Cardiology in the Young

cambridge.org/cty

Two cases of different genetic variants of alveolar capillary dysplasia associated with left-sided obstructive CHDs

Josue Diaz-Frias[1], Paul R. Mark[2,3] and E. Oliver Aregullin[1,3]

[1]Congenital Heart Center, Spectrum Health Helen DeVos Children's Hospital, Grand Rapids, MI, USA; [2]Division of Medical Genetics, Spectrum Health, Grand Rapids, MI, USA and [3]Pediatrics and Human Development, Michigan State University College of Human Medicine, Grand Rapids, MI, USA

Brief Report

Cite this article: Diaz-Frias J, Mark PR, and Aregullin EO (2021) Two cases of different genetic variants of alveolar capillary dysplasia associated with left-sided obstructive CHDs. *Cardiology in the Young* **31**: 1368–1370. doi: 10.1017/S1047951121000676

Received: 25 November 2020
Revised: 5 January 2021
Accepted: 2 February 2021
First published online: 5 March 2021

Keywords:
Alveolar capillary dysplasia; CHD; pulmonary hypertension

Author for correspondence:
E. Oliver Aregullin MD, Helen DeVos Children's Hospital, 100 Michigan NE, Grand Rapids, MI 49503, USA. Tel: +1 616 486 1495; Fax: (616) 267-1408.
E-mail: oliver.aregullin@helendevoschildrens.org

Abstract

Alveolar capillary dysplasia with misalignment of the pulmonary veins is an uncommon disorder that affects the lung vasculature development in the neonatal period and leads to pulmonary hypertension. We describe two patients with alveolar capillary dysplasia associated with left-sided obstructive heart defects with two different genetic variants. Our cases highlight the importance of early recognition of this disease in the setting of persistent and supra-systemic pulmonary hypertension despite surgical correction of the associated lesions. Identification of these cases will facilitate the development of a multidisciplinary approach and provide guidance to the affected families.

Alveolar capillary dysplasia with misalignment of the pulmonary veins is a rare autosomal dominant condition typically presenting within the first 24–48 hours of life with symptoms of respiratory failure.[1] The alveolar-capillary underdevelopment with disproportionate relationship and malposition between the pulmonary vasculature and dilated alveoli results in the development of persistent refractory pulmonary hypertension.[1] Most of the reported cases have been fatal within the neonatal period, with few atypical late presentations that survived beyond this period.[2] It is often associated with extrapulmonary anomalies that involve the cardiac, gastrointestinal, genitourinary, and/or musculoskeletal systems.[3] The association of cardiovascular anomalies has been found in approximately 10%–13% of the affected infants of which left-sided obstructive CHDs have been the most common presentation.[4,9] We report two cases with different genetic variants in the FOXF1 gene associated with left-sided CHDs that presented with persistent supra-systemic pulmonary hypertension despite surgical correction.

Case 1

A full-term female born without prenatal concerns developed signs of respiratory distress and persistent hypoxia in the immediate postnatal period. An echocardiogram was performed and revealed severe discrete aortic coarctation with mildly hypoplastic transverse arch, an apex-forming hypoplastic left ventricle, hypoplastic mitral valve, and bicuspid aortic valve. Due to worsening in clinical status, the patient underwent emergent aortic arch reconstruction on day 3 of life but was unable to be weaned off cardiopulmonary bypass due to evidence of supra-systemic pulmonary arterial pressures requiring transition to veno-arterial extracorporeal membrane oxygenation. Due to unusual clinical presentation, the decision was made to obtain a lung biopsy that showed dysplastic capillaries, dilated bronchial veins within the bronchoarterial bundles (formerly known as misaligned pulmonary veins), and lymphatic dilation. Additional atypical histopathologic features included eosinophilic disease (eosinophilic pneumonia and eosinophilic infiltrates), focal but extensive extramedullary haematopoiesis, and glycogen-rich immature alveolar lining cells. Whole-genome sequencing was ordered reporting a point mutation of c.179C > T (p. Ala60Val) variant in the FOXF1 gene located on chromosome 16q24.1; further analysis of the parental samples was negative indicating a de novo mutation of the patient. These findings confirmed the diagnosis of alveolar capillary dysplasia with misalignment of the pulmonary veins. Although she was decannulated from extracorporeal membrane oxygenation on day 18 of life, and despite aggressive pulmonary vasodilator therapy, she had an acute hypoxic episode three days later with severe respiratory acidosis leading to cardiopulmonary arrest and death despite aggressive resuscitation measures.

Case 2

A full-term male born with prenatal concern for coarctation of the aorta and borderline hypoplastic left ventricle showed no signs of respiratory distress in the immediate postnatal period.

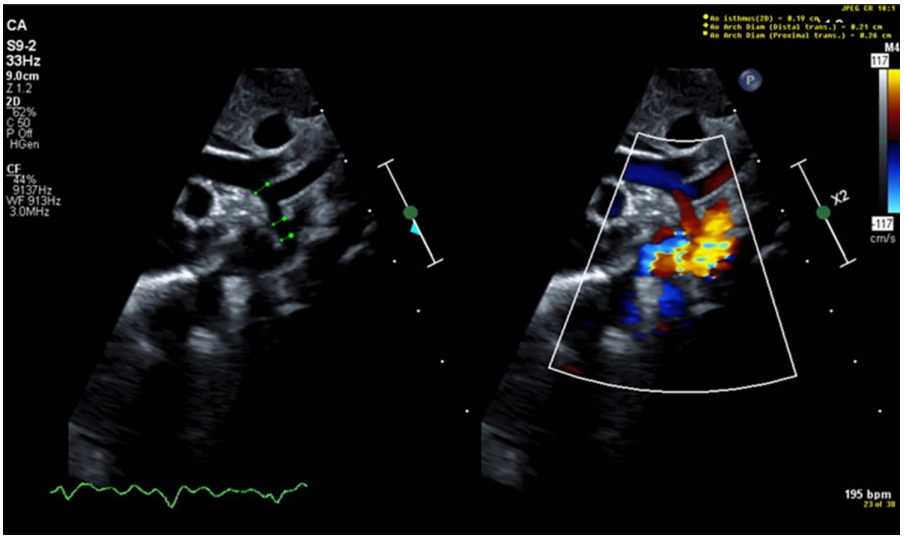

Figure 1. Two-dimensional transthoracic echocardiogram suprasternal notch view (2-D on the left; color flow Doppler on the right) done prior surgical intervention. Demonstrating moderate transverse arch hypoplasia, aortic coarctation with distal displacement of the left subclavian artery, a patent ductus arteriosus with flow acceleration and retrograde flow into aortic arch.

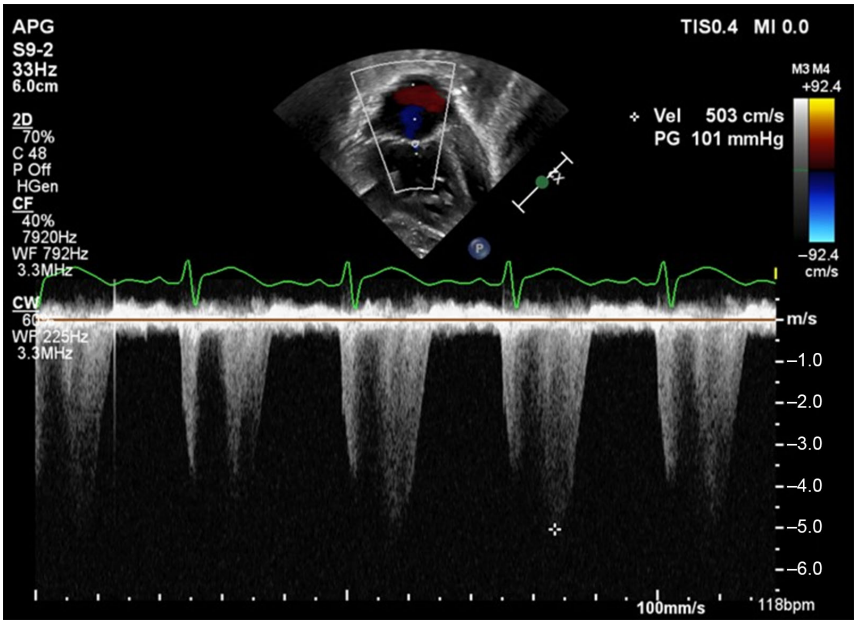

Figure 2. Two-dimensional transthoracic echocardiogram apical view (continuous wave spectral Doppler) on post-operative day 4 after aortic arch reconstruction. The tricuspid regurgitant jet predicted a systolic gradient from the right ventricle to the right atrium of 101 mm of Hg + mean right atrial pressure with a systemic blood pressure at the same time of 75/50 mm of Hg; findings suggestive of supra-systemic pulmonary artery pressures.

Echocardiogram confirmed coarctation of the aorta, mild to moderate transverse arch hypoplasia, small peri-membranous VSD, and a mildly hypoplastic aortic and mitral annulus with dysplastic valves (Fig 1). He remained stable and underwent diverting sigmoid colostomy on day three of life due to associated imperforate anus followed by aortic arch reconstruction on day seven. Post-operative course was complicated by severe persistent pulmonary hypertension with subsequent echocardiograms demonstrating right ventricular dilation with supra-systemic right ventricular pressures (Fig 2). Whole-genome sequencing revealed a deletion of approximately 25.187 Kb, located at 16q24.1 encompassing the FOXF1 gene; analysis of the parental samples showed that the mother was heterozygous for this deletion. He was started on combined vasodilator therapy with inhaled nitric oxide and epoprostenol; a right cardiac catheterisation was performed for haemodynamic assessment showing severe pre-capillary pulmonary arterial hypertension, about 150% systemic, main pulmonary artery 100/42/62 mmHg, systemic 67/31/44 mmHg, with normal capillary wedge pressures, mean 12 mmHg, PVR 8 WU/m2, and no evidence of coarctation of the aorta or pulmonary vein stenosis (Fig 3). Therefore, the decision was to proceed with a lung biopsy that reported dilated bronchial veins and lymphatic vessels, underdeveloped acini, and dysplastic capillaries, confirming the diagnosis of alveolar capillary dysplasia. The patient remained on medical cardiorespiratory support without any improvement and family elected for withdrawal of care on day 21 of life.

Discussion

The presentation of alveolar capillary dysplasia with misalignment of the pulmonary veins represents a diagnostic challenge, especially if associated with extrapulmonary malformations. Left heart obstruction may be the aetiology of persistent pulmonary hypertension, as well as abnormal lung development leading to acute

https://doi.org/10.1017/S1047951121000676 Published online by Cambridge University Press

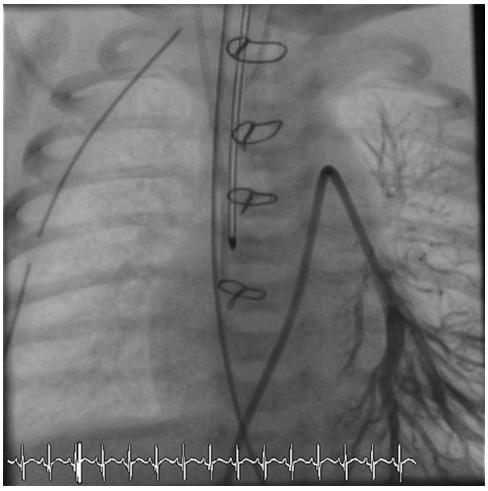

Figure 3. Right cardiac catheterisation performed for haemodynamic assessment coupled with planned lung biopsy. Antero-posterior angiogram of distal left lower pulmonary artery, demonstrating patent first and second order branches with distal pruning (loss of the smaller vessels).

episodes of respiratory failure with low cardiac output, making the diagnosis of alveolar capillary dysplasia even more difficult.[4] Some expert consensus has recommended to consider alveolar capillary dysplasia as a possible cause of persistent pulmonary hypertension and to proceed with biopsy when there is no resolution in the first two weeks after appropriate management has been established.[8] Our approach to do further investigation took place within the first days after surgical correction of the CHDs for both of our patients because of the persistent supra-systemic pulmonary hypertension resistant to vasodilator therapy and haemodynamics that are not typically found in individuals with this type of corrected heart lesions.[9] It is paramount for clinicians to have a high index of suspicion of alveolar capillary dysplasia in the setting of refractory or supra-systemic pulmonary hypertension despite adequate intervention of associated congenital defects.[5] An early recognition of this disease will provide guidance for therapeutic decisions and appropriate counseling for the affected families, identifying those that will have an increased risk of subsequent children that may inherit the condition.[6] Histopathological analysis remains the diagnostic gold standard, although there are atypical cases with differences in their histological features, as with case 1, in which the biopsy had atypical features that have not been previously reported in association with alveolar capillary dysplasia.[3,5] Hence, it is important to consider complementing with chromosomal microarray or whole-genome sequencing to identify individuals with FOXF1 gene mutations.[5] Szafranski et al reported in a large collection of samples 86 pathogenic variants in the FOXF1 locus that included 38 deletions, 1 complex rearrangement, and 47 point mutations.[7] As for our patients, they had different genetic variants: Case 1 had a point mutation in c.179 C > T (p. Ala60Val), and case 2 had a 25.187 Kb deletion encompassing the FOXF1 gene. Further data collection from multiple centres would be beneficial to create a large registry for future references.[5] To conclude it is important to develop a strategic approach for the affected individuals as a multidisciplinary team and consider FOXF1 gene mutation testing in the setting of persistent supra-systemic pulmonary hypertension after surgical repair. In patients with left heart obstructive lesions and post-operative, unrelenting, supra-systemic pulmonary hypertension, we suggest obtaining FOXF1 gene testing prior to any further surgical intervention to guide families and the provider team, avoiding futile interventions.

Acknowledgements. The authors would like to thank Bennett P. Samuel MHA/BSN/RN our clinical research nurse for all the advice and useful suggestions.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

Ethical standards. Not applicable.

References

1. Bishop NB, Stankiewicz P, Steinhorn RH Alveolar capillary dysplasia. Am J Respir Crit Care Med 2011; 184: 172–179.
2. Towe CT, White FV, Grady RM, et al. Infants with atypical presentations of alveolar capillary dysplasia with misalignment of the pulmonary veins who underwent bilateral lung transplantation. J Pediatr 2018; 194: 158–164.e1.
3. Alturkustani M, Li D, Byers JT, et al. Histopathologic features of alveolar capillary dysplasia with misalignment of pulmonary veins with atypical clinical presentation. Cardiovasc Pathol 2020; 50: 107289.
4. Stark VC, Schneider EP, Biermann D, et al. Alveolar capillary dysplasia with left heart obstruction – rare but lethal. J Neonatal Perinatal Med 2018; 11: 289–293.
5. Jourdan-Voyen L, Touraine R, Masutti JP, et al. Phenotypic and genetic spectrum of alveolar capillary dysplasia: a retrospective cohort study. Arch Dis Child Fetal Neonatal Ed 2020; 105: 387–392.
6. Bourque DK, Fonseca IC, Staines A, et al. Alveolar capillary dysplasia with misalignment of the pulmonary veins and hypoplastic left heart sequence caused by an in-frame deletion within FOXF1. Am J Med Genet A 2019; 179: 1325–1329.
7. Szafranski P, Gambin T, Dharmadhikari AV, et al. Pathogenetics of alveolar capillary dysplasia with misalignment of pulmonary veins. Hum Genet 2016; 135: 569–586.
8. Hilgendorff A, Apitz C, Bonnet D, et al. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network endorsed by ISHLT and DGPK. Heart 2016; 102: ii49–ii56.
9. Laux D, Malan V, Bajolle F et al. FOX gene cluster defects in alveolar capillary dysplasia associated with congenital heart disease. Cardiology in the Young 2013; 23: 697–704.

https://doi.org/10.1017/S1047951121000676 Published online by Cambridge University Press