

# A late presenter and long-term survivor of alveolar capillary dysplasia with misalignment of the pulmonary veins

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**Abstract** This report demonstrates a late presenter and long-term survivor (38 months old) of alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) and with a heterozygous frameshift mutation in *FOXF1*. The mild phenotype may be due to his residual normal lung tissue as demonstrated in the chest computed tomography (CT) and histopathological findings.

**Conclusion:** We report the longest survivor of ACD/MPV. The mild phenotype is most likely due to the patient's residual normal lung tissue.

## What is Known:

- Patients with ACD/MPV uniformly die early in life.
- A previously reported case with the same mutation in *FOXF1* died at 15 days after birth.

## What is New:

- The presented case is the longest survivor with this disease.
- The patient's mild phenotype can be explained by his residual normal lung tissue.

**Keywords** ACD/MPV · *FOXF1* · Mild phenotype · CT · Biopsy

## Abbreviations

ACD/MPV	Alveolar capillary dysplasia with misalignment of the pulmonary veins
CT	Computed tomography
NO	Nitric oxide
PCR	Polymerase chain reaction

## Introduction

Patients with alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV; OMIM 265380) usually present with respiratory distress resulting from persistent pulmonary hypertension in the early postnatal period and uniformly die early in life [3]. Recently, Stankiewicz et al. have

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reported genomic deletions and point mutations in the *FOXF1* gene (OMIM 601089) in chromosome 16q24.1 in unrelated patients with histopathologically verified ACD/MPV [9]. So far, 42 *FOXF1* variants and 24 genomic and genic deletions identified in the 16q24.1 region have been reported [7, 9, 10]. All of the 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 known frameshift mutation in *FOXF1*.

## Case report

A 5-month-old boy presented with a 2-month history of cyanosis when crying and failure to thrive. He had been asymptomatic and fed well until poor weight gain was noted last month during a routine checkup. He was born at full term at a weight of 3.3 kg via caesarian section for prolonged labor. He was the first child of non-consanguineous parents without significant family history.

On presentation, the patient was crying, pale, tachypneic (60 breaths/min) with mild intercostal muscle retractions, hypoxic (70 % oxygen saturation on 2-L/min nasal cannula), and tachycardic (140 beats/min). His body temperature was 36.7 °C. Good bilateral air entry was noted on lung auscultation while regular S1 and accentuated S2 sounds without murmurs, rubs, or gallops were heard on cardiac auscultation.

Chest radiograph revealed bilateral haziness with a cardiothoracic ratio of 0.49. Chest computed tomography (CT) demonstrated bilaterally widespread ground-glass attenuation and normal density in the less affected areas (Fig. 1). Echocardiogram showed marked pulmonary hypertension estimated at more than 100 mmHg, a small atrial septal defect, ventricular septal defect in the muscular part, and mild tricuspid regurgitation.

The patient was initially treated with inhaled nitric oxide (NO) (20 ppm) and intravenous milrinone (0.3 µg/kg/min) for severe pulmonary hypertension. During the next 2 days,

because the number of cyanotic episodes increased with agitation along with more pallor, diaphoresis, and lethargy, he was placed on mechanical ventilation. Methylprednisolone pulse dose therapy and intravenous immunoglobulin with empiric antibiotics were started under the clinical suspicion of interstitial lung disease.

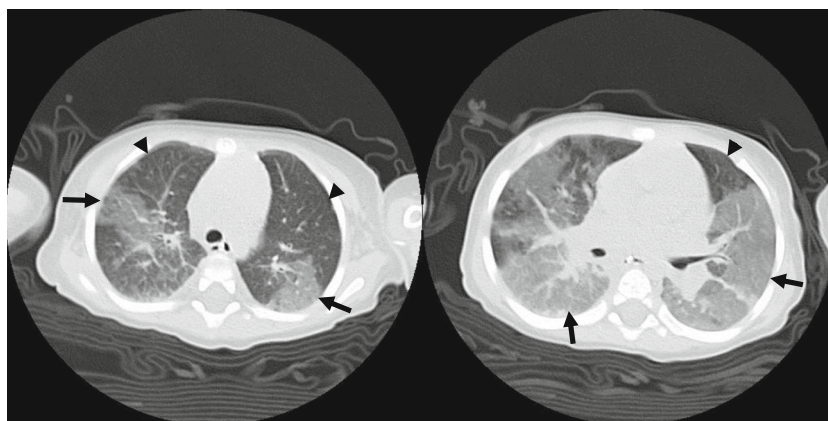
Because the repeated echocardiogram revealed worsening of the pulmonary hypertension on the third hospital day, epoprostenol up to 11 ng/kg/min along with oral pulmonary vasodilators including sildenafil, beraprost, and bosentan was given with symptomatic improvement. Three weeks later, he was extubated although epoprostenol was continued for 2 months.

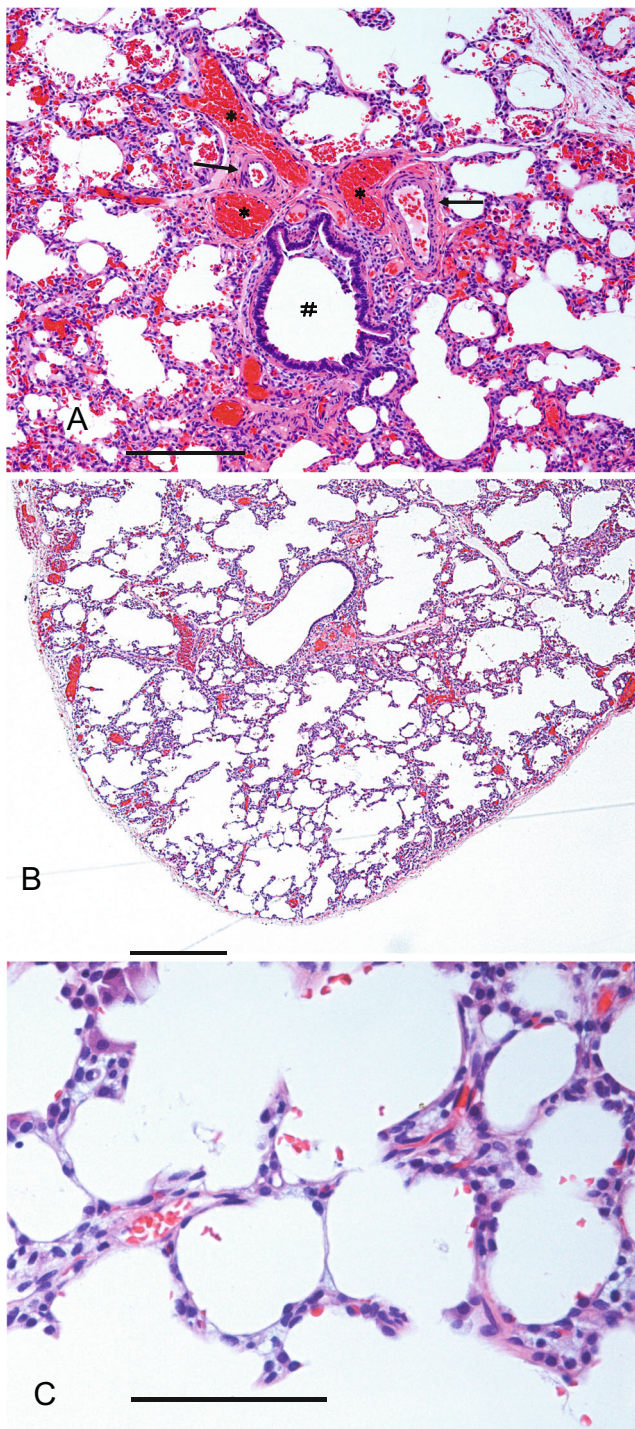
Three weeks after the mechanical ventilation, a surgical lung biopsy from the middle and lower lobes of the right lung was performed. The histopathological findings of the two different lobes of the right lung showed misalignment of the pulmonary veins next to the muscular pulmonary arteries adjacent to the airway in the same bronchiolovascular sheath (Fig. 2a). In the alveolar regions, the alveolar walls were thick with poor development of alveolar capillaries. Only several normal alveolar walls were noted in the diseased lung tissues (Fig. 2b, c). The histopathological diagnosis of ACD/MPV was made.

Genetic analysis using polymerase chain reaction (PCR) and direct DNA sequencing from the patient's peripheral blood revealed a known heterozygous frameshift mutation c.899Tdel, p.L300RfsX79, in the first exon of *FOXF1* [7]. Microarray-based comparative genomic hybridization analysis demonstrated no chromosomal deletions or duplications along the whole genome. The mutation arose de novo as it was not found in his parents.

Two months after admission, cardiac catheterization was performed with results showing a high pulmonary artery pressure (61/28 mmHg) (mean 43 mmHg) compared with femoral artery pressure (86/45 mmHg) (mean 62 mmHg), indicating improvement by the pulmonary vasodilating agents, such as the inhaled NO and epoprostenol. The patient was discharged from the hospital 2 weeks later.

**Fig. 1** CT scan of the chest shows bilateral ground-glass attenuated areas (arrows) and less affected regions (arrow heads)





**Fig. 2** Histopathological findings of the right lung. **a** A membranous bronchiole (*number sign*) is accompanied by muscular pulmonary arteries (*arrows*) and thin-walled small veins (*asterisks*). The three ductal structures are situated in the common bronchiolovascular sheath. **b** Low- and **c** high-magnification photomicrographs of a secondary lobule show normal and thickened alveolar walls. In normal alveolar walls, the thickness is 1–3  $\mu\text{m}$  with alveolar capillaries. In thickened alveolar walls, the thickness is 5–20  $\mu\text{m}$  with an increase of stromal cells and poor development of alveolar capillaries. Hematoxylin and eosin stain. Magnification: **a**  $\times 10$ , *bar*=0.2 mm; **b**  $\times 4$ , *bar*=0.5 mm; and **c**  $\times 40$ , *bar*=0.1 mm

At the time of writing this article, the patient (38 months old) was staying at home and was treated with oral pulmonary vasodilators and supplemental oxygen. Although his current respiratory condition has been stable, he was admitted to the hospital more than ten times for respiratory distress with congestive heart failure. Most of these events were triggered by upper and/or lower respiratory infections.

## Discussion

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 [3]. Thus far, six infants with ACD/MPV beyond the neonatal period have been reported, and the longest survivor has been an 8-month-old child [1–5, 7–9]. One report describing two sibling cases 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 [4]; however, this finding remains controversial because some reports describing histological appearance of lung tissues taken from early and late presenters have been strikingly similar [1–3, 5, 8]. All of the infants with mutations in the *FOXF1* gene, the one responsible for ACD/MPV, have died in the first 4 months of life [7, 9, 10]. The case reported above, however, shows a 38-month-old boy with ACD/MPV carrying a known frameshift mutation in *FOXF1*. It is interesting to note that a previously reported patient with the same mutation in *FOXF1* died just 15 days after birth [7]. To the best of the authors' knowledge, this case shows the longest survivor with ACD/MPV. Recently, the *FOXF1* gene has been reported to be imprinted in humans [10]; it is possible that the above patient may have had the mutation in the partially imprinted paternal allele. Further studies will be needed to clarify the phenotypic difference between the above patient and the previously reported case.

The patient in the above case has been asymptomatic from birth to 3 months of age. His chest CT shows bilaterally widespread ground-glass attenuation and normal density in the less affected areas (Fig. 1). To date, only two cases with ACD/MPV have been reported to be asymptomatic during the neonatal period although no lung CT or magnetic resonance imaging is performed [1, 8]. In the above case, the CT shows areas of normal density in the bilateral lungs; the lung biopsy specimens show capillary deficiency and abnormal, patchy development of air spaces. The mild phenotype can be explained by the unique lung CT and histopathological findings.

Respiratory distress and cyanosis are the most common clinical presentation of ACD/MPV [3]. Thus far, no patient has shown any response to the available pulmonary vasodilators although transient improvement has been observed in some cases. This case's patient, however, recovers from his



pulmonary hypertension crisis by a combination therapy of inhaled NO, epoprostenol, milrinone, and oral pulmonary vasodilators. Although his current respiratory condition remains stable, he may need to undergo lung transplantation when his cardiorespiratory symptoms deteriorate. In Japan, the waiting time for a cadaveric lung transplantation is about two and a half years. No child under 5 years old, however, has received a cadaveric lung transplantation, and only two children have received a living-donor lung transplantation by the end of 2013 [6]. If the patient's symptoms worsen, he will be treated with epoprostenol or ECMO while waiting for a living-donor lung transplantation.

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**Conflict of interest** The authors declare no conflict of interest.

**Authors' contribution** YI, TD, SK, and YK treated the patient (YI wrote the manuscript under SK's supervision, and YK took all responsibility of the therapy). MT and MK made the diagnosis using biopsy samples, and TA identified the FOXF1 mutation. KC and MY were consulted about the patient.

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