor prognosis.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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