Infants with Atypical Presentations of Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins Who Underwent Bilateral Lung Transplantation

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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 sequence 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 with 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 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 of age. Unlike in classic ACDMPV, histopathologic findings were not distributed uniformly and were not diffuse. Three subjects had apparent nonmosaic genetic defects involving *FOXF1*. Two infants had extrapulmonary anomalies (posterior urethral valves, inguinal hernia). Three transplanted children are alive at 5-16 years of age, similar to outcomes for infants transplanted for other indications. Lung explants from infants with atypical ACDMPV demonstrated diagnostic but nonuniform histopathologic findings.

Conclusions The 1- and 5-year survival rates for infants with atypical ACDMPV 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. *(J Pediatr 2017;■■:■■-■■).*

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. Extrapulmonary 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] Owing 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

ACDMPV	Alveolar capillary dysplasia with misalignment of the pulmonary veins
BVB	Bronchovascular bundle
CNV	Copy number variant
CT	Computed tomography
DOL	Day of life
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ILD	Interstitial lung disease
RV	Residual volume
TLC	Total lung capacity

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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 nonuniform 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 the outcomes after bilateral lung transplant in infants with end-stage lung disease owing 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. Herein 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 described previously.[17] We analyzed genomic copy number variants (CNVs) using array comparative genomic hybridization with custom-designed 16q24.1 region-specific 3_720 K microarrays (Roche NimbleGen, Madison, Wisconsin).[17]

A pediatric pathologist with expertise in childhood ILD 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, 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 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, noncollapsed 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 one-half of BVBs), and "focal" (present, but in a 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

A term male infant developed tachypnea at birth, was treated with oxygen, and then discharged home on room air (**Table II**). 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 venoarterial extracorporeal membrane oxygenation 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 nonobstructive posterior urethral valves. Owing 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 L/minute) and nitric oxide (0.5 L/minute; 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 of age. He did well until 4 years of age, when he required a second transplant for chronic lung allograft dysfunction owing to rejection. He is alive at 16 years of age with bronchiolitis obliterans. Most recent (15 years) spirometry revealed forced

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