Autopsy Case Reports

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Congenital generalized lymphangiectasia: a rare developmental disorder for non-immune fetal hydrops

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ABSTRACT

Firstly described by Rudolf Virchow in the 19th century, congenital generalized lymphangiectasia is a rare entity characterized by dilation of lymphatic vessels, and was recently classified in primary or secondary lymphangiectasia. Generalized forms may be diagnosed during pre-natal follow-up with ultrasound examination, and, depending on its severity, the newborn outcome is very poor. The authors report the case of a female newborn with a previous diagnosis of fetal hydropsy who was born after a full-term gestation with respiratory failure due to bilateral voluminous pleural effusion and ascites. Physical examination also disclosed syndromic facies. Despite all efforts of the intensive supportive care, the patient died after 24 days of life. The autopsy findings were consistent with the diagnosis of congenital pulmonary lymphangiectasia. The authors call attention to this rare diagnosis in patients with cavitary effusion and respiratory insufficiency at birth.

Keywords
Lymphangiectasia, pulmonary, congenital; Respiratory Insufficiency; Autopsy

CASE REPORT

A full-term female (39 and 4/7 weeks) was born through a cesarean section with hypotonia and cyanosis, a faint cry, bradycardia, and irregular respiratory pattern. The Apgar score was 3/5/8 and the weight was 3220 g. Plain chest x-ray is shown in Figure 1.

Still in the delivery room, orotracheal intubation, bilateral thoracocentesis, and paracentesis due to anasarca and respiratory failure were performed to achieve some improvement in the newborn vitality.

This was the second pregnancy of the mother who was 30 years old and who had attended four prenatal consultations. Her blood type was A, Rh-positive. The tests for irregular anti-erythrocytes antibodies were negative as well as the serology for HIV, syphilis, and parvovirus. She was immune for

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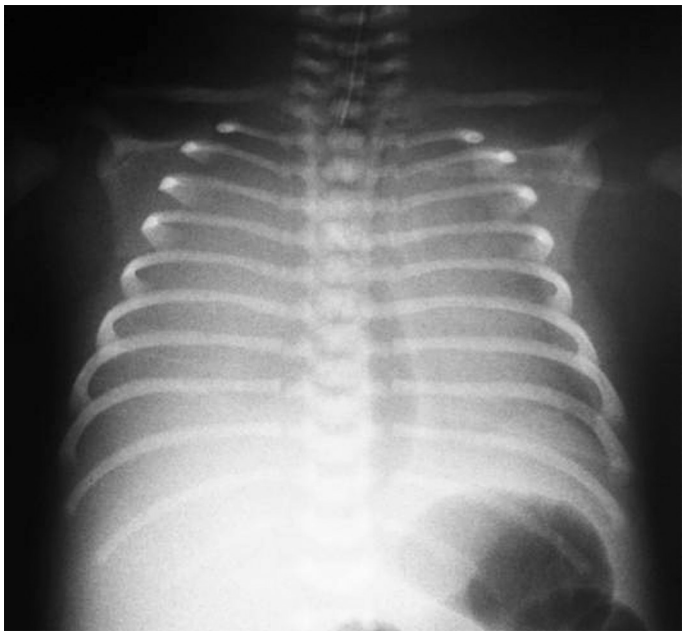

Figure 1. Plain chest x-ray showing bilateral homogeneous opacification due to voluminous pleural effusion.

rubella and cytomegalovirus, but was susceptible for toxoplasmosis. She denied any comorbidity, consanguinity, and illicit drug abuse. She was referred to the hospital for fetal vitality assessment since the pregnancy was at the 40th week. The ultrasound disclosed hydramnios (amniotic fluid index of 31.4 cm [reference value (RV): 5-25 cm]) and signs consistent with fetal hydropsy (pleural effusion and ascites), which were not previously detected. Therefore, the cesarean section was performed. A detailed physical examination of the newborn evidenced flattened nose, low-set ears, a short neck and a nuchal fold, which raised the suspicion of Noonan syndrome. The outcome was characterized by relapsing non-chylous pleural effusion, mainly in the right hemithorax requiring right thoracic drainage. The abdominal ultrasound showed a moderate amount of ascites with thin septa. The echocardiogram did not reveal cardiac malformations and the karyotype was 46XX.

On the 12th day of the neonatal intensive care unit hospitalization, the patient started with fever and worsening of the clinical and laboratory parameters consistent with late neonatal septicemia and shock accompanied by multiple organ failure. *Serratia marcescens* was isolated in the blood cultures. The child died on the 24th day after birth.

AUTOPSY FINDINGS

The ectoscopy showed a female newborn weighing 4.585 g (RV: 2789 ± 520 g) and measuring 51.5 cm in length (RV: 46.7 ± 4.4 cm). The face showed a flattened nose, low-set ears and a short neck. The corpse was in anasarca with marked palpebral and genital edema, and a distended abdomen.

At the opening of the cavities, hemorrhagic ascites and citrine pleural effusion were drained.

The cervical region did not present cystic hygroma or cystic dilation of lymphatic vessels. The thyroid parenchyma presented dilated lymphatic vessels between the follicles.

In the abdominal cavity, the serosa presented a smooth surface without lymphangiectasia macroscopically identified, but at microscopy dilated lymphatic vessels were found in the surface of the small intestine, in the adjacent fibroadipose tissue of adrenal glands, kidneys, retroperitoneum, and peripancreatic adipose tissue (Figure 2).

The pleural surfaces were smooth without cystic lesions The pulmonary parenchyma's cut surface was homogeneous, firm, and purplish colored. The right lung weighed 48.5 g and the left lung weighed 40.5 g (RV: 42.6 ± 14.9 g). The microscopy showed the saccular stage of pulmonary development with areas of atelectasis and several congested capillaries in the alveolar septa. The peribronchial arteries presented marked myointimal hyperplasia with organizing thrombi and plexiform alterations consistent with severe pulmonary hypertension. Dilated interlobular and visceral pleural lymphatic vessels were identified with thin intraluminal septa, which, on the immunohistochemical research, showed positivity for CD31, CD34, and D2-40 (Figures 3 and 4).

The heart weighed 22.1 g (RV: 19.1 ± 2.8 g) and presented patent oval foramen and patency of the arterial duct; however, no malformations were found.

The brain weighed 373.6 g (RV: 337 ± 91 g) and had a softened consistency with congested meninges, which, at microscopy, were thickened due to acute inflammatory infiltrate. Neither Grocott's nor Brown-Hopps staining identified no microorganisms.

Other findings consistent with shock were areas of splenic ischemic infarction, and renal acute tubular necrosis. The liver presented lobular infarction in

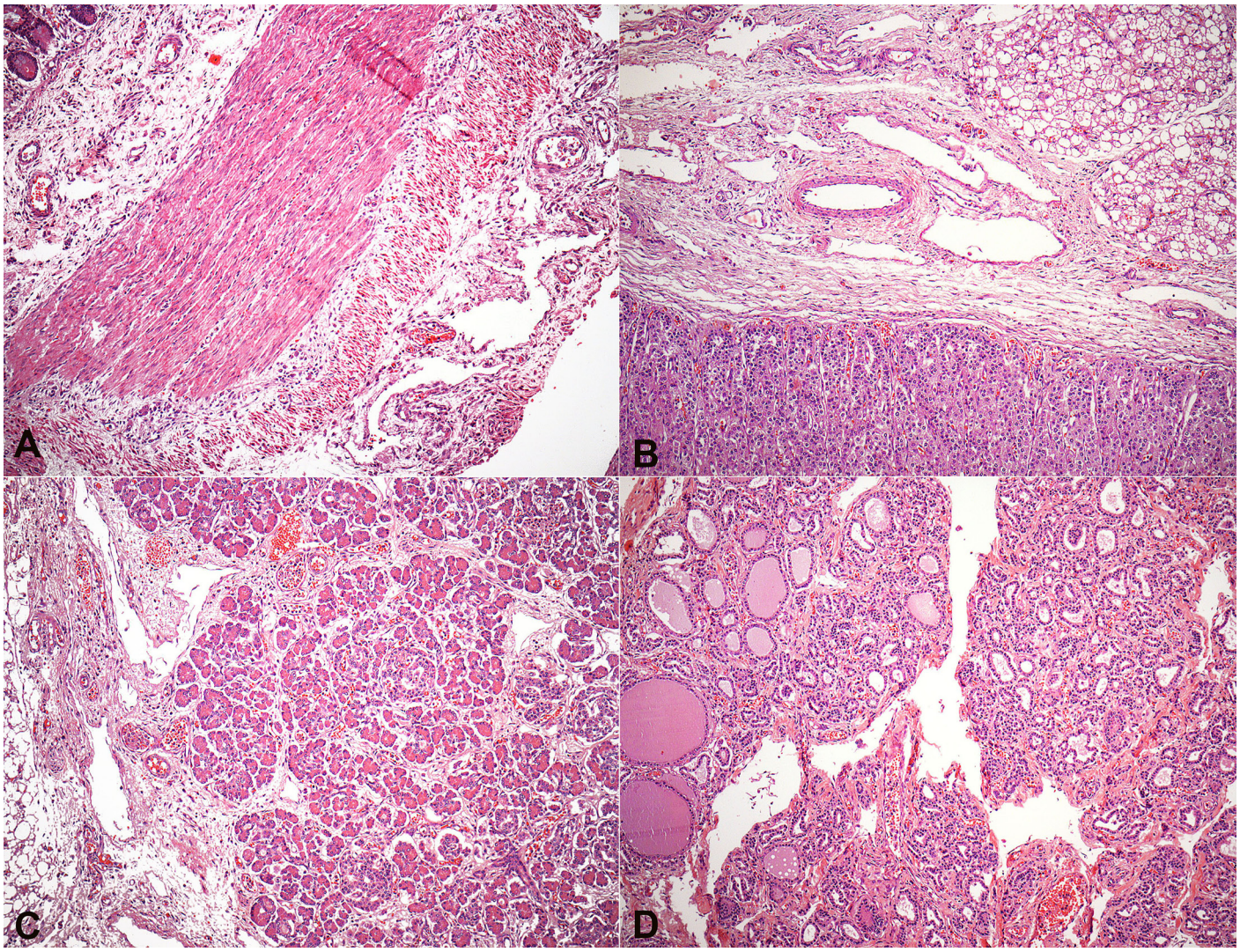

Figure 2. Photomicrography of the lymphangiectasia. **A** - Small bowel serosa (H&E, 100X). **B** - Fibroadipose tissue surrounding the adrenal gland (H&E, 100X). **C** - Peripancreatic tissue (H&E, 100X). **D** - Thyroid parenchyma (H&E, 100X).

zones 2 and 3 with microvesicular steatosis besides extramedullary hematopoiesis (Figure 5).

DISCUSSION

Congenital pulmonary lymphangiectasis (CPL) is a rare vascular disorder characterized by distended or dilated pulmonary lymphatic vessels in the bronchovascular connective tissue along the interlobular septa and in the pleura.[1]

In 1856, Rudolf Virchow[2] was the first to describe CPL, followed by 38 new descriptions until 1968. In 1970, Noonan et al.[3] reported three new cases among another 45 known cases, and classified them into three groups: (i) 5 cases of a generalized form of lymphangiectasis with primarily intestinal involvement and less severe pulmonary disease; (ii) 13 cases of secondary pulmonary lymphagiectasis (PL) due to pulmonary venous hypertension or obstruction (often associated with congenital heart disease); and (iii) 30 cases with primary PL, associated with an aggressive course and poor prognosis.[4] This classification has been modified and divided into two major categories defined as primary and secondary CPL. Primary CPL fits into the category of systemic lymphatic features that include hydrops fetalis, chylous ascites, intestinal lymphangiectasis, pleural and pericardial effusions, and PL. Secondary CPL includes a heterogeneous group of conditions, such as hypoplastic left heart syndrome, pulmonary vein atresia, congenital mitral stenosis, cor triatriatum, and thoracic duct agenesis.[4,5]

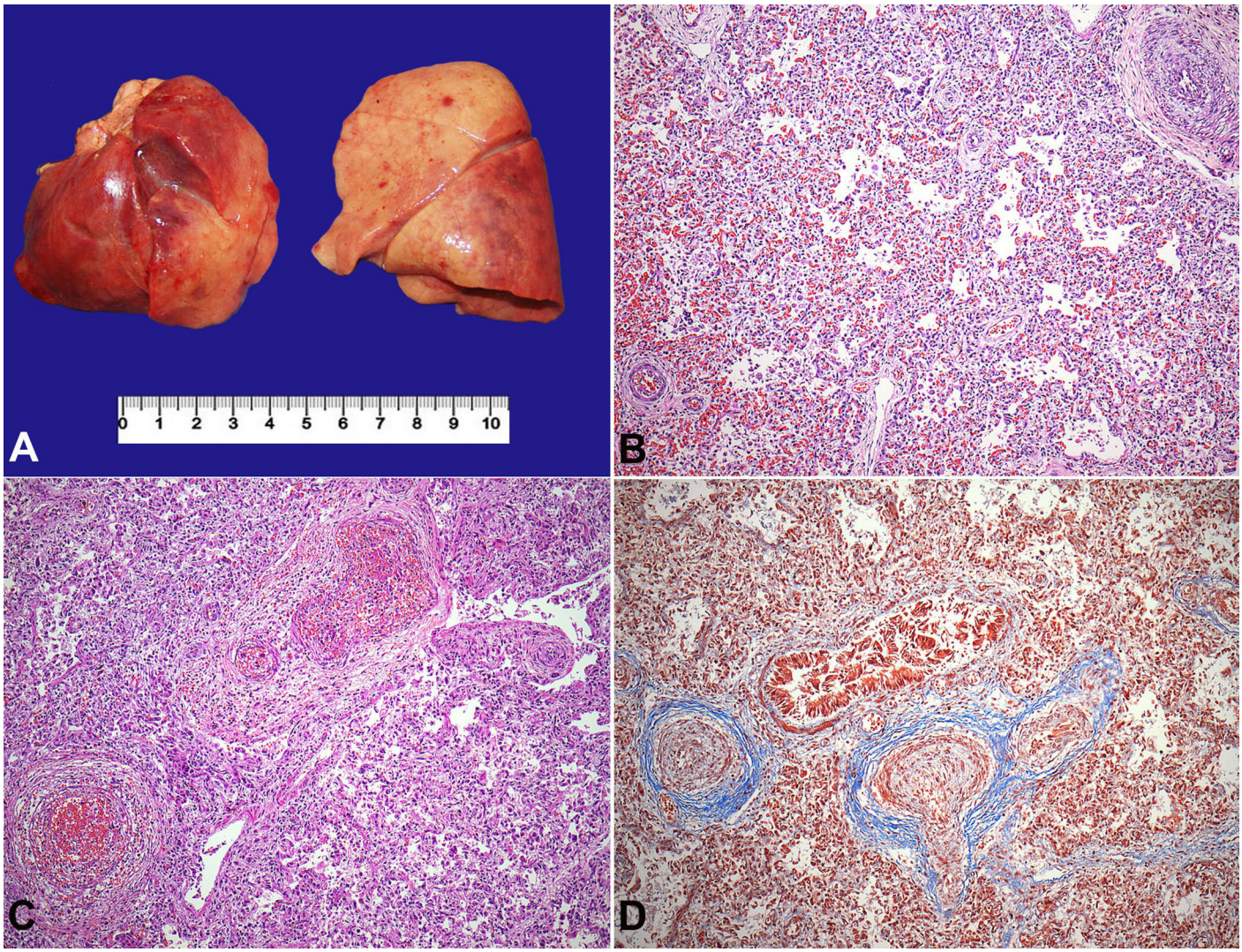

Figure 3. A - Gross findings of the lungs with smooth surface and purplish areas. **B** - Saccular stage of pulmonary development with several congested vessels in the thickened septa (H&E, 100X). **C** - Peribronchial arteries with marked myointimal thickening and organizing thrombosis (H&E, 100X). **D** - Myointimal hyperplasia in the peribronchial arteries (Masson, 100X).

The incidence of CPL is not clearly defined because there were only a few isolated cases or a small series of reported cases. Autopsy studies suggest that 0.5-1% of infants who are stillborn or die in the neonatal period have CPL.[6] A recent report on the histopathological spectrum of congenital pulmonary development disorder stated that out of 2155 stillbirth/neonatal autopsies there were two cases of CPL. These data would suggest that approximately 1/1000 stillbirth/neonatal deaths are—to some degree—attributable to CPL.[4,7]

The etiology of CPL is not known. Blood vessels originate from a mesoderm-derived endothelial cell precursor, and the lymphatic vasculature appears whichever the 9th week of gestation. Between the 12th and 16th weeks of fetal life, the pulmonary lymphatic tissue is well developed. Later, in the 20th week of fetal life, the lymphatic channels become narrower and the surrounding connective tissue diminishes.[4] Laurence[8] postulated a theory that lymphangiectasis is due to a developmental error in which the normal regression of connective tissue elements fails to occur. The presence of a lymphatic septum is not a characteristic of CPL, but we observed a focal lymphatic septum, similar to an intraluminal valve, in an ectatic lymphatic vessel in the pulmonary parenchyma. It could be a sign of lymphatic dysplasia. During development, after the establishment of a primary lymphatic vasculature, lymphatic vessels undergo further remodeling to form a hierarchical vascular tree composed of lymphatic capillaries, pre-collectors, and collecting vessels. Lymphatic capillaries are blind-ended thin-walled

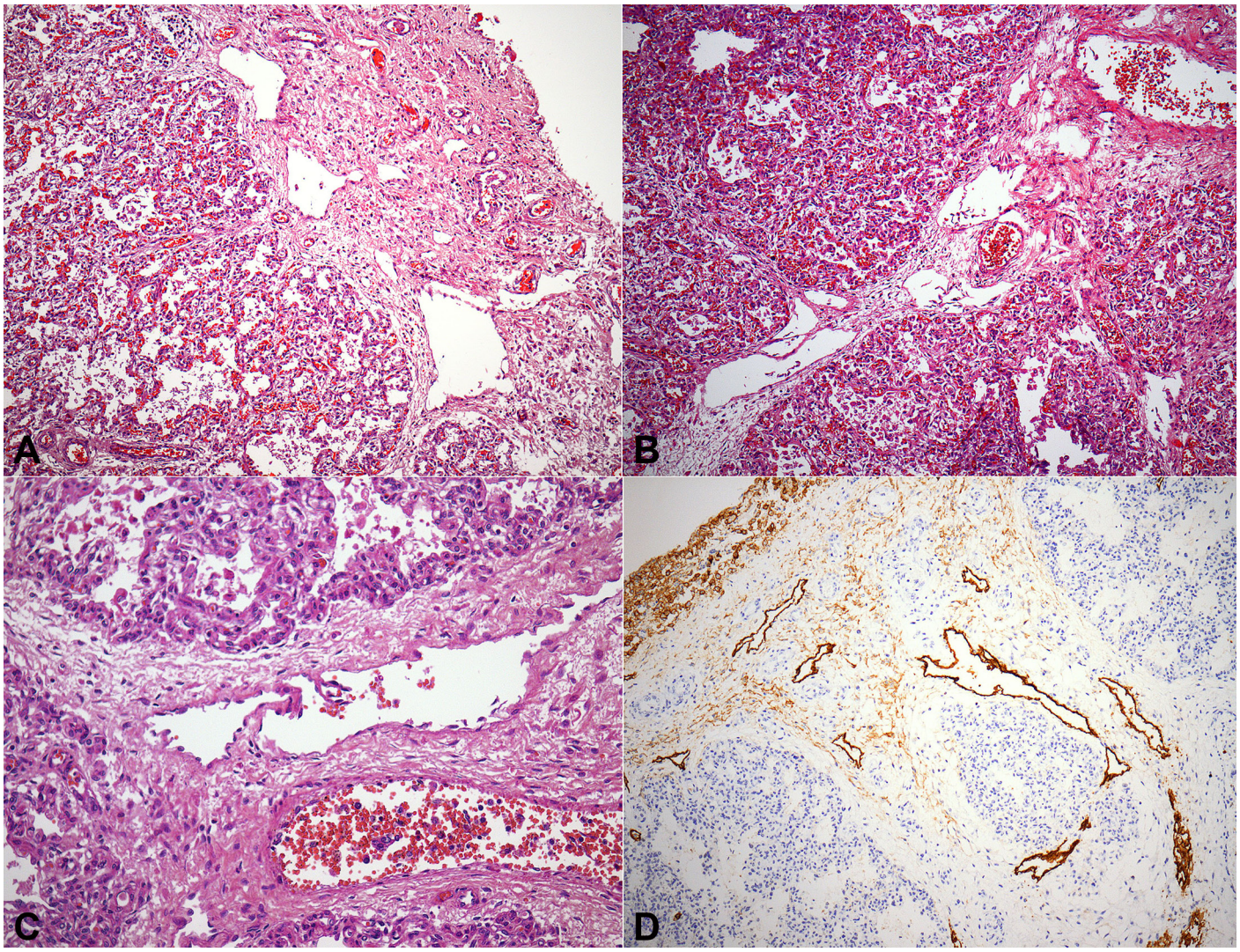

Figure 4. Photomicrography of the lung. **A** - Dilated lymphatic vessels in the visceral pleura (H&E, 100X). **B** - Dilated lymphatic vessels within alveolar septa (H&E, 100X). **C** - Detail of the lymphatic vessel with intraluminal septum (H&E, 200X). **D** - Immunohistochemichal positive reaction for D2-40 in the lymphatic vessels (100X).

vessels, which lack mural cell coverage, and are devoid of a continuous basement membrane. The pre-collector vessels display similar properties as capillaries with the exception that they also contain bi-leaflet intraluminal valves like those seen in the large collecting vessels.[9]

The clinical presentation of CPL in the antenatal period can be similar to non-immune hydrops fetalis with hydrothorax, often in combination with polyhydramnios. Severe respiratory distress, due to unilateral or bilateral pleural effusions, pulmonary hypoplasia, and surfactant deficiency in combination with prematurity leading to intubation and mechanical ventilation, is the usual presentation at birth. Patients with generalized CPL usually have less pulmonary involvement but develop more subcutaneous edema and visceral effusions.[4,10] The main neonatal complications are persistent visceral chylous effusions, mechanical ventilatory support addiction, anasarca, arterial hypotension, heart failure, secondary pulmonary hypertension, nosocomial infections, and neonatal death, usually as a consequence of progressive respiratory failure.[11]

We report the case of a neonate with persistent visceral effusion and anasarca, with autopsy findings showing generalized lymphangiectasis and a less evident pulmonary evolvement, which altogether could represent a generalized form of CPL. The presence of immature pulmonary parenchyma and signals of secondary pulmonary hypertension were noted in this case, which are also described by other autopsy case reports in the literature.[1,9] Although group 1 CPL is usually associated with mild pulmonary involvement and symptoms with a better prognosis, our case had severe pulmonary symptoms, which we attribute to

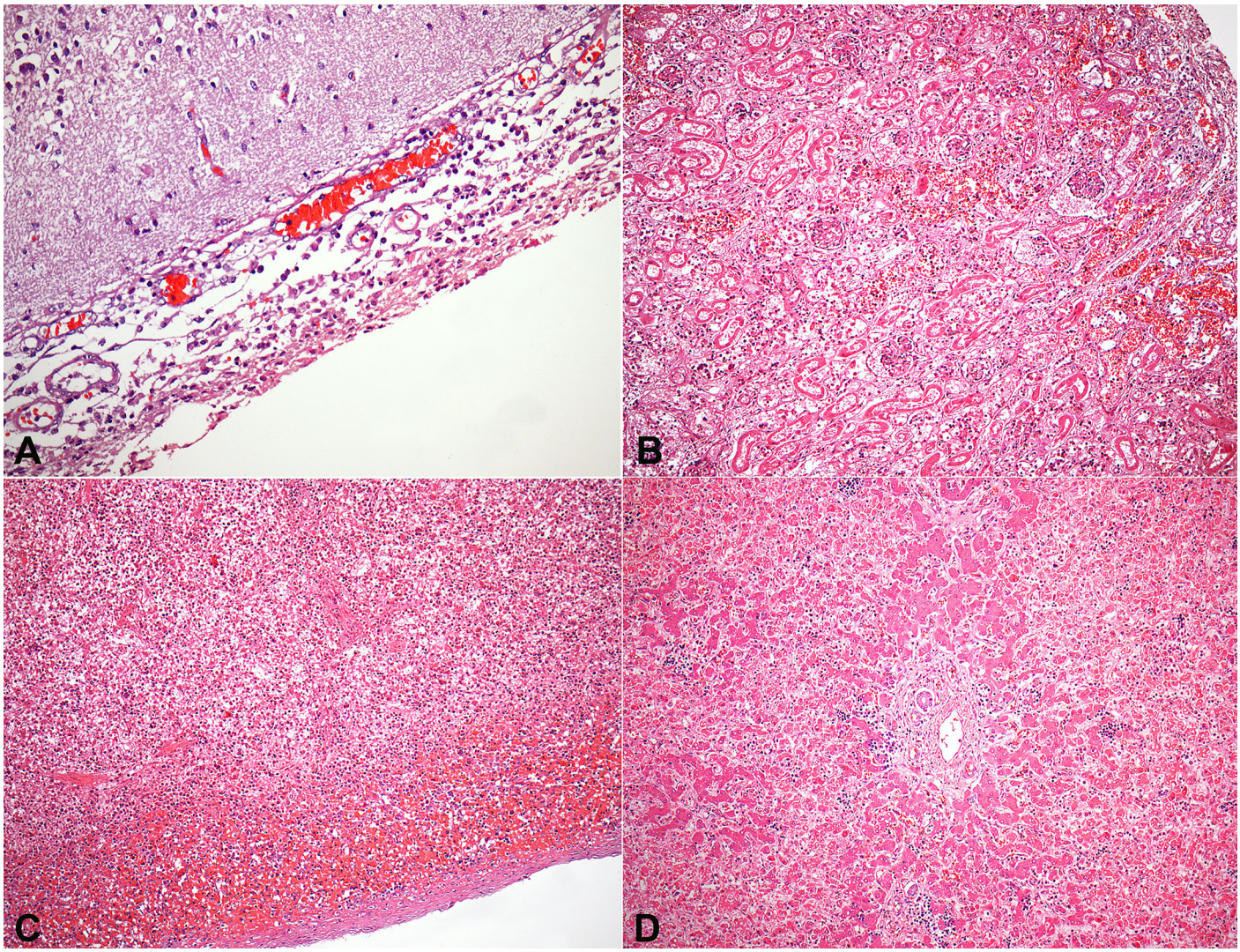

Figure 5. A - Photomicrography of the meninx with acute inflammatory infiltrate (H&E, 200X). **B** - Photomicrography of the kidney with acute tubular necrosis (H&E, 100X). **C** - Photomicrography of the spleen with ischemic infarction (H&E,100X). **D** - Photomicrography of the liver with lobular infarction, sinusoidal congestion, and extramedullar hematopoiesis (H&E, 100X).

the premature and insufficiently expanded pulmonary parenchyma, with secondary pulmonary hypertension, causing the severe pulmonary symptoms. The acute meningitis and septic shock also contributed to the fatal outcome. Even though associated congenital or chromosomal anomalies could not be ruled out by molecular analysis, Noonan syndrome was considered in the differential diagnosis. It is usually associated with congenital heart disease, but that was absent in our case.

Nevertheless, most cases of CPL occur sporadically in association with chromosomal anomalies as Turner, Down, Phelan–McDermid, Noonan, Cardio-Facio-Cutaneous, Costello, and Hennekam.[4] In the presence of intestinal lymphangiectasis, Hennekam syndrome (HS) also should be considered among the differential diagnoses. HS has congenital intestinal lymphangiectasia, without marked respiratory features at birth, with protein-losing gastroenteropathy resulting in peripheral edema, ascites, hypogammaglobulinemia, lymphopenia, and electrolytes imbalance. In this syndrome, facial features are characterized by a flat face, a flat and broad nasal bridge, and hypertelorism, which reflect the extent of the intrauterine facial lymphedema.[1] To date, the CCBE1 mutation is the single detectable genetic alteration for HS.[4]

The diagnosis of CPL is often based on clinical signs, imaging, and histological findings. The gold standard for diagnosis is open-lung biopsy. Histological examination is helpful in the differential diagnosis of diffuse pulmonary lymphangiomatosis, interstitial

pneumonia, interstitial emphysema, and congenital cystic adenomatoid malformation.[4,10] Systemic lymphangiectasis becomes evident only when post-mortem examinations are performed, contributing to the differential diagnosis between CPL groups 1 and 3.[4] Although imaging findings are not specific, thoracic computed tomography or plain chest radiography are usually described as presenting reticulonodular infiltrate with increased interstitial thickening, due to dilated pulmonary lymphatics. An alternate imaging exam is lymphoscintigraphy, which identifies lymph vessel abnormalities, but is rarely reported.[4,12]

The postnatal therapeutics options are primarily supportive care with aggressive mechanical ventilation, surfactant administration, thoracocentesis, cardio-circulatory support, total parenteral nutrition, and substitution of losses of electrolytes, coagulation factors, and immunoglobulin. Octreotide, a somatostatin analog, is a therapeutic option for persistent chylothorax, with a direct effect on the splanchnic circulation resulting in vasoconstriction, and decreasing chyle production. Pleurodesis or surgical interventions, such as pleurectomy or thoracic duct ligation, are possible for cases that evolve with relapsing pleural effusion.[4]

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