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Congenital Pulmonary Lymphangiectasia impersonating pulmonary interstitial emphysema in an extremely low gestational age neonate

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ABSTRACT

Background: The purpose of this case report is to illustrate the clinical course of an extremely rare case of Congenital Pulmonary Lymphangiectasia (CPL) presenting as an early pulmonary interstitial emphysema (PIE) complicating respiratory distress syndrome, in an extremely low gestational age neonate (ELGAN) along with a short review of the literature.

Case presentation: This 24 weeks ELGAN male with radiologic changes consistent with pulmonary interstitial emphysema (PIE) complicating respiratory distress syndrome which later progressed to bilateral cystic lung changes, expired at 23 days of age. Maternal history was complicated by E. coli urinary tract infection and Group-B Strep chorioamnionitis. The infant remained intubated throughout the hospital course and received antibiotics initially and terminally. His tracheal aspirate cultures also grew Mycoplasma hominis, and Ureaplasma urealyticum, treated with azithromycin. An autopsy revealed diffuse bilateral congenital lymphangiectasia. Postmortem blood and lung tissue cultures were positive for methicillin-resistant Staphylococcus aureus (MRSA).

Conclusion: Despite its extreme rarity, the authors recommend considering congenital pulmonary lymphangiectasia in the differential diagnosis, in an extremely preterm neonate, presenting with early pulmonary interstitial emphysema (PIE), and respiratory failure refractory to surfactant, antibiotic therapy, and complex ventilator management.

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Introduction:

Congenital pulmonary lymphangiectasia (CPL) is a very rare disorder of lung development [1], resulting in dilation of lymphatics involving sub-pleural, inter-lobar, peri-vascular and peri-bronchial groups. In this report, we are presenting an autopsy proven extremely rare case of congenital pulmonary lymphangiectasia in a 24 weeks extremely low gestational age neonate (ELGAN) male, and his clinical course. A concise review of CPL literature is included.

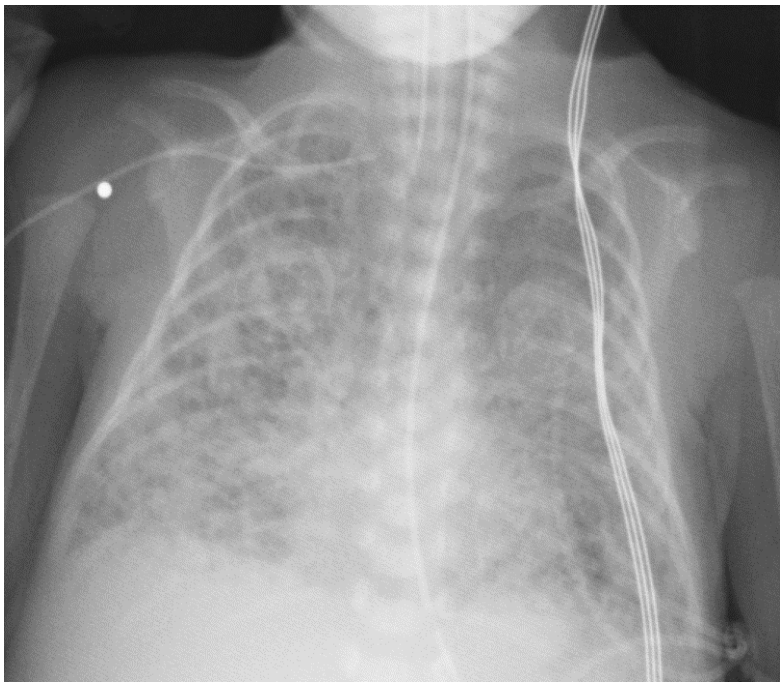

Figure 1: Day 8 Chest x-ray suggestive of bilateral pulmonary interstitial emphysema (PIE) with hyper expanded lung fields

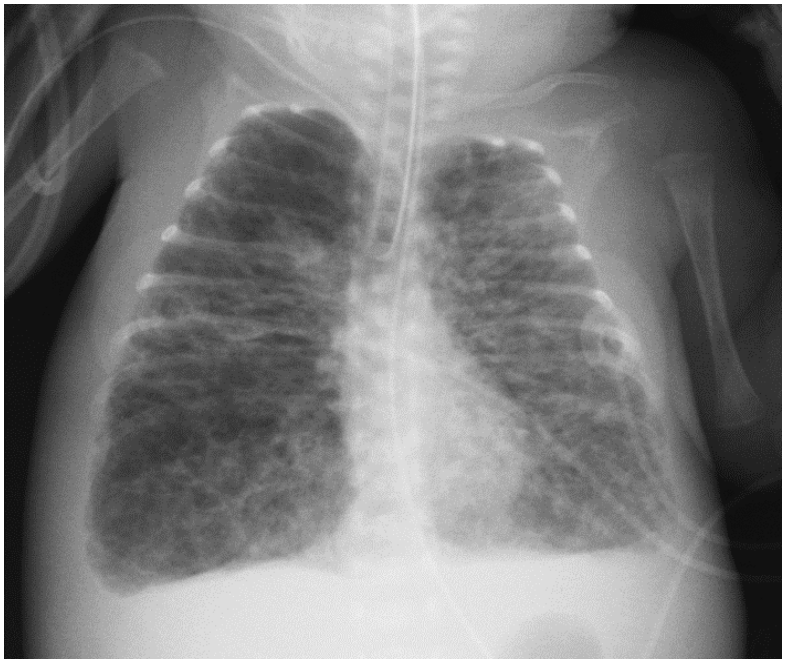

Figure: 2: Day 23 Chest x-ray with bilateral cystic lung fields and hyper-expanded lung fields Resulting in small cardiac silhouette with flattened domes of the diaphragm.

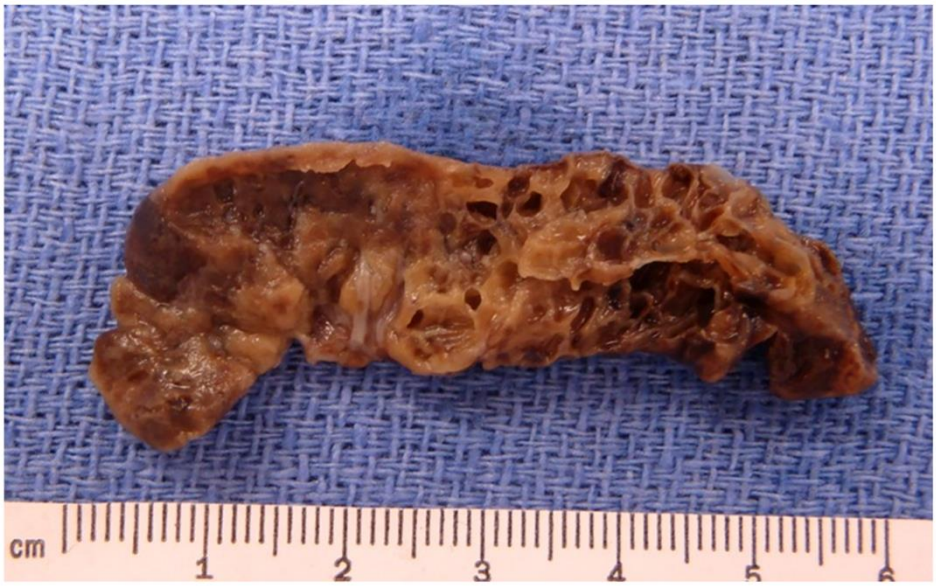

Figure 3. Gross picture of cut surface of the lung shows multiple small cysts scattered throughout the lung parenchyma.

Case Description

This 24 week ELGAN male was born to a 27 year old O negative gravida 1 Spanish speaking mother, by spontaneous vaginal delivery (SVD) with a birth weight of 800 grams (more than 95th%ile as per Fenton's Growth chart). Maternal history included history of frequent vaginal bleeding, and cramping. She had recent urinary tract infection with nitrofurantoin resistant E. coli which was treated with amoxicillin, and was also colonized with group- B strep. During the intrapartum period, she received ampicillin, terbutaline, magnesium sulfate, Rhogam, and betamethasone (two doses given 48 hours prior to delivery). Membranes ruptured at the delivery and the fluid was clear. Delivery room resuscitation steps included free flow Oxygen (FiO2 0.4 to 1), CPAP, bag and mask ventilation, endotracheal intubation and positive pressure ventilation. Surfactant was administered in the delivery room. Apgar scores were 4, 6 and 7. There were no dysmorphic features or external congenital anomalies.

Hospital Course: During his 23 days of fluctuating respiratory status, he required multiple modes of ventilation, including conventional ventilator, high frequency jet ventilator (HFJV), and high frequency oscillator (HFOV). Chest x-ray (CXR) done on day 1 showed granular/mild ground glass appearing lungs but with *hyper-expansion*, atypical for surfactant deficiency with resultant hypovolemic atelectatic lungs. Follow-up CXR films showed clearing of opacification of lung fields, but persistent hyper expansion. CXR done on day 8 showed radiological changes consistent with bilateral pulmonary interstitial emphysema (Figure 1). Follow up CXRs showed hyper-expanded lung fields with cystic lug changes which persisted until the last day of life (Figure 2).

Blood cultures drawn on day 1 showed no bacterial growth. Placental cultures were positive for E. coli. Cerebrospinal fluid cultures showed no growth. Endotracheal cultures at 9 days of age were reported to be positive for *Ureaplasma urealyticum*, and *Mycoplasma hominis* (received azithromycin for 7 days). Initially started on ampicillin, tobramycin, and fluconazole prophylaxis. Later, due to worsening respiratory status and abnormal complete blood count, but with normal C-reactive protein, meropenem was added in place of ampicillin.

Trophic feedings were started on day 2, but were never tolerated. He developed cholestasis with a peak direct bilirubin of 6.7. Abdominal

ultrasound on day 23 showed small amount of ascites. Initially required dopamine for hypotension. Echocardiogram at 1 week of age showed a 1.7 mm patent ductus arteriosus (PDA), a muscular ventricular septal defect (VSD), and a small persistent foramen ovale (PFO). PDA ligation was planned due to failed medical therapy to close PDA. But, it was not done due to infant's critical clinical status. Screening head ultrasound (HUS) exam on 3rd day of life, was normal, but follow-up HUS showed grade III and grade IV intraventricular hemorrhages.

On the day of expiration, he had life threatening bradycardia, not responding to resuscitative efforts. Chest and abdominal films showed bilateral severe cystic lung changes, right tension pneumothorax and suspected air embolism (air in the hepatic veins with translucency in the heart silhouette). After discussion with the clinical team, parents opted for 'allowing natural death' (AND). An unrestricted autopsy was performed after obtaining the parents' consent.

Pathological findings:

The most significant autopsy finding was evidence of congenital pulmonary lymphangiectasia. Grossly, the lungs were enlarged with multiple subpleural bullae and many intraparenchymal small cysts that diffusely affected all lobes of the lung (Figure 3). Microscopically, the lung parenchyma showed numerous cystically dilated lymphatics in the subpleural, peribronchial, septal, and interlobular areas (Figure 4A, 4B). The dilated lymphatics are positive for D2-40 (lymphatic marker) (Figure 4C, 4D) and CD-31 (endothelial marker) immunohistochemical stains. Additional significant autopsy findings in the lungs included atelectasis, focal acute bronchopneumonia, focal mild bronchopulmonary dysplasia, intraalveolar and patchy parenchymal hemorrhage, which were probably secondary to CPL, extreme prematurity, and sepsis. The remaining pathological findings were signs of multiple organ tissue damages that were probably related to hypoxia, extreme prematurity, and sepsis, including multifocal myocardial hemorrhage with ischemic necrosis, acute renal tubular injury and cortical hemorrhages, stress involution of the thymus and spleen, and brain with germinal matrix hemorrhage in lateral ventricles with extension into subarachnoid space of cerebellum and brainstem. Postmortem cultures of heart blood and lung tissue were positive for MRSA, supporting the diagnosis of sepsis.

Discussion:

Congenital Pulmonary Lymphangiectasia (CPL) was first described by Virchow in 1856[2]. More than a century later (1970), Noonan[2, 3] classified Congenital Pulmonary Lymphangiectasia into 3 groups- 1) general lymphangiectasis with mainly intestinal (less involvement of lungs), 2) secondary CPL due to pulmonary venous obstruction (usually associated with congenital heart disease, and 3) primary pulmonary lymphangiectasia. In 2013, Connell et al [2] suggested a modified classification with an algorithm for primary lymphatic dysplasia. Primary CPL refers to the category of systemic lymphatic problems persisting beyond neonatal period, or those that can manifest at any age thereafter. They can be subdivided into isolated, generalized, and syndromic (known, and unknown) [4]. Secondary CPL includes several cardiovascular conditions and thoracic duct obstruction, all causing obstruction and extravasation.

The true incidence and etiology of CPL are unknown. It is heterogeneous, and occurs mostly sporadically. Based on their frequency of occurrence as noted in autopsies, it is postulated that approximately one in a thousand either still-borns or neonatal deaths is attributable to CPL[4]. Previous reports showed male predominance. It was also reported in association with some genetic disorders such as Noonan, Down, Turner, and Fryns syndomes[5]. Bellini et al[6] reported its association with various syndromes including Cumming type Camptomelia, German syndrome, Hennekam lymphangiectasia,

Hypotrichosis-Lymphedema-Telangiectasia (HLT) syndrome, Idiopathic Hydrops Fetalis, Intestinal Lymphangiectasia, Knobloch syndrome, Lymphadema/Cerebral A/V anomaly, Edema Hypothyroidism syndrome, PEHO syndrome, Urioste syndrome, and Yellow nail syndrome[6].

Patho-physiology

During early fetal stage, *vasculogenesis* starts with blood vessels originating from mesoderm derived endothelial cell precursors, and these vessels soon undergo *angiogenesis* and remodel into mature network of blood vessels. Lymphatic vasculature development seems to follow the formation of blood vessels. In 1902, Florence Sabin[7] proposed the theory on lymphatic vasculature development. During 9th week of gestation, lymph vessels start growing, and in the 14th week of fetal life lymph vessels form wide lymph trunks in the connective tissue. They divide the parenchyma of lungs into distinct lobules [4]. By 20th week, narrow lymph channels are formed.

1n 1959, Lawrence[8] felt that CPL stems from the continued growth of these tissues beyond fetal stage. CPL is presumed to be a developmental defect after 16th week of fetal life. On examination, these lungs tend to be bulky and lacking elasticity with large cystic spaces in the sub-pleural area. This results in a honey comb appearance. Due to increased fibrosis, the surrounding alveoli are nearly collapsed, and airless, but bronchiolar ectasis may be present.

The word “ectasia” comes from the Greek word ‘ektasis’, meaning dilated, expanded, or extended Several names are frequently used synonymously (sometimes mistakenly), such as pulmonary lymphangiectasia, pulmonary cystic lymphangiectasia, pulmonary lymphangiomatosis.

Clinical Presentation and Diagnosis

During antenatal evaluation, CPL needs to be considered in the differential diagnosis of cases of hydrothorax, and non-immune hydrops especially when associated with polyhydramnios. At birth, a preterm neonate may present with severe respiratory distress, with or without pleural effusions (unilateral or bilateral), and surfactant deficiency requiring resuscitation and ventilator support. It is considered as uniformly fatal, but recent advances in perinatal and neonatal care have resulted in improvement in survival[4]. Patients with generalized lymphangiectasia tend to have less lung involvement, more often with generalized edema and effusions[9].

The neonatal course is frequently complicated by chylous effusions, anasarca, pulmonary hypoplasia, pulmonary hypertension, progressive respiratory failure, nosocomial infections, and neonatal death[4]. Cases of CPL were reported in older children and even in adults[10, 11].

Diagnosis of CPL is most often based on clinical picture, radiologic manifestations, and histological characteristics noted by either autopsy or lung biopsy. Open-lung biopsy is the gold standard for diagnosing various pulmonary conditions including interstitial lung diseases (such as congenital alveolar capillary dysplasia[12]), and conditions with lymphatic dilations such as CPL. Macroscopic and histologic examination[4] show hypoplastic lungs, with scattered nodular changes along the visceral pleura, cystic changes in intrapulmonary lymphatics, and thickened interlobular connective tissue[4, 13]. The small cysts in PIE are lined by mono-and multinucleated giant histiocytes. In contrast, cysts in CPL are lined with flattened endothelium without histiocytes[5]. In respiratory distress syndrome, the distended lymphatics are located interlobular, but in CPL they tend to be larger and also located in sub-pleural, and peri-bronchial areas. By Immuno-histochemical stain, endothelial cell lining of the lymphatics are shown to be positive for several antibodies, such as CD-31, CD-34, and D2-40. Recent studies linked CPL to FOXC2, Vegfr-3, and integrin alpha9beta1gene mutations[14].

Other useful diagnostic tools in making a diagnosis of CPL, include CXR and high

resolution computed tomography may show reticulo-nodular findings with increased interstitial thickening and bilateral pulmonary inflation. Lympho-scintiography can be used to identify lymph vessel anomalies[4].

Treatment:

CPL's variable clinical presentation, severity and course, make it very difficult for any specific treatment strategy. When hydrops, pleural effusion, or chylothorax are noted during gestation, perinatal approach includes thoracocentesis, thoraco-amniotic drainage/ shunting, or medical pleurodesis[4]. Delivery closer to term is recommended in otherwise uncompromised CPL pregnancies. Neonatal management is mostly supportive, which includes neonatal intensive care management requiring surfactant therapy, ventilator management, thoracocentesis, use of inotropes, diuretics, total parental nutrition etc. Frequently, management of chylothorax of the neonate becomes an essential step. Octreotide is used frequently In addition to providing diet high in medium triglycerides (MCT). Sirolimus, an immunosuppressive drug with antiangiogenic and antiproliferative properties[4, 15], was tried in children having microcystic lymphatic malformations, and visceral chyous effusions. Chemical pleurodesis with intrapleural instillation of agents like OK-432[16], mino-cycline[17], povidone-iodine and autologous blood[4] was tried to induce inflammatory response, which would lead to pleural fibrosis and sclerosis.

Available surgical options for chylothorax include pleurectomy, thoracic duct ligation[4] and pneumonectomy for unilateral CPL[18].

Conclusion

Due to recent advances in diagnostic modalities, more cases of CPL are diagnosed, and reports of documented long term survival are also emerging. Although CPL was once regarded as a disorder of very poor prognosis in neonatal onset cases, teenager and adult patients have shown good outcomes upon long-term follow-up. Open lung biopsy is still the gold standard for the diagnosis of CPL. Because of its extreme rarity, often they are missed and are diagnosed only by autopsy. Despite its extreme rarity, the authors recommend to consider congenital pulmonary lymphangiectasia in the differential diagnosis of an extremely preterm neonate, presenting with early pulmonary interstitial emphysema (PIE), and respiratory failure refractory to surfactant, antibiotic therapy and complex ventilator management. Due to association with multiple genetic disorders, it is recommended to get array-CGH analysis on high resolution. Due to male preponderance, and rare occurrence of CPL in siblings, a Genetic consult and counseling are highly recommended.

References

[1]. Carlo Bellini, Francesco Boccardo, Corradino Capisi and EugenioBonioli: Congenital Pulmonary Lymphangiectasia. Orphanet Journal of Rare diseases. 2006;1:431.

[2]. Connell FC, Gordon K, Brice G, et al. The classification and diagnostic algorithm for primary lymphangiectasia. Clin Genet 2013; 84:303-14

[3]. Noonan JA, Walters LR, Reeves JT: Congenital Pumonary Lymphangiecatasia. Am J Dis Child 1970; 120:314- 319

[4]. Friedrich Reiterer, Karin Grossauer, Nicholas Morris, Sabine Uhrig: Congenital Pulmonary Lymphangiectasis. Paediatric Respiratory Reviews 15 (2014) 275- 280

[5]. Yamada S, Hisaoka M, Hamada T, Araki S, Shiraishi M. Congenital pulmonary lymphangiectasis: report of an autopsy case masquerading as pulmonary interstitial emphysema. Pathology - Research and Practice Volume 206, Issue 7, 15 July 2010, Pages 522-526

[6]. C Bellini 1, F Boccardo, C Campisi, P Toma, G Taddei, G Villa, P Nozza, G Serra, E Bonioli. Pulmonary lymphangiectasia. Lymphology. 2005 Sep;38(3):111-21.

[7]. Sabin FR. On the origin of the lymphatic system from the veins, and the development of the lymph hearts and thoracic duct in the ig. Am J Anat 1902;1:367-89

[8]. Lawrence KM. Congenital pulmonary lymphangiectasis. J Clin Path 1959;12:62-9

[9]. Debruyn G, Casaer A, Devolder K, et al. Hydrops fetalis and pulmonary lymphangiectasia due to FOXC2 mutation: an

autosomal dominant hereditary lymphedema with variable expression. Eur J Pediatr 2012;171:447-50

[10]. Esther Jr CR, Barker PM. Pulmonary lymphangiectasia: Diagnosis and Clinical Course> Pediatr Pulmonol 2004;38:308-13

[11]. Yoshoitomo O, Shin-chi T, Noriyoshi S, Hajime M, Hiroshi H. Pumonary Lymphangiectasia in an Asymptomatic Adult. Respiration2006;73:114-116

[12]. Nandyal RR, Parham D, Yu and Escobedo M. Congenital Alveolar Capillary Dysplasia and New Associations: A Case Series with a Report of New Associations and Literature Review. Med Rep Case Stud 2017, 2:1

[13]. Hagmann C, MD; Berger TM. Congenital pulmonary lymphangiectasia. N Engl J Med 2003;349;e21

[14]. Yuan SM. Congenital Pulmonary Lymphangiectasia: A Disorder not only of Fetoneonates. [Review]. Klin Padiatr. 229(4):205-208, 2017 Jul.

[15]. Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, Elluru R, Dasgupta R, Azizkhan RG, Adams DM. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011 Dec 1;57(6):1018-24.

[16]. Matsukuma E, Aoki Y, Sakai M, Kawamoto N, Watanabe H, Iwagak S, Takahashi Y, Kawabata I, Kondo N, Uchida Y. Treatment with OK-432 for persistent congenital chylothorax in newborn infants resistant to octreotide. J Pediatr Surg. 2009 Mar;44(3):e37-9.

[17]. Kaneko M, Kanai Y, Hayato Go, M.D.,1 Takashi Imamura, M.D., Ph.D.,1 Momoi N and Hosoya M. Five Cases of Congenital Chylothorax Treated by Intrapleural Minocycline.

[18]. Hwang JH, Kim JH, Hwang JJ, Kim KS, Kim SY. Pneumonectomy case in a newborn with congenital pulmonary lymphangiectasia. Journal of Korean Medical Science. 29(4):609-13, 2014 Apr.