



Recurrence of alveolar capillary dysplasia with misalignment of pulmonary veins in two consecutive siblings

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ABSTRACT

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a rare, developmental lung disorder, which has been increasingly reported. This entity usually presents as neonatal persistent pulmonary hypertension that is unresponsive to treatment, and is known to be uniformly fatal. Recent discoveries in the genetic field, and intensive treatments, may change the natural course of this disease, permitting easier diagnosis and giving new hope for the dismal prognosis. The authors present two cases of siblings, with two years of difference, from different fathers - one of them was a first-degree and the other a second-degree cousin of the mother. Both patients were full-term babies born apparently without malformations and were sent to the nursery. Both siblings near 35 hours of age presented severe respiratory failure due to pulmonary hypertension. The outcome was fatal in both cases and at autopsy ACD/MPV was diagnosed. The authors call attention to this entity in the differential diagnosis of acute respiratory distress in early life.

Keywords

Alveolar capillary dysplasia; Respiratory Insufficiency; Hypertension; Pulmonary; Newborn; Siblings; Autopsy.

CASE REPORTS

First Sibling

The first sibling was a full-term female newborn from first-degree cousins; the mother was 27-year-old, gravida 4, para 1, born by cesarean section due to fetal distress and oligohydramnios. The pregnancy was uneventful. At birth, the Apgar score was 7, 10, 10 at 1, 5, and 10 minutes, respectively. The mother's obstetric history was remarkable for two prior pregnancy losses. Her family history was negative for any congenital

cardiac or pulmonary disease. The newborn received routine prenatal care and no congenital abnormality was detected.

At 31 hours of age, the newborn developed progressive tachypnea, pallor, and hyperglycemia requiring neonatal intensive care unit (NICU) support. At admission, she promptly required endotracheal intubation and mechanical ventilatory support. Within 1 hour after admission, the hemodynamic parameters

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deteriorated even after the administration of vasoactive drugs. Despite all efforts, the patient presented six episodes of cardiac arrest in a 1-hour period and died soon after.

Second Sibling

The second sibling was a full-term male born two years after the first sibling by cesarean section due to iteractivity. The father was a second-degree cousin of the mother with whom he had previously had a healthy son. The pregnancy was uneventful. At birth, the Apgar score was 9, 9, and 10 at 1, 5, and 10 minutes, respectively. The infant received routine prenatal care and no congenital abnormality was detected on the physical examination.

At 40 hours of age, the newborn developed progressive tachypnea, pallor, hypotonia and hemodynamic instability, requiring NICU support. On admission, he promptly required endotracheal intubation and mechanical ventilatory support. Despite optimized hemodynamic care with vasoactive drugs (dopamine, dobutamine, milrinone, adrenaline and noradrenaline), hydrocortisone and E-prostacyclin, the hemodynamic parameters deteriorated. The patient presented eight episodes of cardiac arrests in a 12-hour period and died soon after.

AUTOPSIES

First Sibling

The external examination did not show any malformations. The lungs, weighed together 23.4 g (reference value [RV]: 42.6 g +/- 14.9 g), and were reddened and boggy. Histological analyses showed lobular simplification (enlarged, round or elongated, with deficient septation leading to insufficient alveoli within the acinar unit) and immaturity with a somewhat reduced number of alveoli plus widened alveolar septa with areas of a reduced number of capillaries—some of which were located away from the alveolar epithelium. Some areas showed anomalous pulmonary veins accompanying pulmonary arteries and bronchi (misaligned pulmonary veins) together with mild lymphatic dilatation (Figure 1). The medial muscle wall of small pulmonary arteries was thickened, and muscularization of tiny intracinar arterioles was present. Focal thrombi in pulmonary branches were

seen, as well as foci of alveolar damage with hyaline membranes and alveolar hemorrhage (Figure 2).

Other organs and systems showed signs of hypoxic-ischemic damage related to shock; namely, myocardial and encephalic ischemic focal changes, acute tubular necrosis, intense sinusoidal liver and splenic congestion, and generalized visceral congestion.

Second Sibling

Histological analyses of the lungs showed a very similar picture to the findings of the first sibling. Lobular simplification and immaturity, misaligned pulmonary veins (which were more easily found within the adventitia of pulmonary arteries), and muscularization of capillaries located somewhat away from the alveolar septa. A few bronchial arteries were very thickened and foci of alveolar damage with hyaline membranes and alveolar hemorrhage were found as well (Figure 3).

DISCUSSION

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) was thought to be an extremely rare and uniformly fatal neonatal disease.¹ However, this condition has been increasingly reported. Up to 200 cases in the English literature^{2,3} have been reported, and new treatment options have arisen, giving time and opportunity for patients to achieve the lung transplantation.⁴ Since the first report of "congenital alveolar dysplasia of the lungs" in the 1940s, MacMahon⁵ addressed that this condition may have already been seen but not always recognized.^{5,6}

ACD/MPV is the most common interstitial lung diseases of the newborn.^{7,8} In a study undertaken in the UK, the incidence of irreversible lung dysplasia is 1 in 236,947 live births, in which five out of nine patients were diagnosed with ACD/MPV. Moreover, one in six patients, with no obvious cause of severe persistent neonatal pulmonary hypertension, had ACD/MPV. Three out of four newborns who underwent extracorporeal membrane oxygenation (ECMO) due to idiopathic persistent pulmonary hypertension presented ACD/MPV, and 25% of those who died after ECMO, indicated for any reason, were also diagnosed with ACD/MPV.^{3,9}

Over the past last decade, a better understanding of the ACD/MPV genetics has changed the epidemiology,

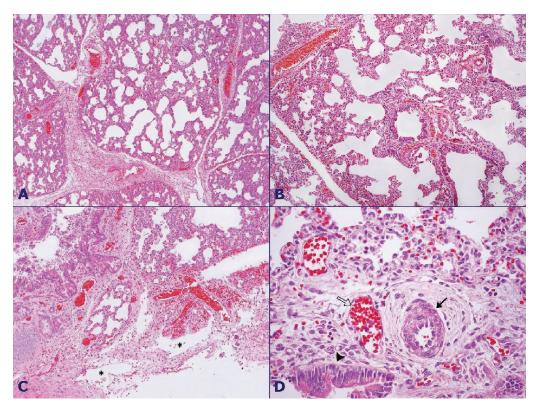


Figure 1. Photomicrography of the lungs (first sibling). **A** - Lobular simplification (H&E, 50X); **B** - Immaturity (H&E, 100X); **C** - Dilated subpleural lymphatics (*) (H&E, 100X); **D** - Thin-walled vein (white arrow) anomalously positioned adjacent to a muscular pulmonary artery (black arrow) close to the airway (bronchioles [arrowhead]) in the bronchovascular bundle (H&E, 400X).

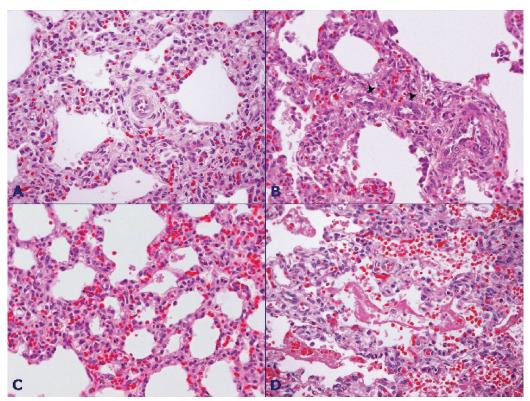


Figure 2. Photomicrography of the lungs (first sibling). **A** - Thickened alveolar septae with poor capillary bed and a thickened arteriole (H&E, 400X); **B** - Extension of smooth muscle into intracinar small arteries (arrowheads) (H&E, 400X); **C** - Small alveoli with a reduced capillary bed (H&E, 400X); **D** - Focal alveolar damage with hyaline membrane and alveolar hemorrhage (H&E, 400X).

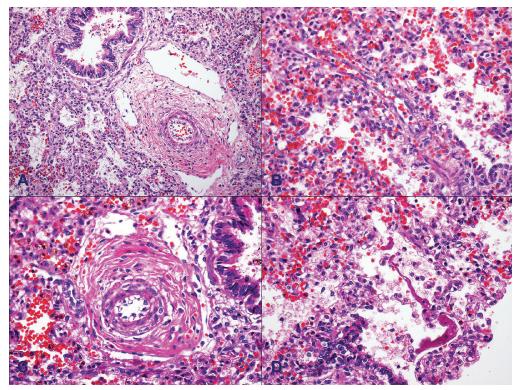


Figure 3. Photomicrography of the lungs (second sibling). **A** - Misalignement of thin-walled veins anomalously positioned within the same adeventitia of the adjacent to a muscular pulmonary artery close to the airway (H&E, 200X); **B** - Muscularization of intracinar small artery (H&E, 400X); **C** - Malpositioning of thin-walled veins adjacent to a thickened pulmonary artery (H&E, 400X); **D** - Focal alveolar damage with hyaline membrane (H&E, 400X).

the phenotype, and the way the diagnosis has been made. In 2009, Stankiewicz et al.¹⁰ demonstrated inactivating mutations in the FOXF1 gene in patients with ACD/MPV.¹⁰ The FOXF1 protein is involved in organogenesis, especially in the lung, but is located in all types of cells; therefore, FOXF1 mutations are related to ACD/MPV with the involvement of other organs². More recently, more mutations and deletions were found in the FOXF1 gene related to ACD/MPV.^{2,6,11} To date, 40% of all ACD/MPV cases have mutations in the FOXF1 gene^{1,12}, the majority are *de novo* mutations, but familial inheritance and siblings' involvement were also reported in some cases.^{13,14,15,16}

ACD/MPV has a constellation of histopathological features, which include immature lobular development, decreased number of pulmonary capillaries located away from the alveolar epithelium, thickened alveolar septae, medial hypertrophy of small pulmonary arteries with muscularization of distal arterioles, and lymphangiectasia (in up to 30%). Malposition of pulmonary vein branches adjacent to pulmonary arteries (usually with the same adventitial sheath) is considered pathognomonic, although it is not detected in every case. ¹⁷

Pathological differential diagnosis includes other diffuse developmental lung disorders or "congenital lung dysplasia", which is clinically indistinguishable.¹⁸ The most relevant are congenital acinar dysplasia and congenital alveolar dysplasia. In acinar dysplasia, there is an almost complete absence of mature alveoli, a large increase in the amount of interstitial connective tissue, and dysplastic bronchial cartilage plates. On the other hand, in congenital alveolar dysplasia there is a very large capillary bed, the alveolar epithelium resembles mature lung, the bronchial epithelium is well developed, and the alveolar walls are very wide and composed of primitive mesenchyme without mature collagen fibers.¹⁹

The natural course of ACD/MPV is not yet fully understood. The majority of the cases occur in full-term neonates, and a slight male predominance has been observed. 1,10,15,16,20-27 Up to 80% have extrapulmonary malformations, which include involvement in the gastrointestinal, genitourinary, and cardiovascular systems. 1,6,10,15,21,26-31 The newborns are usually asymptomatic at the time of delivery, present normal Apgar scores, and are therefore sent to the baby nursery. The onset of symptoms are subtle and usually occur

in the first hours or days of life, and are represented by progressive pulmonary hypertension (respiratory distress, cyanosis, and oxygen desaturation). However, late-onset cases, which become symptomatic after weeks or months, have been reported.^{3,10,15,28,29,32,33}

The initial chest radiography may be normal, or present a hazy pattern or pneumothorax. The echocardiography shows moderate-to-severe pulmonary hypertension causing right-to-left extrapulmonary shunting. 4,10,23,28,32,34 Despite the appropriate treatment in the NICU with pulmonary vasodilators (sildenafil, nitric oxide), prostacyclin, surfactants, bosentan, vasoactive drugs (dopamine, dobutamine, milrinone), ventilatory support (using high-frequency oscillatory ventilation in some cases), and ECMO, the behavior of the disease is still uniformly fatal, and the majority of the patients expire in the first month of life. 6,10,15,16,20-31,33-38 In 2014, Hoganson et al.4 used a pumpless paracorporeal lung assist device in a patient of 9 months old, with ACD, as a bridge to lung transplantation. Hoganson reports that the child was doing well 10 months after the transplantation, giving a new hope of a better prognosis for this disease management.

The diagnosis of ACD/MPV requires an experienced pathologist to identify the characteristic pulmonary histologic features. ¹⁰ Autopsies confirm 90% of the diagnosis and lung biopsies confirm only 10%. ^{1,39} However, potential diagnoses are missed because probable cases are not submitted to lung biopsies nor to post-mortem examinations. ¹⁰ Early lung biopsy should be indicated for neonates requiring ECMO support for refractory pulmonary hypertension. ^{21,40,41} Lung biopsies in patients with ECMO were demonstrated to be safe. ^{39,40} In patients with suspected ACD/MPV and extrapulmonary manifestations, testing for FOXF1 mutation could possibly avoid the need for a future biopsy, but more studies in this setting should be undertaken. ¹³

CONCLUSION

We presented a case of ACD/MPV without extrapulmonary manifestations. This patient died despite intensive care, and the diagnosis was made at autopsy. Increasing knowledge on the genetics, pathophysiology, early suspicion, and diagnosis may help to design better management required to alter the gloomy prognosis of this entity.

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