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Infants with Atypical Presentations of Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins (ACDMPV) who underwent Bilateral Lung Transplantation

Christopher T. Towe, M.D.[1], **Frances V. White, M.D.**[2], **R. Mark Grady, M.D.**[3], **Stuart C. Sweet, M.D., Ph.D.**[3], **Pirooz Eghtesady, M.D., Ph.D.**[4], **Daniel J. Wegner, M.S.**[3], **Partha Sen, Ph.D.**[5], **Przemyslaw Szafranski, Ph.D.**[5], **Pawel Stankiewicz, Ph.D.**[5], **Aaron Hamvas, M.D.**[6], **F. Sessions Cole, M.D.**[3], and **Jennifer A. Wambach, M.D., M.S.**[3]

[1]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[2]Department of Pathology and Immunology, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri

[3]Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri

[4]Department of Surgery, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri

[5]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

[6]Department of Pediatrics, Northwestern University Feinberg School of Medicine Chicago, Illinois

Abstract

Objective—To describe disease course, histopathology, and outcomes for infants with atypical presentations of alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV) who underwent bilateral lung transplantation.

Study design—We reviewed clinical history, diagnostic studies, explant histology, genetic results, and post-transplant course for 6 infants with atypical ACDMPV who underwent bilateral lung transplantation at St. Louis Children's Hospital. We compared their histology with infants with classic ACDMPV and compared their outcomes with infants transplanted for other indications.

Results—In contrast to neonates with classic ACDPMV who present with severe hypoxemia and refractory pulmonary hypertension within hours of birth, none of the infants with atypical ACDMPV presented with progressive neonatal respiratory failure. Three infants had mild neonatal respiratory distress and received nasal cannula oxygen. Three other infants had no respiratory

Corresponding Author: Jennifer Wambach, MD, MS, Campus Box 8116, 660 S. Euclid Ave, St. Louis, MO 63110, Phone: (314)454-2683, Fax: (314)454-4633, wambach_j@kids.wustl.edu.

symptoms at birth and presented with hypoxemia and pulmonary hypertension at 2–3 months of age. Bilateral lung transplantation was performed at 4–20 months. Unlike in classic ACDMPV, histopathologic findings were not uniformly distributed and were not diffuse. Three subjects had apparent non-mosaic genetic defects involving *FOXF1*. Two infants had extra-pulmonary anomalies (posterior urethral valves, inguinal hernia). Three transplanted children are alive at 5–16 years, similar to outcomes for infants transplanted for other indications. Lung explants from infants with atypical ACDMPV demonstrated diagnostic but nonuniform histopathologic findings.

Conclusions—One and 5-year survival rates for infants with atypical ACDM are similar to infants transplanted for other indications. Given the clinical and histopathologic spectra, ACDMPV should be considered in infants with hypoxemia and pulmonary hypertension, even beyond the newborn period.

Keywords

Diffuse developmental lung disorder

Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV, OMIM 265380) is a rare developmental lung disorder with nearly uniform mortality in the first month of life.[1, 2] Neonates with classic ACDMPV are typically born at term and present with progressive, hypoxemic respiratory failure and severe, refractory pulmonary hypertension within the first few hours after birth. Extra-pulmonary anomalies are common and typically involve the gastrointestinal, cardiac, and/or genitourinary systems.[3] Although there are a few case reports of infants with atypical presentations of ACDMPV beyond the newborn period or with less fulminant neonatal disease,[4–9] (Table I; available at www.jpeds.com) the clinical, histopathologic, and genetic factors that contribute to delayed or less severe presentations are not well characterized.

The diagnosis of ACDMPV is made by histologic examination of lung tissue.[10] Due to the high neonatal mortality rate, many infants are diagnosed at autopsy although a steady increase in diagnosis by lung biopsy has recently been observed.[3] The histopathologic features diagnostic of ACDMPV include deficient capillarization of the alveoli (decreased numbers of capillaries with displacement from alveolar epithelium), malposition of pulmonary veins adjacent to small pulmonary arteries within the same bronchovascular bundle (BVB), and medial hypertrophy of small pulmonary arteries and arterioles. Lobular maldevelopment with deficient alveolarization and lymphangiectasis are also commonly observed.[1, 11–13] Although it has been speculated that infants with delayed or less fulminant (atypical) presentations may have non-uniform distribution of disease that does not involve the entire lung, less abnormal density and placement of capillaries, or more normal lobular development,[5, 14, 15] limited information regarding the lung histopathology of these infants is available and often from only a single biopsy site.

Although outcomes after bilateral lung transplant in infants with end-stage lung disease due to genetic disorders of surfactant metabolism, interstitial lung disease (ILD), and pulmonary vascular disease have been reported,[16] the long-term outcomes of patients transplanted after atypical presentation of ACDMPV presentation have not been reported. Here we report

clinical data and histologic characterization from the largest series of infants with atypical presentations of ACDMPV who underwent lung transplantation.

Methods

Through a search of the St. Louis Children's Hospital/Washington University School of Medicine Pediatric Lung Transplantation database, we identified 6 infants with atypical presentations of ACDMPV admitted over an 18 year period (1998–2016) who underwent bilateral lung transplantation. We obtained informed consent from parents of all infants and children and this study was approved by the Human Research Protection Office at Washington University. We reviewed clinical history, results from echocardiogram, cardiac catheterization, and chest computed tomography (CT), explant histology, and post-transplant course. We used Sanger sequencing to identify mutations in *FOXF1* as previously described.[17] We analyzed genomic copy number variants using array comparative genomic hybridization (CGH) with custom-designed 16q24.1 region-specific 3_720 K microarrays (Roche NimbleGen, Madison, WI).[17]

A pediatric pathologist with expertise in childhood interstitial lung disease and the diagnostic features of ACDMPV reviewed all explants. At least 2 sections from each lobe of the explant were reviewed for each subject (median number of sections per explant was 22 (range 12–27)). Explant histology was compared with autopsy histology from 3 infants with classic ACDMPV and genetic defects of *FOXF1* (2 with missense point mutations and 1 with a copy number variant (CNV) deletion upstream of *FOXF1*). ACDMPV histologic criteria were characterized for each explant.[15, 18] Microscopic observations of alveolar capillaries were made on fields of congested, non-collapsed lung, in which architecture and capillaries were well visualized. Findings of deficient capillarization of alveoli were described as "diffuse" (present throughout all fields, with difficulty in identifying normal capillarization in most fields), "mixed" (mixture of both normal and deficient capillarization throughout lung), and "focal" (predominantly normal, with focal areas of deficient capillarization). Findings of pulmonary vein malposition adjacent to small arteries were described as "extensive" (readily identified throughout the lung, with malposition in the majority of BVBs), "patchy" (identified throughout the lung, but in fewer than half of BVBs), and "focal" (present, but in minority of BVBs and not readily identified). Assessment of malposition of pulmonary veins did not include BVBs with tangential orientation in which a vein could not be excluded. Findings of medial hypertrophy of small arteries and arterioles were graded "mild," "moderate," or "severe," ranging from mild medial thickening to occlusive lesions. Lobular maldevelopment with deficient alveolarization was noted based on the presence of enlarged alveoli with apparent decrease in numbers of alveoli and was described as "present," "suggestive," (areas suggestive of deficient alveolarization), or "not suggestive." Lymphangiectasis was characterized as primarily involving the interlobular septae or involving both the interlobular septae and the BVBs.

Infant #1 (Table 2)

A term male infant developed tachypnea at birth, was treated with oxygen, and then discharged home on room air. He was also noted to have an inguinal hernia at birth. During the first few months of life, he experienced several episodes of pulmonary congestion attributed to upper respiratory tract infections before presenting on day of life (DOL) 109 with respiratory distress and severe pulmonary hypertension that required mechanical ventilation, vasopressor support, pulmonary vasodilators, and veno-arterial extra-corporeal membrane oxygenation (ECMO) for 8 days. He remained mechanically ventilated until bilateral lung transplant on DOL 139. He did well post-transplant for several years before developing bronchiolitis obliterans that led to a second transplant at 5 years of age. Two months after his second transplant, he developed progressive renal failure and died.

Infant #2

A term male infant developed neonatal respiratory distress and was treated with supplemental oxygen and continuous positive airway pressure on DOL 2. An echocardiogram demonstrated pulmonary hypertension. He was also noted to have non-obstructive posterior urethral valves. Due to persistent oxygen requirement at 1 month of age, he underwent open lung biopsy which was diagnostic for ACDMPV. At 2 months of age, a cardiac catheterization demonstrated suprasystemic right heart pressures that were mildly responsive to inhaled nitric oxide. He was discharged home on nasal cannula oxygen (0.5 liters per minute (LPM)) and nitric oxide (0.5 LPM, estimated 5 parts per million). His oxygen and nitric oxide requirements gradually increased, and his pulmonary hypertension worsened prompting bilateral lung transplantation at 21 months. He did well until 4 years when he required a second transplant for chronic lung allograft dysfunction due to rejection. He is alive at 16 years of age with bronchiolitis obliterans. Most recent (15 years) spirometry revealed forced expiratory volume in 1 second (FEV1) of 31% predicted, forced vital capacity (FVC) of 40% predicted, and FEV1/FVC of 68% indicating airflow obstruction (no response in FEV1 to bronchodilator therapy). Total lung capacity (TLC) was 2.29L (60% predicted) and residual volume (RV) was 0.99 (111% predicted) with RV/TLC of 43% indicating air trapping. Diffusing capacity of the lungs for carbon monoxide (DLCO) was 67% predicted.

Infant #3

A female infant born at 36 weeks' gestation had no neonatal respiratory symptoms or congenital anomalies, but had a male sibling who died after lung transplantation for ACDMPV. She presented on DOL 71 with respiratory distress, cyanosis, and pulmonary hypertension by echocardiogram and was treated with mechanical ventilation, vasopressor support, and pulmonary vasodilators. She required mechanical ventilation until transplant on DOL 159 and is alive with normal lung function at 14 years of age. Most recent (age 14 years) spirometry was essentially normal (FEV1 90% predicted, FVC 86% predicted, and FEV1/FVC 90%). TLC was 4.66L (110% predicted) and RV was 1.71L (154% predicted) with RV/TLC ratio of 37%, suggestive of mild air trapping. DLCO was normal.

Infant #4

A late preterm female infant born at 34 weeks' gestation developed abdominal distension and intestinal dysmotility on DOL 3 which resolved during a 17 day NICU hospitalization. She did not have respiratory symptoms and remained on room air throughout her NICU course. Echocardiogram on DOL 20 showed no evidence of pulmonary hypertension. On DOL 67, she presented with severe respiratory distress, shock, and cardiopulmonary arrest and was resuscitated with intubation, mechanical ventilation, oxygen, and nitric oxide. A cardiac catheterization demonstrated suprasystemic right heart pressures that were mildly responsive to inhaled nitric oxide. An open lung biopsy was diagnostic for ACDMPV. She remained mechanically ventilated and underwent bilateral lung transplantation on DOL 159. She developed bronchiolitis obliterans and died at 9 years of age.

Infant #5 (previously reported)[19]

A late preterm female infant born at 34 weeks' gestation was healthy at birth without respiratory symptoms. On DOL 24 she was briefly hospitalized for apnea that was attributed to gastroesophageal reflux which did not recur. On DOL 92, she was hospitalized for dehydration secondary to diarrhea and was found to be hypoxemic. Echocardiogram demonstrated pulmonary hypertension. She was treated with supplemental oxygen via nasal cannula and sildenafil until DOL 273 when an open lung biopsy was diagnostic for ACDMPV. Following the biopsy, she required veno-arterial ECMO before transitioning to support from a paracorporeal lung assist device.[19] She underwent bilateral lung transplant on DOL 286 and is alive at 6 years of age. Most recent (6 years) spirometry was normal (FEV1 96% predicted, FVC 105% predicted, and FEV1/FVC 83%). TLC was 1.90L (94% predicted), RV was 0.51L (69% predicted) and RV/TLC was 27%. DLCO was normal.

Infant #6[17]

This term female infant had transient tachypnea of the newborn with possible pneumonia.[17] An echocardiogram revealed a patent ductus arteriosus without evidence of pulmonary hypertension. She was discharged from the NICU on supplemental oxygen on DOL 17 which was continued until DOL 21. Over the next 5 months, she had poor weight gain and persistent retractions. She presented with respiratory distress and hypoxemia on DOL 212 during travel at high altitude. Cardiac catheterization demonstrated near systemic right heart pressures that were responsive to inhaled nitric oxide. Open lung biopsy was diagnostic of ACDMPV. She was gradually weaned off supplemental oxygen and nitric oxide and was discharged on DOL 249 on sildenafil and furosemide. On DOL 423, she developed an upper respiratory tract infection with coronavirus and progressive hypoxemic respiratory failure and required veno-venous ECMO. She improved, was extubated, and received non-invasive positive pressure ventilation until bilateral lung transplant on DOL 464. During the 3 months after transplant, she had recurrent episodes of respiratory failure of unclear etiology and died at 18 months of age.

FOXF1 Sequencing and Assessment of Copy Number Variants

We obtained DNA from peripheral blood from 5 subjects (Subjects #2–6). DNA was not available for Subject 1. Two subjects had apparent non-mosaic missense variants in *FOXF1*

(c.146C>A: p.P49Q (subject 2) and c.377C>T: p.P126L (Subject 4))[3] (Table 3). Both variants are novel and not present in the Exome Aggregation Consortium (ExAC) database (exac.broadinstitute.org)[20] and are predicted to be deleterious by *in silico* algorithms including SIFT, Polyphen, LRT, Mutation Taster, GERP++, and PhyloP in ANNOVAR (annovar.openbioinformatics.org)[21] and CADD (cadd.gs.washington.edu/).[22] Subject 6 had an apparent non-mosaic a 1.5Mb CNV deletion mapping 306kb upstream to *FOXF1* that removed 26kb of the proximal portion of the *FOXF1* enhancer region.[17] Parental DNA sequencing for subjects 2 and 6 revealed that both the c.146C>A point mutation and the 1.5Mb CNV deletion arose *de novo*. No point mutations or CNV deletions involving *FOXF1* were identified in subject 3 who had a sibling with ACDMPV, nor in Subject 5.

Explant Histology

All 6 lung explants demonstrated the histologic features diagnostic of ACDMPV (Table 3, Figure). The main findings of deficient capillarization and malpositioned pulmonary veins were focal or patchy as compared with infants with classic ACDMPV (Table 4). All explants demonstrated moderate to marked medial wall thickening of the small pulmonary arteries and arterioles consistent with the clinical histories of pulmonary hypertension. Lymphangiectasis was present in all explant specimens, including subjects #2 and #6 who were not mechanically ventilated at the time of transplant. Although lobular maldevelopment with deficient alveolarization was diffuse and readily observed in all infants with classic ACDMPV, the explanted lung of infants with atypical ACDMPV were more heterogeneous. Two of the explants (subjects #3 and #4) had focal areas with definite deficient alveolarization as well as other areas suggestive of maldevelopment. The other 4 atypical ACDMPV explants had focal areas suggestive of deficient alveolarization. Findings consistent with secondary remodeling were also present in the explanted lungs. There were no obvious differences in explant histopathology among infants with or without *FOXF1* point mutations or CNV deletions.

Discussion

Delayed presentations of ACDMPV after the neonatal period [4–9] or with prolonged survival[8, 9, 23, 24] suggest biologically and developmentally diverse mechanisms contribute to disease presentation. In contrast to the classic neonatal presentation of ACDMPV, only 3 subjects (#1, 2, 6) had respiratory symptoms in the newborn period. Two infants (#1, #6) were treated with nasal cannula oxygen which was discontinued by 3 weeks of life, and then presented with fulminant symptoms at 3 months and 7 months, respectively. The third infant (subject #2) had a persistent oxygen requirement and echocardiographic evidence of pulmonary hypertension which prompted diagnostic lung biopsy at 1 month of age. Although this infant had the earliest presentation, biopsy, and diagnosis, he underwent lung transplant at the oldest age (633 days) and required the least respiratory support at the time of transplant (supplemental nasal cannula oxygen and nitric oxide). His explant histology demonstrated focal findings which may have contributed to his comparatively indolent course. The remaining 3 subjects had no significant respiratory symptoms within the first 2–3 months of life, including the infant with a family history of ACDMPV (Subject #3). Because of the wide variability and timing of presentations, atypical ACDMPV should

remain in the differential diagnosis of any infant with hypoxemia and idiopathic pulmonary hypertension.

The histopathologic characteristics of capillary dysplasia and misaligned pulmonary veins ranged from focal to patchy in the explanted lungs but did not correlate with the age of fulminant presentation or the presence of *FOXF1* point mutations or CNV deletion. Although our study is limited in that explant histology may be confounded by differences in pre-transplant treatment (mechanical ventilation, prolonged oxygen exposure) and chronologic age, the non-uniformity of histopathologic characteristics suggests that disruption of lung development in this disease is location-specific and may be influenced by the local cellular and growth factor milieu. It is important to note that all 6 explants had areas of lung with normal capillary loops, a finding which illustrates the challenge of making a diagnosis of ACDMPV on a single specimen lung biopsy for patients with atypical presentations. As point mutations or CNV deletions that involve *FOXF1* are present in approximately 80–90% of infants with classic ACDMPV [10] and 3 of 5 infants tested in our series, diagnostic sequencing of *FOXF1* may preclude the need for lung biopsy.[25] Failure to identify *FOXF1* point mutations or CNV deletions in 2 of the 5 subjects tested suggests that other genes may contribute to or modify the ACDMPV phenotype.[10]

All 6 infants in our series had clinical and histologic evidence for significant pulmonary hypertension. Medial wall hypertrophy, while present, was less pronounced among the 3 infants with classic ACDMPV (Table 4). It is unclear whether this difference reflects a primary process related to endothelial cell proliferation or is secondary to therapies or chronic/prolonged disruption of the pulmonary vascular bed. For 5 atypical ACDMPV infants, the severity of their pulmonary hypertension contributed to the eventual need for intensive medical and mechanical respiratory support prior to transplant. Presumably, their pulmonary hypertension resulted from anatomically fixed, decreased number of pulmonary capillaries within the alveolar epithelium, misaligned pulmonary veins, and abnormal lobular development. Although neonates with classic ACDMPV typically have transient but non-sustained responses to pulmonary vasodilators,[1] 3 atypical ACDMPV infants (#2, 4, 6) demonstrated reduction in pulmonary resistance with inhaled nitric oxide administration during cardiac catheterization and successful treatment of all 6 infants with pulmonary vasodilators suggests pharmacologically reversible components of pulmonary hypertension. However, our study was not specifically designed to determine the effects of these therapies thereby limiting this finding. The utility of these medications among infants with atypical ACDMPV compared with classic ACDMPV may in part reflect the heterogeneous nature of their disease or the diversity of the underlying biologic or developmental mechanisms.

Five infants in our series had chest CT scans which demonstrated findings of ILD with ground glass opacities and septal thickening. In contrast to infants with atypical ACDMPV, infants with idiopathic primary pulmonary hypertension typically are not hypoxemic without a significant intracardiac shunt and usually do not have abnormalities of the pulmonary parenchyma on chest CT.[26] Infants with biallelic loss of function mutations in surfactant proteins (*SFTPB, ABCA3*) typically present with severe neonatal respiratory distress syndrome and have chest radiograph findings consistent with surfactant deficiency.[27] Infants with dominant point mutations in *SFTPC* or missense variants in *ABCA3* can present

beyond the newborn period with childhood interstitial lung disease (chILD) and pulmonary hypertension, which when present, is associated with increased mortality.[28] The presentation of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) with hypoxemia, pulmonary hypertension, and abnormal CT scan results (patchy centrilobular pattern of ground glass opacities, pavement appearance to lobules) can make differentiation from ACDMPV potentially difficult. Due to the wide variability and timing of presentations, atypical ACDMPV should remain in the differential diagnosis of any infant with hypoxemia and idiopathic pulmonary hypertension including those with chest CT findings of ILD; clinical testing of *FOFX1* in these patients may be diagnostic.

Although lung transplant is a recognized therapy for children with end-stage lung disease,[29] successful transplant for ACDMPV is limited to two case reports.[17, 19] In a large international registry, median survival of all children after lung transplant is 5.3 years, with infants' having a slightly better median survival of 6.4 years.[30] The mortality and outcomes of the patients transplanted for ACDMPV in our series are comparable with infants and children transplanted for genetic disorders of surfactant metabolism at our institution.[31] Prospective studies such as those being performed through the childhood interstitial lung disease research network (chILDRN) are needed to identify genetic, therapeutic, or environmental factors that contribute to delayed presentation or prolonged survival without transplant.[32]

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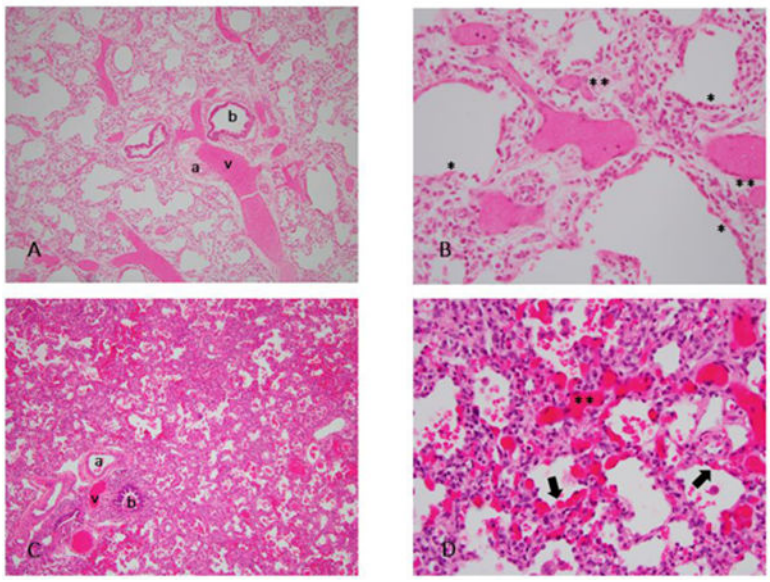

Figure 1. A–D: Histology from infants with classic and atypical presentations of ACDMPV

Hematoxylin and eosin stained sections of lung with low (10×) and high (40×) power views of classic ACDMPV (A,B) and atypical ACDMPV (C,D). Congested areas were selected for better visualization of the capillaries. A: Malposition of veins adjacent to small arteries within bronchovascular bundles (BVBs) and lobular maldevelopment with decreased alveolarization. B: Almost complete absence of capillary loops adjacent to alveolar epithelium (*), with fewer and displaced capillaries in septae (**). C: Malposition of veins adjacent to small arteries in BVBs. Compared to histology of classic ACDMPV, decreased alveolarization is not readily apparent. D: Areas of both normal capillarization with capillaries adjacent to alveolar epithelium (arrow), and deficient capillarization with displaced capillaries in septae (**). v=vein, a=artery, b=bronchus

Table 1

Published Reports of Infants with Delayed Presentation of ACD/MPV

Age at presen-tation	EGA wks	Sex	Family history	Neonatal Symptoms	Additional Anomalies	Pulmonary Hypertension Medications	Histology	FOXF1 Sequencing	Outcome	Ref.
5 weeks	Term	Female	Male sibling with ACD/MPV	Cyanosis at respiratory distress, episodes of tachypnea and lethargy, discharged home at 10 days	None	Norepinephrine, intrapulmonary prostaglandin E_1,	Capillaries of alveolar septa did not reach alveolar epithelium, muscularization of peripheral arterial branches, misalignment of the pulmonary veins, dilated lymphatics	NR	Death at 5 weeks	([1])
4 weeks	NR	NR	NR	None	None	iNO, prostatcylin	Alveolar capillary dysplasia	NR	Death during hospital course	([2])
7 weeks	Term	Female	NR	None	Aganglionosis of colon	Dopamine, milrinone, iNO	Malalignment of pulmonary veins, paucity of alveolar capillaries, prominent muscularization of arterioles, thickening of alveolar septa, widened interstitium	NR	Death at 4 months	([3])
7 months	Term	Female	NR	Cyanotic episode after birth, received 0.1L/min oxygen for 13 days, mild pulmonary hypertension on echocardiogram	Small ventricular septal defect	Dopamine, milrinone, iNO	Small pulmonary lobules, few normally positioned capillaries, muscularized small arterioles, misalignment of the pulmonary veins, patchy lymphatic dilation	NR	Death at 7–8 months	([4])
3 months	Term	Male	Negative	None	Muscular ventricular septal defect, small atrial septal defect	Milrinone, iNO, pulse methylprednisolone, IVIG, sildenafil, prostacyclin, bosentan, supplemental oxygen	MPV, thick alveolar walls with pool alveolar capillary development, several normal alveolar walls	c.899Tdel p.L300Rfs*79 *de novo*	Alive at 38 months per manuscript, alive at 62 months*	([5])

EGA= estimated gestational age, iNO= inhaled nitric oxide, NR= not reported

*Personal communication: Dr. Satoru Kumaki 1/2017

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Table 2

Clinical Characteristics of Infants with Atypical Presentation of ACDMPV

Patient	EGA (wks)	Neonatal Symptoms	Age at Presentation	Cardiac Anomalies	Additional Anomalies	CT imaging	Cardiac Catheterization	Pulmonary Hypertension Medications	ECMO	Support at Time of Lung Transplant	Age at Transplant (months)	Outcome
1	Term	Transient tachypnea at birth, discharged home on room air	3 months (109 days)	None	Inguinal hernia	Not available	Not performed	Prostacyclin, inhaled NO (iNO)	Prior to transplant	Mechanical Ventilation	4	Second transplant at 4 years; died at 5 years
2	Term	Respiratory distress, pulmonary hypertension	Birth	Patent foramen ovale	Posterior urethral valves	Ground glass opacities, enlarged pulmonary vessels	Suprasystemic right ventricular (RV) pressure, responsive to iNO	Nifedipine, iNO	No	NO and O_2 via nasal cannula	20	Second transplanted at 4 years; alive at 16 years
3	36	None	2 months (71 days)	Patent foramen ovale	None	Diffuse interstitial lung disease, associated cystic areas	Not performed	Milrinone, methylprednisolone, iNO	No	Mechanical Ventilation	5	Alive at 14 years
4	34	Poor feeding, abdominal distension at 3 days	2 months (67 days)	Secundum atrial septal defect	None	Ground glass opacities, interstitial septal thickening	Suprasystemic RV pressure, responsive to iNO	Sildenafil, milrinone, iNO	No	Mechanical Ventilation	5	Died at 9 years
5	34	Apnea at 3 weeks	3 months (92 days)	Patent foramen ovale	None	Ground glass opacities	Not performed	Sildenafil Prednisolone, iNO	At transplant	ECMO	9	Alive at 5 years
6	Term	Transient tachypnea, discharged home on O2 for 21 days	7 months (212 days)	Patent ductus arteriosus	None	Ground glass opacities with septal thickening	Near systemic RV pressure, responsive to iNO	Sildenafil, methylprednisolone, iNO	Prior to transplant	Positive pressure ventilation via RAM cannula	15	Died at 18 months

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Table 3

Histology of Lung Explants for Infants with Atypical Presentations of ACDMPV

Histologic assessment focused on areas of congested, non-collapsed lung, in which architecture and capillaries were well visualized.

Infant	1	2	3	4	5	6
Deficient capillarization of alveoli	Mixed	Focal	Focal	Focal	Mixed	Mixed
Malposition of pulmonary veins	Patchy	Focal	Focal	Focal	Patchy	Patchy
Medial hypertrophy of small arteries and arterioles	Moderate to marked	Moderate	Moderate to marked	Moderate to marked	Moderate to marked	Moderate to marked
Lobular maldevelopment	Suggestive	Suggestive	Present	Present	Suggestive	Suggestive
Lymphangiectas is	Interlobular and bronchovascular bundles	Interlobular and bronchovascular bundles	Interlobular	Interlobular	Interlobular	Interlobular and bronchovascular bundles
***FOXF1* Sequencing**	DNA not available	P49Q ([1])	No point mutations or deletions identified	P126L ([1])	No point mutations or deletions identified	1.5Mb deletion upstream of *FOXF1* ([2])

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Table 4
Histology from Autopsies of Infants with Classic Presentation of ACDMPV

Histologic assessment focused on areas of congested, non-collapsed lung, in which architecture and capillaries were well visualized.

Infant	1	2	3
Age at Presentation	Birth	Birth	1 day
Age at Death	15 days	9 days	8 days
Deficient capillarization of alveoli	Extensive	Extensive	Extensive
Malposition of pulmonary veins	Extensive	Extensive	Extensive
Medial hypertrophy of small arteries and arterioles	Mild	Mild	Mild
Lobular maldevelopment	Definite	Definite	Definite
Lymphangiectasis	Diffuse, interlobular	Diffuse, interlobular	Diffuse, interlobular