H56 Alveolar Capillary Dysplasia With Misalignment of the Pulmonary Veins: Histopathology and Applicability to Autopsy

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Learning Overview: After attending this presentation, attendees will be able to: (1) identify the pathognomonic histologic features of a rare lung development disorder, Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins (ACD-MPV); and (2) recognize its clinical presentation and understand confirmatory testing.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by elucidating a rare disease process that may present as unexplained cardiopulmonary arrest in an infant and providing diagnostic criteria that can help make a diagnosis.

Herein, a case of ACD-MPV is presented in which this diagnosis was not initially suspected clinically. The patient presented with respiratory failure within hours of birth, with subsequent development of pulmonary hypertension refractory to treatment. He received near-constant ventilator support and was put on Extracorporeal Membrane Oxygenation (ECMO) twice during his three weeks of life. Several hours after his second ECMO decannulation, he acutely decompensated with systemic hypotension and pulmonary hypertension requiring the use of vasopressors and fluid resuscitation. Infection was suspected clinically due to a rising white blood cell count in the context of hypotension, but all cultures were negative. The patient's ultimate demise was precipitated by an acute hypoxic event; his family opted to have an autopsy performed. Gross autopsy findings included left pulmonary artery stenosis with ostial stenosis, pulmonary trunk dilation, and right ventricular hypertrophy. Light microscopy revealed a decreased number of pulmonary capillaries and increased distance from alveolar epithelium in conjunction with pulmonary veins and pulmonary arteries in the same adventitial sheath. Genetic testing performed on the patient identified a c.691_698delGCGGCGGC frameshift mutation in the *FOXF1* gene.

ACD-MPV is a rare but generally fatal developmental disorder of pulmonary vasculature. Genetic variations of the *FOXF1* gene, including heterozygous point mutations, deletions, and mutations of an upstream enhancer region have been identified in patients with ACD-MPV, and mutations in *FOXF1* have been shown to cause similar pulmonary vascular abnormalities in mice. However, pedigree analysis suggests that mutations in other still unknown gene(s) may also result in ACD-MPV. The initial presentation of this disorder typically involves neonatal respiratory distress and pulmonary hypertension, both of which are refractory to supportive measures. Respiratory distress typically occurs within 24–48 hours after birth and may be accompanied by central cyanosis and tachypnea. The clinical presentation may be exacerbated by a concomitant hypoplastic left heart. The *FOXF1* gene is also involved in gastrointestinal tract development, and malrotation or intestinal atresia may be identified alongside lung abnormalities. Rarely, genitourinary malformations are identified.

Histopathology is considered the gold standard for diagnosis of ACD-MPV. Tissue may be collected via a lung biopsy, if tolerated, but is often collected at the time of autopsy. Five histopathologic findings are diagnostic of ACD-MPV: immature lobular development; decreased number of pulmonary capillaries located away from alveolar epithelium; thickened alveolar septa; arteriolar and arterial changes, including medial hypertrophy and muscularization; and malposition of pulmonary veins within the same adventitial sheath as pulmonary arteries. In up to 30% of cases, lymphangiectasis may also be identified.

This case report highlights the importance of autopsy in elucidating a disease process that was not initially suspected clinically. It is important for pediatric critical care teams to include ACD-MPV in the differential diagnosis of patients with severe and refractory respiratory failure and pulmonary hypertension. Definitive diagnosis can be made by lung biopsy, if tolerated. Identification of an inactivating *FOXF1* mutation can confirm the diagnosis, but absence of such a mutation cannot definitively rule out ACD-MPV. Prompt antemortem diagnosis may allow the development of treatments that can prolong survival, as no effective treatments for ACD-MPV exist currently, and may assist families in coping with their child's prognosis. In the broader context of forensic autopsies, the diagnosis of ACD-MPV may be identified histopathologically within the context of an otherwise unexplained cardiopulmonary failure in a term neonate.

Alveolar Capillary Dysplasia, Misalignment of Pulmonary Veins, Histopathology