CASE REPORT

Alveolar-Capillary Dysplasia with Misalignment of the Pulmonary Veins

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Abstract

Alveolocapillary dysplasia with misalignment of pulmonary veins is a rare pathology of the lung development that causes persistent pulmonary hypertension in the newborn. The clinical case of a male newborn with respiratory distress and hypoxemia, without any perinatal or family background is presented. Empirical antibiotic therapy and non-invasive ventilation connection were initiated and afterwards, required intubation due to critical hypoxemia. Indirect data of pulmonary hypertension with no other associated pathology was observed. Nevertheless, he needed to be connected to veno-arterial extracorporeal membrane oxygenation for a week. Due to bad evolution with severe hypoxemic refractory crisis, adaptation of therapeutic effort was agreed between the family and the medical team and the extracorporeal membrane oxygenation was weaned. Necropsy was performed and confirmed the diagnosis of alveolo-capillary dysplasia with misalignment of pulmonary veins. Genetic test revealed heterozygosity for a new missense mutation of *FOXF1* (c. A266C: p.Y89S).

Keywords: Infant, Newborn; Persistent Fetal Circulation Syndrome/diagnosis; Pulmonary Alveoli/abnormalities; Pulmonary Alveoli/pathology; Pulmonary Veins/abnormalities

Introduction

Alveolar capillary dysplasia with the misalignment of the pulmonary veins is a rare disorder involving the vascular development of the lungs that causes the persistent pulmonary hypertension of the newborn, with hypoxemia and respiratory failure.[1] It is frequently associated with cardiovascular, digestive, and genitourinary malformations. Currently, definitive diagnosis is based on the histological examination of lung tissue.[2,3]

Genetic studies have identified associations with mutation or deletion in the locus of the transcription factor *FOXF1*.[4] The prognosis is fatal, with death in the first month of life in most of the cases. Bilateral lung transplant remains the only curative treatment.

Case Report

We report the case of a male newborn, with no maternal or familiar background of interest, but the father's information was not available. He was born at term, after a normal vaginal delivery, with the appropriate weight for gestational age, Apgar score 9/10. At 12 hours of life, he was admitted at the neonatal intensive care unit due to respiratory distress and hypoxemia.

After admission, empiric antibiotic therapy was initiated, blood cultures were obtained, and non-invasive respiratory support was started. Due to increasing dyspnea, the child was intubated and there was a need of support with high frequency oscillatory ventilation and inhaled nitric oxide. He also suffered a right pneumothorax that was drained.

The chest radiography showed unspecific features, such as bilateral fine granular infiltrates with solved pneumothorax (Fig. 1). Indirect data of pulmonary hypertension with no structural heart disease were demonstrated by echocardiography.

Due to poor evolution, with a maximum of 65%-70% oxygen saturation (no pre or postductal differences), venoarterial extracorporeal membrane oxygenation (ECMO) support was elected. Echocardiographic study showed right ventricular dilatation with suprasystemic pulmonary pressures. Systemic steroids (methylprednisolone), inotropic support and intravenous

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pulmonary vasodilators (sildenafil) were associated.

After three days on ECMO, a first attempt of weaning was performed but it failed due to suprasystemic pulmonary hypertension and collapse of the left ventricle on bedside echocardiography. Pulmonary biopsy was ruled out because of severe coagulopathy. After treatment optimization, the resolution of pulmonary hypertension and good cardiac output were achieved, allowing weaning from ECMO and decannulation at 5 days of life. Sixteen hours later, he presented a severe hypoxemic crisis with no response to usual measures, mixed refractory acidosis, and severe right ventricular failure.

At 8 days of life, the cessation of intensive medical treatment was elected, together with the patient's mother, because of the unfavorable predicted outcome. All microbiological tests were negative.

The *post-mortem* evaluation revealed low alveolarization, a decrease in the number of capillaries and thinning of the capillary walls with the malposition of the pulmonary veins (Figs. 2 and 3). These findings are correlated with the diagnosis of alveolar capillary dysplasia with the misalignment of the pulmonary veins. Intestinal malrotation was also observed.

About the genetic test, the patient was heterozygous for a new missense mutation of *FOXF1* (c. A266C: p.Y89S), but it could not be described as a *de novo* mutation because the father could not be studied.

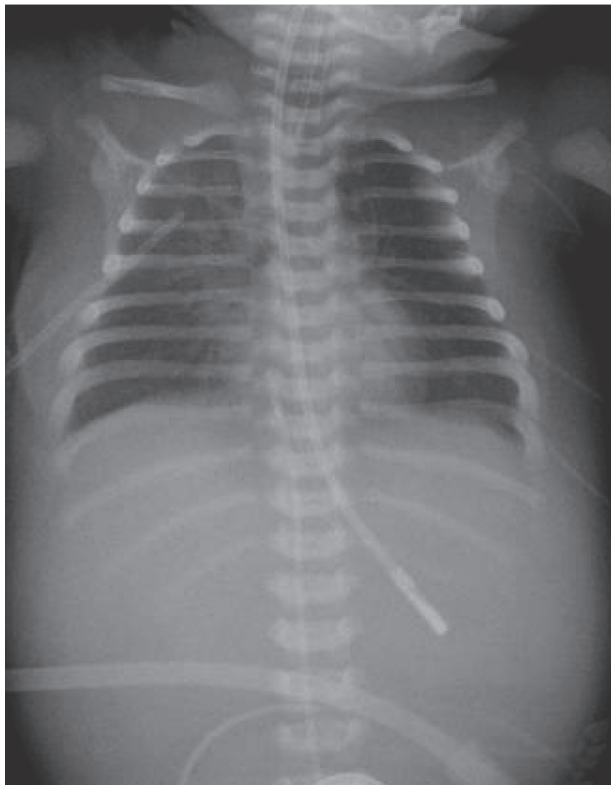

Figure 1. Chest radiograph (anteroposterior view) at 12 hours of life. Bilateral fine granular infiltrates with solved pneumothorax.

Discussion

Congenital pulmonary dysplasia with the misalignment of the pulmonary veins constitutes an uncommon group of primary lung diseases that affect capillary alveolus diffusion. Since alveolar capillary dysplasia with the misalignment of the pulmonary veins was first described in 1981, over 100 cases have been reported.[3] The incidence can be estimated at approximately 1/100,000. It remains of unknown etiology, although it is believed to be caused by genetic mutations or teratogenic exposure during the first months of pregnancy and can affect angiogenesis and pulmonary development.[5] They are categorized into acinar dysplasia, capillary alveolus dysplasia, and capillary alveolus dysplasia with pulmonary vein malposition,[6] according to histological findings, which depend on when alterations occur during fetal development.

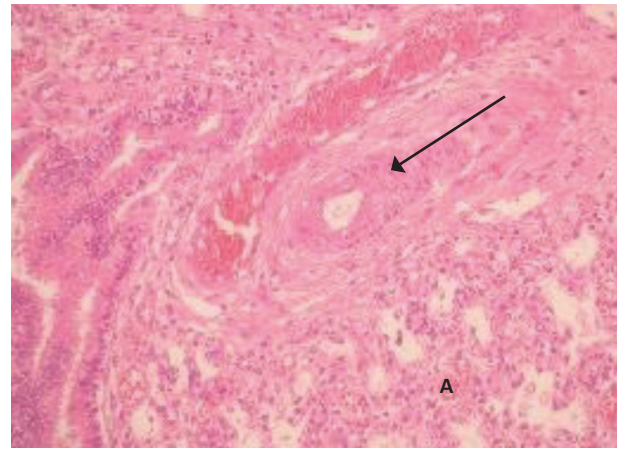

Figure 2. Postmortem pulmonary histopathology. Low alveolarization (A), with slight and diffuse thickening of the alveolar septa as well as thickening of the arterial wall secondary to hyperplasia of the middle arterial layer of the intra-acinar arteriole (thin arrow) (hematoxylin eosin, 20x).

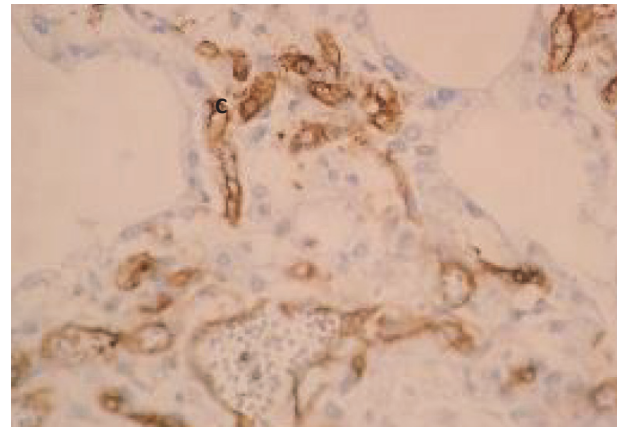

Figure 3. Postmortem pulmonary histopathology. Decrease in the number of capillaries located in the alveolar septa, which are also located far from alveolar epithelial lining (C) (immunohistochemistry for CD31, 40x).

Most patients develop symptoms of severe and persistent pulmonary hypertension within the first 48 hours of life. Persistent pulmonary hypertension presents as hypoxemia, tachypnea, respiratory distress, loud single second heart sound, or a harsh systolic murmur. In rare cases, a later onset of symptoms has been described, at 5 and 7 months of life.[7,8]

In most patients, the prognosis is fatal, with death during the first month of life. Nevertheless, a recent study revealed several patients with an atypical phenotype and relatively long survival.[8] The patient with the longest survival[1] is a 56 month old child who was still alive at the time of this publication. This suggests that there are milder forms of the disease with a better prognosis.[11,12]

Extrapulmonary malformations are present in 50%-80% of cases, mostly digestive (omphalocele, malrotation-volvulation), cardiovascular (patent *ductus arteriosus*, patent *foramen ovale*, pulmonary atresia), and genitourinary (Mullerian *ductus* malformation, hypoplasia of left ovary).[13] In our case, he had an intestinal malrotation, which was already described in other publications, although it was also associated with other disorders.[14,15]

The chest radiography is nonspecific and may show diffuse opacity or a frosted glass pattern. Echocardiography shows a normal heart structure with indirect evidence of pulmonary hypertension. Pulmonary angiography does not replace histological diagnosis.

A pulmonary biopsy is the gold standard test for *in vivo* diagnosis. Performing pulmonary biopsy during ECMO support carries risks but now can be considered a safe procedure with minimal risk of bleeding and infection.[16] According to some authors, the biopsy should be performed before cannulation or after seven days on ECMO. There is an exception with alveolar capillary dysplasia with the misalignment of the pulmonary veins or association of other lethal malformation. In these cases, the time recommended is within the first week.[17] However, as suggested by other authors, a normal lung biopsy does not exclude the diagnosis as there may be a patchy involvement of the lung, which could explain the clinical variability of affected patients.[18,19] In the study of the lung biopsy, the high diagnostic suspicion of the pathologist is important.

Pneumothorax and atelectasis are common complications of these patients.

The identification of the involvement of the *FOXF1* gene in alveolar capillary dysplasia modified the understanding of this entity.[20] According to recent research, variations in this gene can inhibit *STAT3*, a critical regulator of angiogenesis and cause capillary alveolus dysplasia in mice.[21]

Loss of the heterozygous function of the *FOXF1* gene is identified in 40%-70% of patients.[3] Typically, transmission is due to *de novo* mutations. In addition, other heterozygous genomic variants of the *FOXF1* locus of alveolar capillary dysplasia with the misalignment of the pulmonary veins have been described by other research groups.[12,22-24]

Nevertheless, it seems that the *FOXF1* gene is not the only gene involved in this entity. Recently published studies have suggested that other genes can cause (*ESRP1*) or modify (*PLXNB2*) the phenotype of alveolar capillary dysplasia with the misalignment of the pulmonary veins.[24]

The clinical approach of patients with alveolar capillary dysplasia with the misalignment of the pulmonary veins does not differ from the approach in other newborns with persistent pulmonary hypertension. Management includes supportive and pharmacological therapy with high frequency oscillatory ventilation, systemic glucocorticoids, oral, intravenous, and/or inhaled pulmonary vasodilators (nitric oxide, inhaled, or intravenous prostacyclin) and ECMO therapy.

The response to treatment is usually poor, which is common in pulmonary hypertension due to alveolocapillary dysplasia. That is why mortality has not decreased.

Lung transplantation is currently the only treatment that could prolong survival. In a series of patients with alveolar capillary dysplasia with the misalignment of the pulmonary veins and atypical presentation of lung transplant described a survival rate similar to a lung transplant in children with other disorders between one and five years old.[1] In our patient, this option was refused due to the severe involvement at debut.

The previously described 56-month-old patient, as a survivor with medical therapy, had been under the effects of metformin in the prenatal period due to maternal gestational diabetes. It is postulated whether this drug could modify the severity of the disease by favoring angiogenesis, suppressed by the gene mutation *FOXF1* through an increase in the adenosine monophosphate protein kinase pathway.[24]

Currently, therapeutic clinical trials are not being carried out in this entity.

WHAT THIS CASE REPORT ADDS

- Alveolar capillary dysplasia with the misalignment of the pulmonary veins is a rare and lethal disease that causes severe hypoxemia secondary to critical pulmonary hypertension, refractory to current therapies including ECMO.
- Although most patients could be diagnosed by lung biopsy and the pulmonary biopsy is the gold standard test for in vivo diagnosis, at the present time most confirmed diagnoses are still made by necropsy. We must have a high index of suspicion when a patient presents refractory persistent pulmonary hypertension, especially if it is associated with cardiovascular, genitourinary of digestive malformations.
- Given the poor prognosis of this entity, an early diagnosis is recommended to avoid futile treatments and provide adequate support to the patients and their families.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Displasia Alvéolo-Capilar com Desalinhamento das Veias Pulmonares

Resumo

A displasia alvéolo-capilar com desalinhamento das veias pulmonares é uma doença pulmonar do desenvolvimento rara que provoca hipertensão pulmonar persistente no recém-nascido. Apresentamos o caso clínico de um recém-nascido do sexo masculino com dificuldade respiratória e hipoxemia, sem antecedentes perinatais e familiares relevantes. Foi iniciada antibioterapia empírica e conexão para ventilação não invasiva, necessitando de intubação devido à hipoxemia crítica. Sinais indiretos de hipertensão pulmonar sem outra patologia associada foram observados. Dada a má evolução, foi necessária circulação com membrana extracorpórea veno-arterial, que foi mantida por uma semana. Por má evolução, com crises graves de hipoxemia refratária, a adequação do esforço terapêutico foi acordada entre a família e a oxigenação por membrana extracorpórea foi terminada. Foi realizada necropsia, confirmando-se o diagnóstico de displasia alvéolo-capilar com mau alinhamento das veias pulmonares. O estudo genético detetou uma mutação no gene *FOXF1* (c. A266C: p.Y89S) não descrita anteriormente.

Palavras-Chave: Alvéolos Pulmonares/anomalias; Alvéolos Pulmonares/patologia; Recém-Nascido; Síndrome da Persistência do Padrão de Circulação Fetal/diagnóstico; Veias Pulmonares/anomalias