P-45

Pathology and genetics of alveolar capillary dysplasia with misalignment of the pulmonary veins and its association with congenital heart defects

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Objective: Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is a rare and lethal congenital lung disease characterized by severe pulmonary arterial hypertension (PAH) and refractory hypoxemia. The mortality is nearly 100%, irrespective of the co-morbidities. The objective is to describe the pathology, genetics and clinical course of two patients with ACD/MPV and its potential impact on clinical decision-making.

Methods/Results: We retrospectively reviewed the records of all patients with ACD/MPV in our institution from 2015 to 2018 and the current literature. In this time period, we treated two patients. In both cases, a coarctation was seen. In the second case, an unbalanced partial atrioventricular septal defect (pAVSD) was detected as well. In both cases, first symptoms appeared during the first 24 hours of life. Main symptoms were PAH and refractory hypoxemia. X-Ray and cardiac catheterization were not conspicuous for a pulmonary vascular pathology. In both cases, aggressive management of PAH was not sufficient to ensure oxygenation. Thus, extracorporeal membrane oxygenation (ECMO) became necessary. However, patients could not be weaned from ECMO and died after ECMO therapy of 11 and 18 days due to complications, respectively.
We performed autopsy and array analysis for genetic testing. Histopathology revealed classical signs of ACD/MPV with reduced numbers of alveolar capillaries located away from the alveolar epithelium and malposition of pulmonary veins adjacent to pulmonary arteries. Array analysis showed de novo deletions in the chromosomal region 16q24.1q24.2. Both deletions included the FOX Gene Cluster FOXF1, FOXC2 and FOXL1. Loss of function mutations of FOXF1 as well as deletions of the FOX gene cluster have been reported as disease associated.

Conclusions: Initially, ACD/MPV can be easily confused with persistent pulmonary hypertension of the newborn. This can prolong time to confirm diagnosis. Thus, ACD/MPV should be suspected in neonates with congenital heart disease and unexpectedly elevated pulmonary vascular resistances, especially in cases of obstructive left heart disease or AVSDs. It is important to increase the awareness of physicians. Further, it is crucial to perform lung biopsy and genetic testing at an early stage and to counsel the parents regarding future pregnancies.