E5 Fatal Alveolar Capillary Dysplasia (ACD) in Two Siblings: A Rare Heritable Form of Persistent Pulmonary Hypertension in Neonates

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Learning Overview: After attending this presentation, attendees will understand the necessary elements for the diagnosis of ACD, a fatal lung disorder in premature or full-term infants. ACD is an uncommon interstitial lung disease causing Persistent Pulmonary Hypertension in Neonates (PPHN). Without responding to therapy, it is characterized with a mortality rate that approaches 100%.[1] The diagnosis of ACD is difficult because the etiopathogenesis of ACD and associated pulmonary hypertension remain to be fully explained.[1] Furthermore, an autopsy is not always performed after an infant's death, and ACD can be associated with other congenital system anomalies that are often considered to be the primary cause of death.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by highlighting that ACD must be suspected and immediately investigated in all infants with irreversible persistent fetal circulation. The literature review, conducted by the PubMed database, yielded 30 papers about ACD. It is described as a cyanogenic disorder characterized by failed postnatal decrease of the vascular pulmonary resistance, associated with the typical intrauterine right-to-left shunt. The disorder affects primarily the alveolar components leading to respiratory insufficiency early in life.[2]

Most ACD cases are *de novo* events but approximately 10% are heritable forms possibly involving siblings. 16q24.1 deletion and FOXF1 inactivating mutations have been identified as responsible in 40% of cases.[1] Currently, a definitive diagnosis depends on histological lung features found at autopsy or antemortem lung biopsy: (1) immature lobular development; (2) decreased number of pulmonary capillaries, dilated and located away from the alveolar epithelium; (3) thickened alveolar septa; (4) lymphangiectasis in interlobular septa; and (5) sometimes misalignment of pulmonary veins adjacent to pulmonary arteries.[1] In the case reported, two siblings born two years apart died after a severe and irreversible pulmonary hypertension with hypoxemia developed a few hours after their birth.

A 37-week gestational age (2,900g of weight, 9/9 Apgar score) male infant was born to a primipara via induced vaginal childbirth in view of polyhydramnios. The infant's respiratory status declined within the first 12 hours of life. Despite the immediate mechanical ventilation and inhaled nitric oxide, the neonate died 96 hours after birth because of irreversible respiratory failure. At autopsy, the histological examination of lung tissue showed immature and dilated alveolar capillaries distant from the alveoli through thickened septa, associated with lymphangiectasis. A 16p13.3 deletion was found through array Comparative Genomic Hybridization (CGH) analysis.

During the second pregnancy, the fetus shared the same 16p13.3 deletion through array CGH analysis on fetal DNA. Colon-sigma and rectum dilatation were detected by echocardiography at 17 weeks of gestation. A male infant was born by vaginal delivery at 38 weeks gestation (3,040g of weight, 6/9 Apgar score), but he developed serious pulmonary hypertension a few hours after birth. After detecting anorectal atresia, a right hemicolectomy was performed. Despite the regular clinical course, a respiratory failure occurred, not responding to any therapy until the infant's death 25 hours after birth. Autopsy and histological analysis showed underdeveloped acini and dysplastic and sparse capillaries within the thick interstitium in the lungs. In both cases, analysis of the lung tissues showed characteristic features of ACD as the cause of death. The recurrence of ACD and genetic tests (16p13.3 deletion) suggested an autosomal recessive or X-linked mode of inheritance.

Histological and genetic examinations have a key role in the diagnosis of ACD, especially in the prenatal period. An accurate assessment is fundamental for the management of PPHN because of the high rate of mortality. If death occurs, autopsy is recommended to verify system malformations. This approach may help to define the correct cause of death when related to ACD.

Reference(s):

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2. Giuseppe Distefano, Pietro Sciacca. Molecular Physiopathogenetic Mechanisms and Development of New Potential Therapeutic Strategies in Persistent Pulmonary Hypertension of the Newborn. *Italian Journal of Pediatrics*, 41 (2015): 6. 10.1186/s13052-015-0111-0.

Alveolar Capillary Dysplasia, Neonates, Persistent Pulmonary Hypertension