Congenital Pulmonary Airway Malformations and other Lung Developmental Disorders

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Learning Objectives:

• Describe the stages of lung development.

• Recognize how specific disorders relate to different stages of lung development.

• Understand relationship between CPAM, Pleuropulmonary Blastoma, and DICER1.
Stages of Lung Development

- Embryonic
- Pseudo-Glandular
- Canalicular
- Saccular
- Alveolar

**Pulmonary Agenesis**
**CPAM**
**BPS**
**Acinar Dysplasia**
**Alveolar Dysplasia**

**Pulmonary Hypoplasia**

**BPD**
Embryonic Phase (4 – 7 weeks)

Respiratory diverticulum arises from ventral foregut

Extends caudally, separates from esophagus

Forms trachea and lung buds

Bronchi progressively divide to form segmental airways (Branching morphogenesis)

Vasculature develops in surrounding mesenchyme
Pseudoglandular (5 – 17 weeks)

Development of conducting airways

Segmental bronchi undergo asymmetric branching to terminal bronchioles.

Cartilage and smooth muscle of proximal airways arise from mesenchymal cells.

Proximal airway epithelial differentiation

Vascular growth follows airway branching
Canalicular (16-26 weeks)

Branching continues, respiratory airways form.
Terminal bronchioles continue branching
  → Respiratory bronchioles

Mesenchyme thins

Capillaries “canalize” lung parenchyma
  Increased capillary bed development
  Formation of early air-blood interface

Earliest stage when gas exchange possible

At end of canalicular phase alveolar type 2 cells (AEC2s) can begin to produce surfactant.
Saccular (24-36 weeks)

Thin-walled saccules form in distal lung; Alveolar ducts

Double layer capillary network forms

Lymphatic network more developed

AEC2s produce more surfactant

Interstitium thins

Alveolar-capillary membrane thins

Changes allow for gas exchange; survival possible
Diffuse Developmental Abnormalities (rare)

Arrest in development at:

Late pseudoglandular

Acinar dysplasia

Small lung
Thickened interlobular septa
Nearly absent acinar development

Late canalicular stage

Congenital alveolar dysplasia

Thickened septa
Reduced capillary density

Images courtesy of Gail Deutsch, Seattle Children’s
Localized Congenital Lung Lesions: Terminology

Bronchial atresia

Bronchogenic Cyst

Congenital Lobar Emphysema (CLE)
  Congenital Lobar Overinflation (CLO)
  Congenital Lobar Hyperinflation (CLH)

Bronchopulmonary Sequestration (BPS)
  Intralobar (75% - 85%)
  Extralobar (15%-25%)

**Hybrid lesions**

Congenital Pulmonary Airway Malformation (CPAM)
  Old: Congenital Cystic Adenomatoid Malformation (CCAM)

Pleuropulmonary Blastoma (PPB)

Terminology, classification based upon pathology descriptions
Lack of understanding of underlying causes / mechanisms
Congenital Lung Lesions – alternative classifications

Seear et al, Ped Surg Int 2017

Based on prenatal US and initial CXR

**Group 1**  Congenital Solid/cystic Malformations
- Bronchial atresia
- Bronchogenic cyst
- BPS
- CPAM
- Mixed lesions

**Group 2**  Congenital Hyperlucent Lobe
- CLE
- Polyalveolar lobe

**Group 3**  Congenital Small Lung
- Lung/lobar agenesis
- Pulmonary Hypoplasia
Dissecting microscope, N = 7, 2002-2005

Atresia of lobar, segmental or subsegmental bronchus:

- CLE: 50% (4)
- CPAM: 70% (20)
- BPS (ILS): 82% (11)
- BPS (ELS): 100% (11)

Vascular? Intrinsic?
Bronchogenic Cyst

1 in 20,000, M=F

2/3 mediastinal, usually single
1/3 parenchymal, may be multiple

Fluid filled cysts, lined with respiratory epithelium
No connection to airways

No associated anomalies

Present at birth to adulthood
Mass effect (Respiratory Distress)
Infection

Risk of malignancy

Surgical resection
Bronchogenic Cyst: Imaging

Chowdhury et al., *Semin Ped Surg*, 2015;24:168-175

Thacker et al., *J Thorac Imag* 2015;30:29-45
Congenital Lobar Overinflation

1 in 20,000 – 30,000; 3:1 M=F

Upper lobes

Intrinsic, extrinsic obstruction
Histologically normal epithelium
Connected to airways (stenotic, obstructed)

Can be associated with other anomalies

Present birth to childhood
Respiratory Distress, Asymmetry of chest breath sounds

Surgical resection
Very small, asymptomatic - expectant
Congenital Lobar Overinflation

Chowdhury et al., *Semin Ped Surg*, 2015;24:168-175

Thacker et al., *J Thorac Imag* 2015;30:29-45
Bronchopulmonary Sequestration (BPS)

Incidence: < 1 in 100,000, 6% of congenital lung lesions
   Abnormal microcystic lung tissue
   Predominantly lower lobes
   Arise as accessory pulmonary bud?

Do not communicate with tracheobronchial tree
   Arterial supply from arterial circulation

Intralobar:  75-90%, M = F
   Enveloped by pleura adjacent lung
   Drain via pulmonary veins
   No associated anomalies

Extralobar:  10-25%, M:F = 3:1
   Own pleural margin
   Drain via systemic veins
   Associated anomalies ~40%

Presentation: prenatal to later
Bronchopulmonary Sequestration: Imaging

Chowdhury et al., *Semin Ped Surg*, 2015;24:168-175
Congenital Pulmonary Airway Malformation

1 in 10,000 – 30,000; increasing?; M=F
30% – 40% of congenital lung lesions

Cystic and solid
Tracheal, bronchial, bronchiolar, alveolar epithelium
Arise pseudoglandular > canalicular period > sacular
Connected to airways
All lobes
Largely diagnosed prenatally, to childhood

In utero demise to asymptomatic, in utero treatment
Recurrent Infection
Risk of Malignancy (Type 1, Type 4)
Hybrid lesions

Various classification schemes – largely pathology based
<table>
<thead>
<tr>
<th>Type</th>
<th>0 Acinar Dysplasia</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 PPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel. %</td>
<td>&lt;2</td>
<td>65-70</td>
<td>10-20</td>
<td>5-10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Macro</td>
<td>Small, firm Lungs</td>
<td>Macrocysts &gt; 2 cm</td>
<td>Multicystic 0.5-2 cm</td>
<td>Microcystic &lt; 0.5 cm</td>
<td>Large Cysts</td>
</tr>
<tr>
<td>Origin</td>
<td>Tracheobronchial</td>
<td>Bronchial Bronchiolar</td>
<td>Bronchiolar Bronchoalveolar Duct</td>
<td>Distal acinar Single lobe</td>
<td></td>
</tr>
<tr>
<td>Epithelium</td>
<td>Ciliated Columnar</td>
<td>Cuboidal Columnar</td>
<td>Cuboidal</td>
<td>Alveolar Columnar</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Newborn Lethal</td>
<td>Prenatal &gt; Older</td>
<td>Prenatal &gt; infancy</td>
<td>Prenatal, NB &gt; months</td>
<td>NB to Early child</td>
</tr>
<tr>
<td>Etiology</td>
<td>Genetic</td>
<td>In utero airway obstruction</td>
<td>Hybrid lesion</td>
<td>Hamartoma?</td>
<td>DICER1</td>
</tr>
</tbody>
</table>
CPAM: Imaging

Prenatal

Thacker et al., J Thorac Imag 2015;30:29-45

Postnatal

Chowdhury et al., Semin Ped Surg, 2015;24:168-175
DICER1 and Pleuropulmonary Blastoma

Pre-miRNA

DICER1

miRNA

mRNA 5’

miRNA

Translation

AAA AAA AA
DICER1 and Pleuropulmonary Blastoma

Pre-miRNA → DICER1 → miRNA

mRNA 5’ → miRNA → AAAAAAAAA

Translation

Familial Pleuropulmonary Blastoma: Germline DICER1 Mutations
Tumor: Second somatic mutation

Growth Factors
Cell Proliferation
Cell Cycle
Oncogenesis
# CPAM vs PPB

Feinberg et al., *J Ped Surg* 2016

<table>
<thead>
<tr>
<th>CPAM</th>
<th>PPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal detection</td>
<td>DICER1 mutation</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Bilateral or Multisegment</td>
</tr>
<tr>
<td>Hyperinflated</td>
<td></td>
</tr>
<tr>
<td>Systemic feeding vessel</td>
<td></td>
</tr>
<tr>
<td>Solid component on CT</td>
<td>Complex cyst on CT</td>
</tr>
<tr>
<td>Simple cyst on CT</td>
<td></td>
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</tbody>
</table>

May be feasible to individualize approach
Prenatal Assessment of CPAM
Crombleholme et al.  *J Ped Surg* 2002; 37:331

Hydrops imports poor prognosis

**CVR**: CAM Volume Ratio
3-D volume measurement / HC

Retrospective (N=32):
- Hydrops: CVR 3.1±1.1 (N=8)
- Non-Hydrops: 0.74±0.96 (N=24)

Prospective (N=58):
- CVR < 1.6: 8/42  Hydrops
  7/8 with dominant cyst
- CVR > 1.6: 12/16 Hydrops

\[
\text{CVR} = \frac{L \times W \times H \times 0.52}{\text{Head Circumference}}
\]
CVR and Outcome

**Prenatal diagnosis and outcome of fetal lung masses**
Darrell L. Cass*, Oluyinka O. Olutoye, Christopher I. Cassady, Kenneth J. Moise, Anthony Johnson, Ramesha Pappanna, David A. Lazar, Nancy A. Ayres, Bella Belleza-Bascon
*J Ped Surg 2011; 46:292*

CVR > 2.0 correlated hydrops;
10/18 > 2 fetal intervention vs 2/60 < 2

N = 64, retrospective
CVR > 1 correlated resp morbidity
Sens: 90%, Spec 93%

**Am J ObGyn 2013; 151:e1**

**Fetal lung lesions: can we start to breathe easier?**
Stacey Ehrenberg-Buchner, MD; Alyssa M. Stapf; Deborah R. Berman, MD; Robert A. Drongowski, MS;
George B. Mychaliska, MD; Marjorie C. Treadwell, MD; Shaun M. Kunisaki, MD, MSc

**Neonatal Outcomes of Prenatally Diagnosed Congenital Pulmonary Malformations**
Ruchonnet-Metryalier et al., Pediatrics 2014; 133:e1285

CVR < 0.84
Oxygen need at birth

N = 67, retrospective
50 /51 nonhydropic survived
3 / 7 hydropic survived
CVR < 0.91: Sens: 89%, Spec: 71%

**PLOS One 2016**

**Pulmonary Malformations: Predictors of Neonatal Respiratory Distress and Early Surgery**
J Neonat Surg 2016; 5:27
Sara Costanzo,*, 1 Claudia Filisetti, 1, 2 Claudio Vella, 1 Mariangela Rustico, 2 Paola Fontana, 1
Gianluca Lista, 1 Salvatore Zirpoli, 5 Marcello Napolitano, 5 Giovanna Riccipienti 1

N = 70, retrospective
CVR >1.6; 14/16 complications

**J Ped Surg 2011; 46:292**

Specific cut-off varies, but consistently predictive
Is CPAM that rare?

Lau et al., Pediatr Surg Int 2017; 33:105

Historical incidence 1 in 25,000 – 1 in 30,000

Antenatal Screening; prospective registry, 2009 -2014

66 cases; 62 antenatal vs.

45 cases; 27 antenatal 1989 – 2008 (retrospective)

1989 – 2008 incidence: 1 in 27,400

2009 – 2014 incidence: 1 in 7,200

Increased ascertainment vs. increased incidence
Summary

• Normal lung development well orchestrated, complex spatial and temporal expression of transcription, growth factors

• Variety of congenital lung malformations arise during different stages of lung development

• Understanding of etiology/pathogenesis poor

• Leads to confusing array of terms and classification schemes

• Rare, but increasingly diagnosed, especially prenatally

• Uncertainty as to approach for asymptomatic lesions
References


