Alveolar Capillary Dysplasia
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Case Presentation
- A 2.8 kg female infant was delivered at 40 weeks gestation after an uncomplicated pregnancy. Apgar scores were 8/9.
- An imperforate anus was noted in the delivery room.
- She initially did well, but noted to have a ‘blue spell’ at 26 hours of life.
- SpO₂ 80’s in room air, CXR was normal.
- Echocardiogram showed normal cardiac anatomy.

Case Presentation
- Oxygenation improved only transiently with initiation of CMV, HFOV, inotropic support, forced alkalosis, iNO
- On day two of life, VA ECMO was initiated without difficulty, infant decannulated on day 7 of life
- The infant did well for the first 48 hours following ECMO, but she gradually worsened with severe pulmonary hypertension.
- She was recannulated for ECMO, continued to require aggressive support to maintain oxygenation, and died of sepsis on day 24 of life.

Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins
- Rare, lethal developmental disorder of alveoli & pulmonary vessels
- Presents most often in term or near term neonates within the first 48 hours of life; increasing recognition of “late presenters”
- Incidence unknown; estimated ~1:100K-1/500K
- Early course clinically mimics idiopathic PPHN:
  - Labile oxygenation (cyanosis)
  - Pulmonary hypertension
  - Respiratory distress
CD/MPV vs. PPHN

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>ACD/MPV</th>
<th>Term or near-term</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>Unknown</td>
<td>~1/100K (~0.2%)</td>
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<tr>
<td>Risk Factors</td>
<td>Unknown</td>
<td>Sepsis, MAS, CDH, asphyxia, DA closure</td>
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<tr>
<td>Clinical Presentation</td>
<td>Cyanosis, Resp Distress Pulmonary HTN</td>
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<tr>
<td>Diagnosis</td>
<td>Clinical, biopsy/autopsy, +/-cardiac cath</td>
<td>Clinical (Pre/Post Ductal PaO2, AaDO2, OI)</td>
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<td>Treatment (effective)</td>
<td>--------</td>
<td>HFOV, NO, PGI2, +/-ECMO</td>
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<tr>
<td>Survival</td>
<td>1 (with transplant)</td>
<td>&gt;80% (variable)</td>
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Associated Anomalies

- Present in 50% - 80% of infants
- Gastrointestinal (40%)
  - Malrotation, atresias, intestinal aganglionosis
- Genitourinary (30%)
  - Hydronephrosis, UPJ obstruction, bladder hypertrophy
- Cardiovascular (15%)
  - Mostly left-sided lesions
  - HLHS & aortic coarctation most common, ASD & AV Canal also reported
  - +/- Altered left-right asymmetry of thoracic organs

ChILD Classification

**Diffuse Lung Disease in Young Children**
Application of a Novel Classification Scheme

Gail H. Deutsch, Lisa R. Young, Robin R. Deterding, Leland L. Fan, Sharon D. Dell, Judy A. Bean, Alan S. Brody, Lawrence M. Nogee, Bruce C. Trapnell, Claire Langston and the Pathology Cooperative Group, Eric A. Albright, Frederic B. Askin, Peter Baker, Pauline M. Chou, Carlyne M. Cool, Susan C. Coventry, Ernest Cutz, Mary M. Davis, Megan K. Dishop, Csaba Galambos, Kathleen Patterson, William D. Travis, Susan E. Wert, Frances V. White, and on behalf of the ChILD Research Co-operative

ChILD Classification: <2 Years

n=165

- Diffuse developmental: 28%
- Growth abnormality: 11%
- NEHI: 14%
- PIG: 17%
- Surfactant dysfunction: 11%
- Normal host: 4%
- Immunocompromised: 5%
- Systemic: 3%
- Vascular: 11%
Diffuse Developmental ILD

- Rare, poorly understood primary disorders of lung development marked by growth arrest at various stages
- Histologically demonstrate profound arrest in lobular development and reduced alveolar capillary density
- Outcomes poor for all Diffuse Developmental ILDs

Diffuse Developmental ILD

- Acinar Dysplasia: term, F, least common
  - Respiratory failure at birth
  - Survive hours even with support
  - Rarely familial
- Congenital Alveolar Dysplasia: term, M=F
  - Respiratory failure at birth
  - Survive weeks to months with supportive measures
  - Rarely familial
- ACD/MPV: term, M=F, most common
  - Respiratory distress, cyanosis, PPHN
  - Survival: hours-months, rarely >1 year (with transplant)
  - >50% with associated GI, GU, Cardiac anomalies
  - ~ 10% familial

Theories on Pathogenesis

- Lung development: carefully orchestrated signaling between angiogenic growth factors in airspace epithelium (e.g., VEGF & angiopoietin families) & targets in pulmonary vascular endothelium (eNOS & others)
- Microvascular growth is a prerequisite for alveolarization
- Conditions or events that disrupt normal signaling pathways result in alterations in pulmonary vascular & alveolar development

Genetic Transmission

Defective Lung Vascular Development in Endothelial Nitric Oxide Synthase-Deficient Mice
Robin N.N. Hun and Duncan J. Stewart

Lung Bud → Primitive Respiratory Tubules → Primitive Acinar Structures
Pathophysiology

- Pulmonary hypertension, hypoxemia, Right → Left Shunt
- Hypoxemia:
  - Diffusion defect at alveolar-capillary interface
  - Intrapulmonary R→L shunt due to paucity of capillaries & ‘misalignment’ of pulmonary veins
  - Extrapulmonary R→L shunt via PFO/PDA
- Pulmonary Hypertension:
  - Fixed component due to arteriolar hypertrophy & muscularization
  - Reduced capillary surface area
  - Reactive vasoconstriction

Diagnosis

- Clinical diagnosis
  - Requires familiarity with phenotype, high level of suspicion
- Histology (Current gold standard)
  - Confirmation on autopsy (>90%)
  - Pre mortem lung biopsy preferred
  - Yield depends on adequacy of specimen and proficiency of pathologist
- Cardiac catheterization: absent capillary blush phase
- Genetics
  - Most cases are sporadic
  - ~10% familial, with >1 affected sibling

Clinical Diagnosis

- Neonate (Classic Presentation):
  - Early course often indistinguishable from idiopathic PPHN
  - Respiratory distress or cyanosis with no risk factors
  - CXR: clear or diffuse ground glass appearance
  - Early pneumothoraces common
  - ECHO findings of severe PPHN
  - Associated anomalies of kidneys, gut, heart
- Late Presentation
  - Initially asymptomatic
  - Unknown trigger leads to deterioration
  - Symptoms mimic fulminant, neonatal disease

Chest Radiograph
Histologic Findings

- Immature/abnormal lobular development
- Paucity of capillaries in the alveolar walls
- Thickened alveolar septae
- Medial hypertrophy of small pulmonary arteries & increased muscularization of arterioles
- Malposition of pulmonary vein branches adjacent to pulmonary arteries
- Lymphangiectasis (~30%) of cases
- Distribution of histologic defects tends to be diffuse regardless of time of presentation
Genetic Transmission

- Inheritance pattern AR (familial), AD (de novo), germ line mosaicism
- Candidate Genes:

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<th>Gene</th>
<th>Description</th>
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<tr>
<td>BMPR2</td>
<td>Mutated in familial primary pulmonary hypertension</td>
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<tr>
<td>EMAPII</td>
<td>Inhibitor of vessel growth &amp; differentiation prominent in lung in pseudoglandular stage</td>
</tr>
<tr>
<td>STRA6</td>
<td>Stimulated by retinoic acid 6 (STRA6)</td>
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Sequence analysis negative for all above candidate genes


Genomic and Genic Deletions of the FOX Gene Cluster on 16q24.1 and Inactivating Mutations of FOXF1 Cause Alveolar Capillary Dysplasia and Other Malformations


Genetic Transmission

Forkhead Box F1 (FoxF1) family of genes: transcription factors expressed in endothelial and smooth muscle cells in fetal and adult lung

Microdeletions in 16q24.1

- About 40% of ACD/MPV is due to microdeletions or inactivating point mutations in FOXF1 gene
- Deletion vs. mutation:
  - Deletions
    - airspace enlargement, thinner septal walls
    - Intestinal atresias & severe cardiac anomalies (HLHS)
    - Lymphangiectasis
  - Mutations
    - less airspace enlargement, thicker airspace walls
    - Malrotations
    - GU anomalies
Treatment

- Transient improvement seen with:
  - 100% oxygen
  - Nitric Oxide (Steinhorn 1997)
  - NO + PGI₂ (Kinusaga, Parker 1997)
  - Prostacyclin (PGI₂) (Kelly 2004)
  - ECMO

- Only definitive treatment to date: lung transplant
  - 2 reported for ACD/MPV

Response to Inhaled NO

Response to NO & IV PGI₂

Response to Inhaled iPGI₂
**Treatment: ECMO**

- Number of infants with ACD on ECMO unknown; ~50% of reported infants with ACD/MPV progress to ECMO
- Cassidy UK Study (2002): 173 neonates on ECMO, 5 out of 15 deaths with confirmed ACD
- Not curative; pulmonary hypertension returns, Case reports of >1 ECMO run
- “ECMO failure” may be added to clinical diagnostic criteria for ACD
- Early diagnosis with open lung biopsy could help diminish time on ECMO

**Late Presentation**

- 4-5 case reports
  - 3 weeks – 7 months at time of presentation
  - All reportedly asymptomatic with normal growth
  - Acute onset of critical illness and PAH
  - Trigger unknown (URI?)
- Theories for mechanism of late onset include:
  - Better lobular development
  - Patchy distribution of disease – not supported on inspection of lung specimens

**Case Report: 21 year old Female**

**Summary**

- ACD/MPV: rare, lethal disorder of alveoli & pulmonary vascular development
- Identified by distinct clinical features
- Diagnosis based on histology
- Ante mortem lung biopsy preferable
- FOX F1 gene analysis now available at Baylor; new possibility for antenatal diagnosis
- Treatment options currently ineffective (transplant)
Links

- www.breathoflifeproject.com
- www.3angelsfund.org
- www.acd-association.com

State of the Art

Alveolar Capillary Dysplasia

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