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CASE REPORT

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Unusual presentation of alveolar capillary dysplasia with misalignment of the pulmonary veins in a child with respiratory syncytial virus pneumonia: A case report

Kantisa Sirianansopa[1] | **Pharsai Prasertsan**[1] | **Kanokpan Ruangnapa**[1] | **Kantara Saelim**[1] | **Phawin Kor-anantakul**[2]

[1]Division of Pulmonology and Critical Care Medicine, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[2]Excellence Center for Genomics and Precision Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, and Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Correspondence
Kantisa Sirianansopa, Division of Pulmonology and Critical Care Medicine, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla 90110 Thailand.
Email: kantisa.s@psu.ac.th

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Abstract

Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV) is a rare congenital diffuse lung disorder, with a fatal course during the neonatal period. We describe an 18-month-old boy who presented with respiratory syncytial virus pneumonia and pulmonary hypertensive crisis requiring extracorporeal membrane oxygenation. Exome sequencing revealed a *FOXF1* frameshift variant, NM_001451.2: c.995_998delACTC, inherited from his asymptomatic mother. Genetic findings were compatible with histopathology findings from a lung biopsy. Based on the disease course, histopathology, and outcomes of this case, we believe ACDMPV should be considered a possibility in an infant presenting with hypoxemic respiratory failure, resistant pulmonary hypertension, and vasodilator-induced pulmonary edema. Genetic testing can contribute to the diagnostic process.

KEYWORDS

alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV), extracorporeal membrane oxygenation (ECMO), *FOXF1* gene, respiratory syncytial virus pneumonia, unexplained pulmonary hypertension

INTRODUCTION

Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV, MIM #265380) is a rare congenital lung disorder with a fatal course in the early neonatal period. The classical presentation of ACDMPV is the development of refractory hypoxemia in neonates born at term, with severe pulmonary hypertension and no cardiac defects. ACDMPV diagnosis is made by pathological examination and genetic sequencing. Typical histopathological findings of ACDMPV include thickening of the muscular layer of pulmonary arterioles, malposition of the pulmonary vein adjacent to pulmonary arterioles, and maldevelopment of the pulmonary acinus with a reduction in volume and simplification in structure. *FOXF1*, located on chromosome 16q24.1, is the causative gene of ACDMPV.[1] Many types of disease-causing variants of FOXF1 have been described, including missense, nonsense, and copy-number variants. Extrapulmonary anomalies are generally identified in *FOXF1*-associated diseases, such as hypoplastic left heart syndrome, gastrointestinal malrotation and genitourinary system anomalies. We present a case of late and atypical presentation of ACDMPV which was confirmed by histopathological findings and genetic sequencing.

CASE REPORT

A previously healthy 18-month-old boy was admitted to the intensive care unit due to pneumonia and acute respiratory failure. He was born at term without asphyxia. He was the first child of non-consanguineous parents, with no significant family history. On examination, the patient was tachypneic, with crackles in both lungs and normal heart sounds on auscultation. Respiratory syncytial virus was identified as the respiratory pathogen from testing using a nasopharyngeal

swab. Chest radiography revealed a prominent pulmonary trunk, without cardiomegaly and diffuse ground glass opacities. Routine laboratory examinations were unremarkable, sputum and blood cultures were negative.

His condition rapidly deteriorated into pulmonary hypertensive crisis. The estimated systolic pulmonary arterial pressure (sPAP) was 55 mmHg, with bidirectional flow across PFO, mainly left to right shunt, and systolic D-shaped LV with LVEF 60% identified on echocardiography. After nitric oxide inhalation (iNO) therapy (20 parts per million), the patient developed severe pulmonary edema. Owing to persistent pulmonary hypertension and low cardiac output, veno-arterial extracorporeal membrane oxygenation (ECMO) was initiated as life-saving therapy. On ECMO day 5, the patient's hemodynamics gradually improved, with a return to normal pulmonary blood flow confirmed on chest radiograph and echocardiogram. Bilateral ground glass opacities persisted. The multidisciplinary team consensus on diagnosis was underlying interstitial lung disease with pre-existing pulmonary arterial hypertension or pulmonary veno-occlusive disease. Treatment consisted of methylprednisolone (2 mg/kg/day) combined with pulmonary vasodilators and diuretics. As the patient's condition improved, ECMO was discontinued. Successful weaning from ventilator support was achieved over the subsequent 2 weeks. Chest computed tomography (CT) and surgical lung biopsy were performed subsequently. Chest CT revealed an enlarged pulmonary artery, diffuse heterogeneous ground glass opacities, and interlobular septal thickening in both lungs, with areas of preserved normal parenchyma (Supplemental Figure 1). The lung tissue and exome sequencing are demonstrated in Figures 1 and 2, respectively. The clinicopathological and genetic findings support the ACDMPV diagnosis. There was no evidence of an extrapulmonary manifestation of the *FOXF1* variant in this patient.

Follow-up echocardiography (Supplemental Figure 2), performed at post-admission 2 months, revealed severe pulmonary arterial hypertension (estimated sPAP 64 mmHg, TAPSE 8 mm). The patient was referred for lung transplantation. While awaiting lung transplantation, he was receiving supplemental oxygen therapy at home, without readmission until age 40 months when he passed from COVID-19 related pneumonia.

DISCUSSION

Important findings leading to the ACDMPV diagnosis in our case were refractory severe pulmonary hypertension, vasodilator-induced pulmonary edema, and ILD-like pattern on chest imaging. The diagnosis was confirmed by histopathology and genetic sequencing. The proposed clinical algorithm for diagnosing ACDMPV is shown in Supplemental Figure 3. Few cases of unusual presentation of ACDMPV have been published, with the oldest age of symptom presentation being 7 months, the oldest age of transplant-free survival 38 months, and the longest duration of survival with a second transplantation 16 years.[2] Our case in which the disorder presented at 18 months and transplant-free survival was noted until age 40 months is, thus, important.

Although haploinsufficiency is accepted as the basis of *FOXF1*-associated diseases, the genotype–phenotype correlation remains unclear.[3] Cases of later presentation than that of classical cases, with asymptomatic parental inherited variants, have been reported.[4] Factor influencing the expressivity of *FOXF1* may be associated with incomplete penetrance in ACDMPV. Variants in the enhancer region proximal to *FOXF1* and epigenetic factors such as DNA methylation are proposed to be possible mechanism behind the variable expressivity of *FOXF1*-associated disease. Another explanation for the asymptomatic parents is the concept of mosaicism. A limitation of this study is that we did not perform additional tests to prove whether the proband's mother has the *FOXF1* frameshift variant in a heterozygous or mosaic form.

Standard ACDMPV treatment includes artificial ventilation, iNO, pulmonary vasodilator drug therapy, and ECMO. Although, the pulmonary arterial bed may be acutely

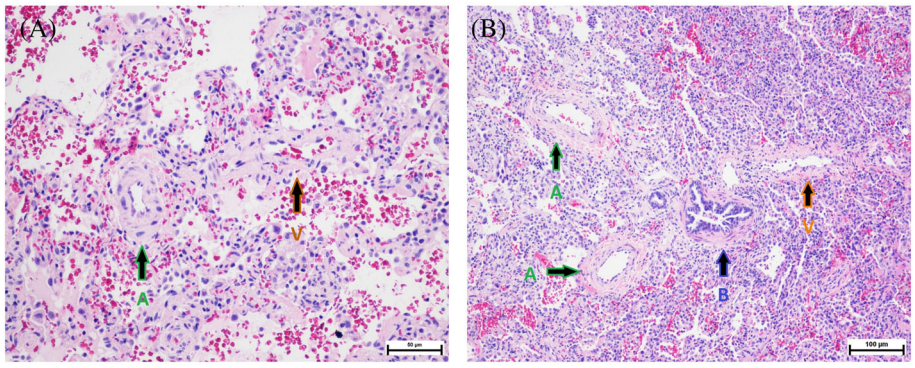

FIGURE 1 (A) High magnification of lung tissue obtained by surgical biopsy showing thickening of the pulmonary artery (**A**), with adjacent misalignment of the pulmonary vein (**V**). The remaining lung parenchyma shows a decrease in alveolar capillaries, particularly in the area of the thickened alveolar capillary wall. (B) The bronchovascular bundle includes marked thickening of pulmonary arteries (**A**), and misalignment of the pulmonary vein (**V**) and bronchiole (**B**), confirming the diagnosis of ACDMPV

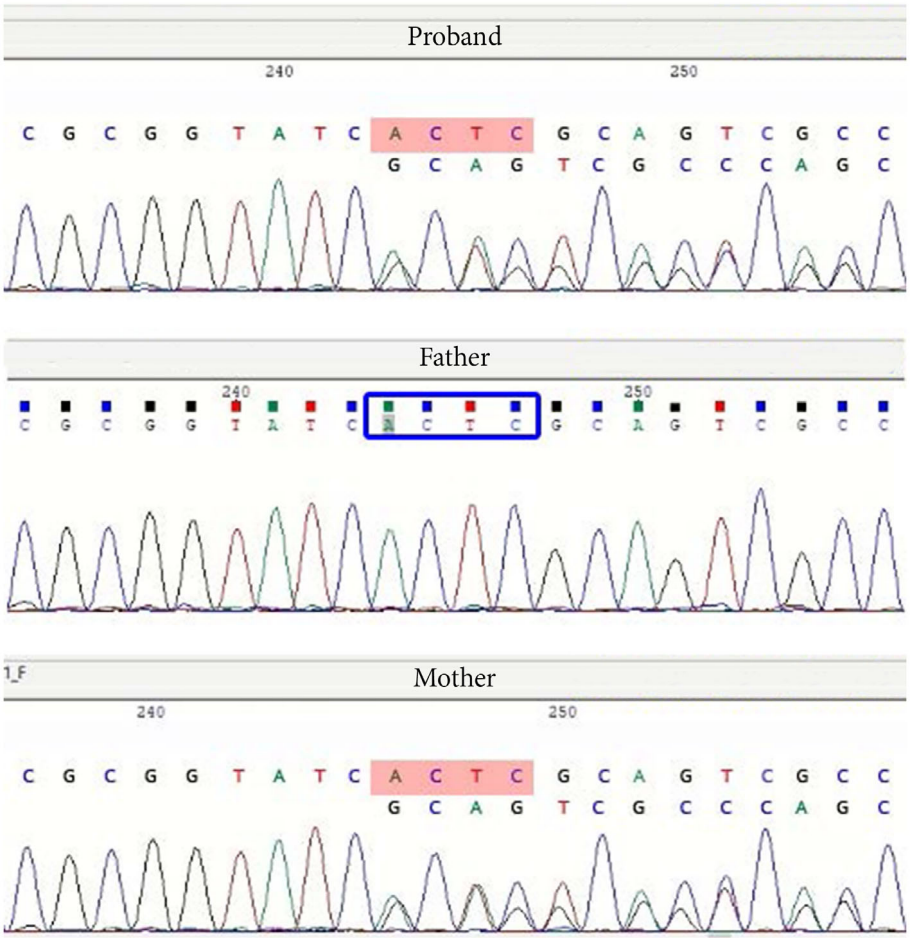

FIGURE 2 Electropherograms of the Sanger sequencing for the patient and both parents confirms heterozygous small deletion of *FOXF1* NM_001451.2; c.995_998delACTC, p.(His332ArgfsTer46) in the patient and mother

responsive to pulmonary vasodilators, capillary obstruction leads to severe pulmonary edema. However, patients with ACDMPV are often unresponsive to treatment. Lung transplantation has been performed for atypical ACDMPV, with expected outcomes comparable to those of other indications.[5]

Finally, for a child presenting with hypoxemic respiratory failure, resistant pulmonary hypertension, and vasodilator-induced pulmonary edema, the possibility of ACDMPV should be considered, with the use of histopathology and genetic testing to confirm the diagnosis. The severity of the presentation will depend on the type of *FOXF1* variant and the presence of extrapulmonary comorbidities. Extracorporeal support while awaiting lung transplantation for patients with mild-form ACDMPV can increase life expectancy.

AUTHOR CONTRIBUTIONS

Kantisa Sirianansopa, Pharsai Prasertsan, and Kanokpan Ruangnapa treated the patient during the period of critical illness and Kantara Saelim participated during the follow up period. Kantara Saelim and Phawin Kor-anantakul wrote the manuscript and Kantara Saelim completed the final editing of the manuscript

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

ORCID

Kantisa Sirianansopa https://orcid.org/0000-0003-0441-8570

Phawin Kor-anantakul https://orcid.org/0000-0001-9318-3974

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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