Living with Alveolar capillary dysplasia with misalignment of the pulmonary veins – case report

Renata Cohen[1], Flavio Sztajnbok[1], Evanice Lima de Marca[2], Vera Luiza Capelozzi[3], Dafne Dain Gandelman Horovitz[4], Eloa Nunez[2], Henrique de Campos Reis Galvão[5], Joselito Sobreira[5], Diana Carolina Salazar Bermeo[5], and Tânia Folescu[4]

[1]Universidade do Estado do Rio de Janeiro
[2]Hospital Jutta Batista
[3]Universidade de Sao Paulo
[4]Instituto Fernandes Figueira
[5]Diagnosticos da America SA

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Authors

Renata Wrobel Folescu Cohen

Instituto Fernandes Figueira IFF/FIOCRUZ Rio de Janeiro, RJ, Brazil

Universidade do Estado do Rio de Janeiro (UERJ) Rio de Janeiro, RJ, Brazil

Flavio Sztajnbok

Universidade Federal do Rio de Janeiro (UFRJ) Rio de Janeiro, RJ, Brazil

Universidade do Estado do Rio de Janeiro (UERJ) Rio de Janeiro, RJ, Brazil

Evanice Lima de Marca

Hospital Pediátrico Jutta Batista, Rede Dor Rio de Janeiro, RJ, Brazil

Vera Luiza Capelozzi

Universidade do Estado de São Paulo, São Paulo, SP, Brazil

Dafne Dain Gandelman Horovitz

Instituto Fernandes Figueira IFF/FIOCRUZ, Rio de Janeiro, RJ, Brazil

Eloa Nunez

Hospital Pediátrico Jutta Batista, Rede Dor, Rio de Janeiro, RJ, Brazil

Henrique de Campos Reis Galvão

Diagnósticos da América S.A., DASA, São Paulo, SP, Brazil.

Joselito Sobreira

Diagnósticos da América S.A., DASA, São Paulo, SP, Brazil.

Diana Carolina Salazar Bermeo

Diagnósticos da América S.A., DASA, São Paulo, SP, Brazil.

Tania Wrobel Folescu

Instituto Fernandes Figueira IFF/FIOCRUZ, Rio de Janeiro, RJ, Brazil

To the editor,

Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is a rare and lethal disorder mainly involving the vascular development of the lungs. The clinical presentation is characterized by respiratory distress and cyanosis caused by severe pulmonary hypertension (PH) and insufficient oxygen uptake. 95% of ACD/MPV patients are born at full term with normal Apgar scores and develop symptoms within the first 24 hrs of life. In up to 80% of the cases, associated malformations are found, for which surgery is occasionally needed[1]. These malformations predominantly affect the gastrointestinal tract, but also may affect the cardiovascular and urogenital systems. The mortality of ACD/MPV is almost 100%[1]. Atypical, milder cases of ACD/MPV patients that present after 24 hrs of life or survive beyond the neonatal period have occasionally been described[2]. The current gold standard to unambiguously diagnose ACD/MPV is histological examination of the lungs. In most studies, cases were diagnosed postmortem by autopsy[3].

It is postulated that the milder phenotype of atypical ACD/MPV patients, including late presenters and long-term survivors, is correlated with the extent of affected lung tissue. A recent study showed a heterogeneous non-uniform distribution of histological findings in all atypical ACD/MPV patients[4].

Recently, Sen et al[5] have reported genomic deletions and point mutations in the FOXF1 gene (OMIM 601089) in chromosome 16q24.1 in unrelated patients with histopathological verified ACD/MPV. So far, 42 FOXF1 variants and 24 genomic and genic deletions identified in the 16q24.1 region have been reported. All patients have died in the first 4 months of life.

This case report describes a patient as a late presenter and long-term survivor of ACD/MPV with a non previously described de novo variant in FOXF1. Informed consent statement was obtained from parents. Written informed consent to participate in this study was provided by the participant legal guardian. This study was approved by the Instituto Fernandes Figueira Ethical Committee, under the ethical approval number 59963822.0.2001.5269 (chILD - RJ).

CASE REPORT:

Full-term female born to non-consanguineous parents. GII/PII mother was 38yo and pregnancy was uneventful; Apgar scores 9/10, phototherapy needed for 4 days due to jaundice. There was no respiratory distress, nor congenital abnormalities were detected. Pulse oximetry was 98% (upper end lower limbs), transfontanelle and doppler ultrasound were normal. Family history negative for congenital cardiac or lung disease.

At nine months she presented cough and wheezing and received salbutamol and prednisolone at home. At 14mo, there was a new respiratory distress, with no response to Salbutamol, Prednisolone and antibiotics, requiring her first ICU admission: Her weight was 8.4kg; pulse oximetry:96% with oxygen therapy support. She presented increased AP diameter, intercostal retraction, reduced air flow with crackling sounds in both lungs and hepatosplenomegaly.

On admission, laboratorial exams revealed: Hb:10.6g/dL; Hto:34%; RDW:18,4%; platelets:196000/mm^3; WBC:2100/mm^3; Reticulocytes:13,4%; Serum iron:17mcg/dL; Ferritin:24ng/ml; Transferrin:267mg/dL; HIV and mycoplasma serology were negative. Nasopharyngeal material was negative for SARASCOV2, RSV, Influenza A and B. Immunoglobulin and lymphocytes were normal for age.

Echocardiogram presented situs solicitus; levocardia; concordant atrioventricular and arterial ventricle connections; intact interatrial and interventricular septa; pulmonary trunks and branches were confluent and without obstruction; pulmonary venous drainage to the right atrium; dilation of the right cavities; signi-

ficant right ventricular (RV) systolic overload; mild RV systolic dysfunction, normal left ventricular function. Systolic pressure in the pulmonary artery (SPPA) was 70mmHg. Inferior vena cava with normal caliber.

Thorax high resolution computed tomography (HRCT) showed extensive diffuse ground-glass opacity in both lungs (FIG1-A,B). Bronchoscopy revealed: hyperemia and moderate mucosal edema with thick and yellowish secretion in the main bronchi. The secretion collected from bronchial lavage was negative for pyogenic germs, fungi, mycobacteria, and*Pneumocystis jirovecci.* She was discharged home using sildenafil, captopril, furosemide + hydrochlorothiazide, spironolactone and carvedilol.

She progressed with worsening respiratory pattern and hypoxemia, being readmitted at 16mo. New exams showed negative viral and SARSCOV-2 panel; negative blood cultures; echocardiogram: SPPA 88-100mmHg. Salbutamol, fluticasone, sildenafil, Captopril furosemide, hydrochlorothiazide, spironolactone and carvedilol were maintained. A new HRCT scan detected ground-glass opacities affecting both lungs (FIG1-C,D), with the appearance of septal thickening and diffuse thickening of the bronchial walls.

After this, she underwent a lung biopsy and the histopathological report (FIG2) showed muscular hypertrophy of the middle layer of medium and small pulmonary arteries; reduction of capillary loops in the microcirculation along the alveolar septa; ectasia and tortuosity of pulmonary veins and lymphatics; misalignment of pulmonary veins adjacent to the terminal bronchiole; discrete inflammatory infiltrate represented mainly by small lymphocytes; there were no signs of malignancy. Perls staining was positive for macrophages with hemosiderin. Electron microscopy showed abnormal lamellar bodies of varying shapes and sizes with dense inclusions inside. Heteromorphic mitochondria with cristae fusion. There was no evidence of glycogenosis or storage diseases. No ciliary abnormalities were detected.

She was discharged with regular monitoring by a pediatric cardiologist and pulmonologist, and receiving sildenafil, captopril and furosemide, spironolactone, carvedilol, hydrochlorothiazide, salbutamol and fluticasone.

In parallel, exome analysis was carried out. A heterozygous variant in the FOXF1 gene was identified (NM_-001451.3: c.359A>T; p.(His120Leu)), classified as probably pathogenic, considering that the variant is absent on populational databases, in silico algorithms predict damaging impact of the variant on protein function, parental testing for the variant was negative and this indivudual phenotype is highly specific for the disease.

Thus, the diagnosis of alveolar-capillary dysplasia with misalignment of pulmonary vessels was confirmed.

During the last two years, she has been receiving the same medication, and was admitted in hospital por 3 times due to respiratory exacerbation following viral infection. She needed during admission period, oxygen supplementation, non invasive ventilation, antibiotics and systemic corticosteroids. Cardiac catheterization at 3yo showed a high pulmonary artery pressure (100mmHg) and Bosentana was started after this exam.

CONCLUSION

Infants affected with ACD/MPV usually develop respiratory distress and severe pulmonary hypertension, have no sustained response to supportive treatments, and die early in life. Few patients with ACD/MPV have been reported beyond the neonatal period. One report describing two siblings shows that a patient with less severe symptoms has a patchy pattern of capillary deficiency and abnormal distal air space, which may be correlated with the late onset. All infants with pathogenic/probably pathogenic variants in the FOXF1 gene, responsible for ACD/MPV, have died in the first 4 months of life. Our case, however, shows a 3yo girl with ACD/MPV carrying a *de novo* variant in FOXF1, which configurates quite a long survival with ACD/MPV. This is a missense mutation, absent in population databases with predicted in silico impact in the protein function. Based in normal parental investigation and compatible pathologic study, we considered it as phenotype-causing. Further studies will be needed to clarify the phenotypic difference between the above patient and the previously reported cases. Although phenotypical differences are present, genetic testing could contribute to earlier detection and allows adequate consultation about the prognosis and the process of decision-making.

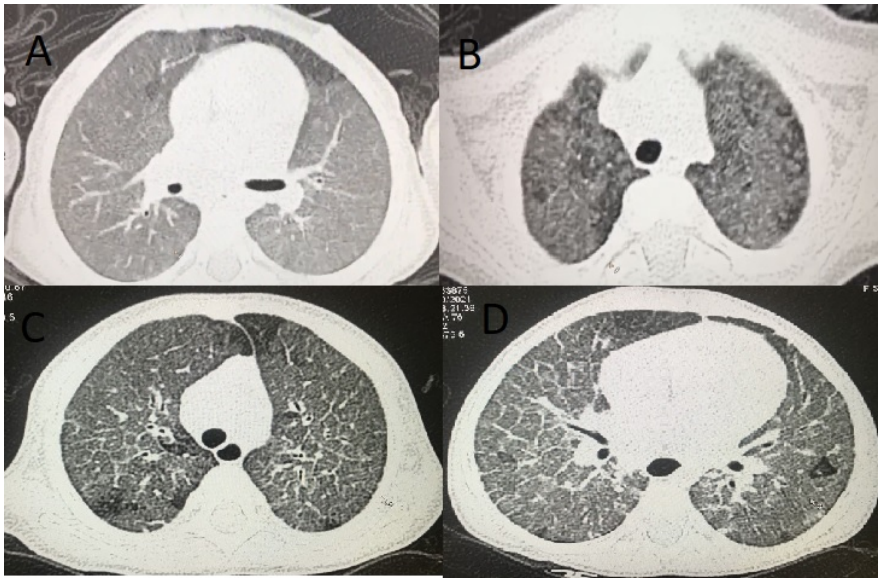

FIG 1 Thorax high resolution computed tomography (HRCT) images. A and B-First HRCT at 14mo showed extensive diffuse ground-glass opacity in both lungs. C and D- HRCT at 17mo detected ground-glass opacities affecting both lungs, with the appearance of septal thickening and diffuse thickening of the bronchial walls.

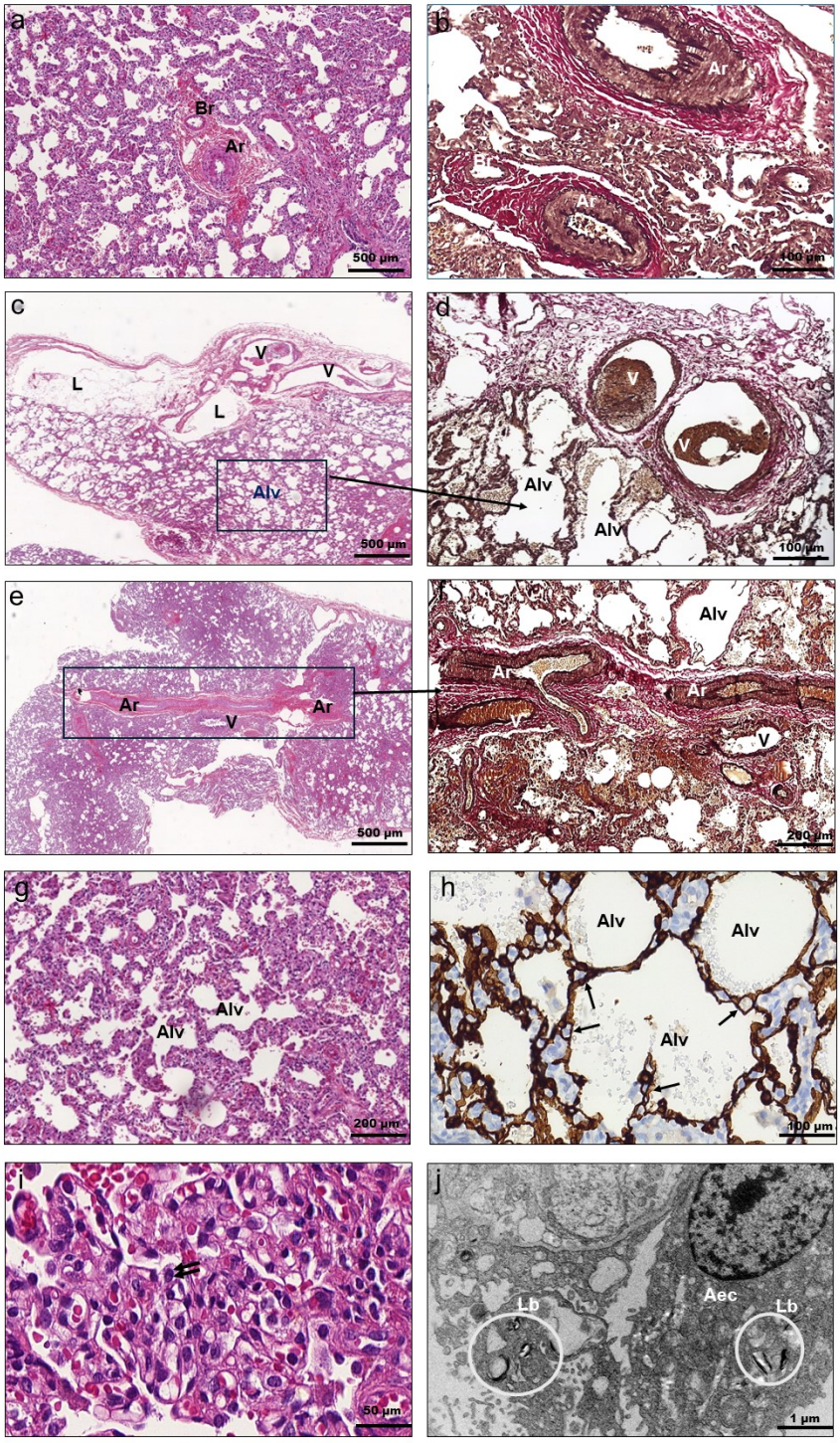

FIG 2 Lung histology of 9mo with ACD/MPV. (a) Representation of a hypertrophic arterial wall (Ar) in

hematoxylin and eosin and (b) Verhoeff stained. (c) Representation of the misaligned pulmonary veins (V) adjacent to the lymphatic vessel (L) and (d) alveolar dysplasia of the lung parenchyma (Alv) in Verhoeff stained. (e) Hematoxylin-eosin illustration of the misaligned pulmonary veins (V) and (g) alveolar dysplasia (Alv) adjacent to the thickened pulmonary arteriole (Ar) in (f) Verhoeff stained. (g, h) Hematoxylin-eosin and immunostaining for CD31 (brown color) highlighting a reduced number of alveolar capillary endothelial cells located away from the inner side of the alveoli (arrows) in ACD/MPV (i) Hematoxylin and eosin illustration of the alveolar dysplasia at high magnification.(j) Transmission electron microscopy showing abnormal lamellar bodies (Lb) in alveolar epithelial cells of alveolar dysplasia. The 1.5 cm straight line corresponds to magnifications of (a,e) 500; (f,g) 200; (b,d,h) 100; (i) 50 and (j) x 15.000.

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