Congenital Lung Disease
Spectrum, Complications, Controversies

J. Thomas Stocker, M.D.
Professor of Pathology, Pediatrics and
Emerging Infectious Disease
Department of Pathology
Uniformed Services University of the Health Sciences
Bethesda, Maryland
Congenital Lung Disease
Upper Respiratory Tree

• Laryngeal Stenosis and Atresia
• Laryngotracheoesophageal Cleft
• Tracheal Agenesis and Stenosis
• Tracheo/bronchomalacia
• Tracheoesophageal Fistula and Esophageal Atresia
• Bronchial Isomerism Syndromes
• Bronchiectasis – e.g. William-Campbell Syndrome
• Bronchogenic Cyst
Congenital Lung Disease
Lower Respiratory Tree

- Pulmonary Agenesis
- Extralobar Pulmonary Sequestration
- Pulmonary Hypoplasia
- Congenital Lobar Emphysema
- Congenital Pulmonary Lymphangioleciatasis
- Congenital Alveolar Capillary Dysplasia
- Congenital Pulmonary Airway Malformation
- Pleuropulmonary Blastoma
Congenital Lung Disease
Lower Respiratory Tree

- Pulmonary Agenesis
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- Congenital Alveolar Capillary Dysplasia
- Congenital Pulmonary Airway Malformation
- Pleuropulmonary Blastoma
The Origin of CPAM

Chin KY, Tang MY. Congenital Adenomatoid Malformation of One Lobe of a Lung with General Anasarca 1949 Arch Pathol Lab Med 48:221-229


Stocker JT, Madewell JE, Drake RM. Congenital Cystic Adenomatoid Malformation of the Lung: Classification and Morphologic Spectrum
1977 Hum Pathol
8:155-171
Rutledge, JC, Jensen P.
Acinar Dysplasia:
A New Form of Pulmonary Maldevelopment
1986 Hum Pathol
17:1290-1293
Congenital Pulmonary Airway Malformation (CPAM)

Subtypes based primarily on cyst size, but associated with area of tracheobronchial tree involved

O - Tracheal/bronchial
1 - Bronchial/bronchiolar
2 - Bronchiolar
3 - Bronchiolar/alveolar duct
4 - Alveolar
CPAM – 0
Acinar Dysplasia

- Tracheal/bronchial malformation
- Age group - newborn
- Symptoms - immediate, severe respiratory distress
- Imaging - small, “atelectatic” lungs
- Frequency – rare <2%
CPAM-0
DeBoer, EM et al.
Identical twins with lethal CPAM 0 (acinar dysplasia): further evidence of familial tendency
2012 Fetal Pediatr Pathol 31:217-224
CPAM - 1

- Bronchial/bronchiolar malformation
- Age group - birth to adolescence
  - most in first month of life
- Symptoms - neonatal respiratory distress
- Imaging - intrauterine ultrasound - cysts
  - X-ray, CT, MRI - single or multiple large cysts
- Frequency – 60+% 
- Associated anomalies - unusual
This 8 year old boy presented to his pediatrician with a 3 week history of a mild nonproductive cough. A chest x-ray revealed a 2 cm opacity in the right lower lobe with a faint consolidation of the lung distal to the lesion.

The child had had a partial right lower lobectomy shortly after his birth for an air-containing multicystic lesion diagnosed as a CPAM type one lesion with clusters of mucogenic cells along the walls of the larger cysts.
Case History (cont)

- The boy has experienced no pulmonary problems over the next 7 years.
- The reminder of the right lower lobe was resected and contained an ill-defined tan-white 2.3cm lesion surrounded by a rim of parenchyma from which mucoid material could be compressed.


BAC was KRAS mutation positive
Ishida M, Igarashi T, et al
Mucinous bronchioloalveolar carcinoma with K-ras mutation
arising in a type 1 congenital cystic adenomatoid malformation:
a case report and review of the literature
Nov 2013 Intl J Clin Exp Pathol
6:2597-2602

K-ras gene - codon 12(GGT-GCT)

25 cases of BAC arising in CPAM1 –
four now with documented K-ras mutation
Also reports same mutation in intracystic mucinous cell clusters

Supports the concept that malignant transformation progresses from CPAM 1
to mucous cell/ globet cell hyperplasia
to atypical cell adenomatous hyperplasia
to mucinous BAC
to invasive adenocarcinoma

CPAM - 2

- **Bronchiolar malformation**
- **Age group** - first week to month
- **Symptoms** - usually related to associated anomalies
  - respiratory distress if large pulmonary lesion
- **Frequency** – 10-15%
Rhabdomyomatous Dysplasia
CPAM 2
Associated Anomalies

  – Renal dysgenesis/agenesis, sirenomelia, diaphragmatic hernia, and extralobar sequestration (in 50% of type 2 cases)


  – Ipsilateral renal dysgenesis, contralateral renal agenesis, ovarian germ cell hypoplasia
CPAM - 3

• The Original Adenomatoid Malform.
• Bronchiolar/alveolar duct malform.
• Age group - first week of life
• Symptoms - maternal polyhydramnios
  – respiratory distress - mass effect
• Associated anomalies - pulmonary hypoplasia of uninvolved lung
• Frequency – 5%
CPAM - 4

- Peripheral acinar malformation
- Age group - birth to 5+ years
- Imaging - multiple, large cysts - 2-10 cm
- Symptoms - wide range
  - asymptomatic
  - progressive resp. distress in neonate
  - sudden resp. distress – pneumothorax
- Frequency - ?10-15%
2 year old male
Cystic lesion
RLL
SMA – vessel walls
CD31 - endothelium
Desmin – neg.
myoD1 – neg.
Pleuropulmonary blastoma
A unique intrathoracic-pulmonary neoplasm of childhood

Dehner LP, Watterson J, Priest J
Perspect Pediatr Pathol
1995;18:214-226
Pleuropulmonary Blastoma

Differential Diagnosis

Congenital Pulmonary Airway Malformation - 4

Congenital Pulmonary Airway Malformation - 1

Primary or metastatic rhabdomyosarcoma

Other primary sarcomas of the lung
Pleuropulmonary Blastoma

Clinical Presentation

Respiratory difficulty
Fever
Chest pain
Persistent cough
Spontaneous, recurrent pneumothorax
Pleuropulmonary Blastoma

• Age at presentation
  Median - 32 months
  Range - 15 months to 36 years
  Vast majority - 1-4 years
Pleuropulmonary Blastoma

Signs and symptoms

- Respiratory distress 42%
- Fever 32%
- Pneumonia 30%
- Pain 26%
- Cough 26%
- Anorexia 12%
- Malaise 10%
Conditions associated with PPB

Family history of childhood neoplasms

– PPBs in siblings, cousins and other close relatives
– medulloblastoma
– ovarian teratoma
– Hodgkin disease
Conditions associated with PPB

Family history of childhood neoplasms

– leukemia
– thyroid dysplasia and neoplasia
– malignant germ cell tumor
– nephroblastic lesions
Pleuropulmonary Blastoma

• 17p deletion
• P53 deletion using PCR demonstrates
  – Val to Leu substitution at Codon 173
  – Arg Arg to Trp Cys substitution at Codons 282 & 283
• Fli-1 positivity
• Chromosomal Abnormalities
  – Trisomy 8 & 18
  – Tetrasomy 8
  – Diploidy
• Dicer 1 mutation**
Pleuropulmonary Blastoma

Imaging Studies
Multicystic transformation of a lobe
Pneumothorax
Partial or complete opacification of hemithorax
Pleural effusion
Pleural or diaphragmatic mass
Mediastinal shift
Cystic/Solid

Solid

Cystic/Solid
Pleuropulmonary Blastoma

Primary Tumor Site

- Lung alone 54%
- Lung and pleura (parietal) 24
- Lung, mediastinum and pleura 14
- Lung and mediastinum 8
<table>
<thead>
<tr>
<th>Classification</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I - Cystic</td>
<td>14%</td>
</tr>
<tr>
<td>Type II - Cystic/Solid</td>
<td>48%</td>
</tr>
<tr>
<td>Type III - Solid</td>
<td>38%</td>
</tr>
</tbody>
</table>
Pleuropulmonary Blastoma

Type 1 - *purely cystic*

Multiple large cysts with no solid areas

Resembles CCAM-4 with large cysts “lined” by bland cuboidal to columnar epithelium.

Cyst walls have areas which display a distinct “Cambian layer”
Purely cystic PPB with "Cambium" layer of rhabdomyosarcoma cells
<table>
<thead>
<tr>
<th>Feature</th>
<th>CPAM-4</th>
<th>PPB - pure cystic type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>Birth to 5 years</td>
<td>2-12 years</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Respiratory distress, Asymptomatic</td>
<td>Pneumothorax Asymptomatic, Respiratory distress</td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Large, multicystic</td>
<td>Single to multiple cysts</td>
</tr>
<tr>
<td>Cyst lining</td>
<td>Alveolar lining cells</td>
<td>Strips of cuboidal to columnar epithelium overlying Cambium layer</td>
</tr>
<tr>
<td>Cyst wall</td>
<td>Loose to dense (older patients) mesenchyme, rare cartilage island</td>
<td>Fibrovascular tissue with segments of embryonal rhabdomyosarcoma in Cambium layer</td>
</tr>
<tr>
<td>Vasculature</td>
<td>Capillary bed (prominent in neonatal patients), arterioles, thick muscular arteries</td>
<td>Arteries, arterioles and capillaries</td>
</tr>
<tr>
<td>Immunostaining</td>
<td>CD31 (capillaries), AE1/AE3 and TTF-1 (alveolar lining cells), MSA (vessel wall only)</td>
<td>MyoD1</td>
</tr>
</tbody>
</table>
Pleuropulmonary Blastoma

Type 2 - *Intermediate cystic/solid*

Epithelial lined cysts

Solid nodules

- Blastematous islands amid loose mesenchyme and fibrosarcoma-like foci
- Cartilage - benign to overtly sarcomatous
- Rhabdomyoblasts
- Highly pleomorphic, anaplastic cells
Pleuropulmonary Blastoma

Type 3 - *Predominantly solid*

Large, friable mass weighing up to 1000gms.

Solid nodules

- Blastematous islands amid loose mesenchyme and fibrosarcoma-like foci
- Cartilage - benign to overtly sarcomatous
- Rhabdomyoblasts
- Highly pleomorphic, anaplastic cells
Pleuropulmonary Blastoma

Immunohistochemistry

• Rhabdomyoblasts - Vimentin, muscle specific actin, desmin, smooth muscle actin, myogenin, myoglobin
• Blastemal cells - vimentin
• Mesenchyme/spindle cell sarcoma - vimentin, muscle specific actin
Pleuropulmonary Blastoma

Immunohistochemistry

• Immature cartilage/chondrosarcoma - S100 protein
• Lipoblasts/liposarcoma - S100 protein
• MFH-like cells - A1At, A1ACT, lysozyme, CD68
• Benign Epithelium (nonneoplastic) - cytokeratin, EMA
Pleuropulmonary Blastoma

Treatment

Surgical resection
Postoperative irradiation and chemotherapy if incomplete resection
Pleuropulmonary Blastoma

Prognosis - 36 cases - Dehner 1995

Survival 58%
1-180 months (median 21)
Died of tumor 39%
Recurrence - median - 7 months (range 1-30)
Local metastases to other lobes or CNS
Germline **DICER1 Mutations** in Familial Pleuropulmonary Blastoma


Dicer1 also associated with renal development and tumors
DICER1 mutations in childhood cystic nephroma and its relationship to DICER1-renal sarcoma.

Doros LA, Rossi CT, Dehner LP, Hill DA.

Mod Pathol. 2014 Jan 31. doi: 10.1038/modpathol.2013.242
CPAM 4
and/or
Pleuropulmonary Blastoma
Ishida M, et al. 2013
“Mucinous BAC with KRAS mutation arising in a CPAM 1: A case report and review of the literature.”
Int J Clin Exp Pathol 6:2597-2602

• **K-ras** mutation at codon 12

• 25 cases in literature
  – In those cases examined for **K-ras** (4 to date), all have been positive

• Propose concept of malignant transformation of CPAM 1
  – To Mucous cell hyperplasia
  – To Atypical adenomatous hyperplasia
  – To BAC and invasive adenocarcinoma

• **DUE TO K-RAS MUTATION**
CPAM – associated conditions

- CPAM 1 – BAC to Adenocarcinoma
- CPAM 2 – Rhabdomyomatous dysplasia
- Renal Dysgenesis
- CPAM 3 – Pulmonary Hypoplasia
- CPAM 4 – Pleuropulmonary Blastoma