Cystic lung lesions in paediatric population

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Congenital pulmonary airway malformation (CPAM)

- Congenital cystic adenomatoid malformation (CCAM)
- Bronchial atresia with bronchocele
- Bronchopulmonary sequestration (BPS)
- Congenital lobar emphysema (currently “congenital large hyperlucent lobe CLHL/ congenital lobar overinflation CLO”)
- Bronchogenic cyst
- Others
**Congenital pulmonary airway malformation (CPAM)**

**Definition:** developmental malformation of the lower respiratory tract

**Incidence:** 1:5,000 - 1:35,000 livebirths

**Relevance:** 4%–10% of all lung malignancies that affect children and adolescents are associated with cystic malformations.
Congenital cystic adenomatoid malformation (CCAM) & congenital pulmonary airway malformation (CPAM)

• 1949: Ch’in and Tang: congenital cystic adenomatoid malformation (CCAM)
• However, as this is a heterogeneous group w cystic & non-cystic lung lesions that result from early airway maldevelopment, it was later proposed as CPAM
In 2000: **Stocker** reviewed 200 cases.

Proposed new classification in 5 types based on their clinical, gross and histological appearance and “probable” site of origin within the developing T-B tree.

- **Type 0**: “acinar dysplasia”: abnormal bronchial structures in loose vascular mesenchyme
- **Type 1**: > frequent. **Large cysts**. First days of life but also in young adults.
- **Type 2**: back-to-back bronchiolar; > **small cysts** structures. 50% with other anomalies (often severe).
- **Type 3**: true “adenomatoid” large “bulky” lesion.
- **Type 4**: multiple **large cysts** lined by types 1 and 2 alveolar cells.

Only type 3 is “adenomatoid” and 1,2,4 are “cystic”: renamed as CPAM.
Bronchus-like and proximal bronchiole-like structures ~ distal br tree + proximal acinus

Bronchiole str, alveolar ducts and saccules ~ midacinar region

~ distal acinar component

Sites of origin of congenital cystic adenomatoid malformation (CCAM). (Courtesy Dr. J. Thomas Stocker.)

Third Edition, Stocker and Dehner's Pediatric Pathology
CPAM and BPS (ILS and ELS)

- CPAM and BPS: abnormalities during the branching and proliferation stages of the bronchial structures.
- Insult occurs during the pseudoglandular phase of lung development: 7-17 weeks of gestation.
- CPAM: hamartomatous tissue from different pulmonary origins.
- BPS: made of non-functioning lung tissue that has separated itself from the normal pulmonary structure.
- Hybrid lesions with features of both.
- ELS associates to CPAM Type 2 in 50% cases.
- DD: CPAM Type 3.

### Differences Between CCAM and BPS

<table>
<thead>
<tr>
<th></th>
<th>CCAM</th>
<th>BPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1/11,000-1/35,000</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Vascular supply</strong></td>
<td>Pulmonary</td>
<td>Systemic: lower thoracic or upper abdominal aorta</td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td>80%-95% unilateral, either lobe</td>
<td>60% left sided</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male &gt; Female</td>
<td>Male = Female</td>
</tr>
<tr>
<td><strong>Tracheobronchial communication</strong></td>
<td>Present, constricted/anomalous</td>
<td>None</td>
</tr>
<tr>
<td><strong>Associated anomalies</strong></td>
<td>Rare except for Type 2 (60%)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40%</td>
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</tbody>
</table>

BPS, bronchopulmonary sequestration; CCAM, congenital cystic adenomatoid malformation.
<table>
<thead>
<tr>
<th></th>
<th>Type 0</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ frequency (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyst size (max)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular wall thickness (mm) if cysts</td>
<td>100-500</td>
<td>100-300</td>
<td>50-100</td>
<td>0-50</td>
<td>25-100</td>
</tr>
<tr>
<td>Mucous cells</td>
<td>Present in all cases</td>
<td>Present (33% of cases)</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Present in all cases</td>
<td>Present 95-10% cases</td>
<td>Absent</td>
<td>Absent</td>
<td>Rare</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Absent</td>
<td>Absent</td>
<td>Present (5% of cases)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Acinar dysplasia
Not CPAM

NEW CONCEPTS
Large cyst type
small cyst type
Pulmonary hyperplasia
(airway obstruction during development)

PPB type 1

Sites of origin of congenital cystic adenomatoid malformation (CCAM). (Courtesy Dr. J. Thomas Stocker.)

Third Edition, Stocker and Dehner's Pediatric Pathology
# New Concepts in the Pathology of Congenital Lung Malformations

By Claire Langston  
*Houston, Texas*

## Table 3. Classification of Congenital Lung Malformations

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary malformation</td>
<td></td>
</tr>
<tr>
<td>Bronchogenic cyst (noncommunicating bronchopulmonary foregut malformation)</td>
<td></td>
</tr>
<tr>
<td>Bronchial atresia</td>
<td>Isolated</td>
</tr>
<tr>
<td></td>
<td>With systemic arterial/venous connection (intralobar sequestration)</td>
</tr>
<tr>
<td></td>
<td>With connection to gastrointestinal tract (intralobar sequestration/complex or communicating bronchopulmonary foregut malformation)</td>
</tr>
<tr>
<td></td>
<td>Systemic arterial connection to normal lung</td>
</tr>
<tr>
<td>Cystic adenomatoid malformation, large cyst type (Stocker type 1)</td>
<td>Isolated</td>
</tr>
<tr>
<td></td>
<td>With systemic arterial/venous connection (hybrid lesion/intralobar sequestration)</td>
</tr>
<tr>
<td>Cystic adenomatoid malformation, small cyst type (Stocker type 2)</td>
<td>Isolated</td>
</tr>
<tr>
<td></td>
<td>With systemic arterial/venous connection (hybrid lesion/intralobar sequestration)</td>
</tr>
<tr>
<td>Extralobar sequestration</td>
<td>Without connection to gastrointestinal tract (with/without CAM, small cyst type)</td>
</tr>
<tr>
<td></td>
<td>With connection to gastrointestinal tract (complex/communicating bronchopulmonary foregut malformation)</td>
</tr>
<tr>
<td>Pulmonary hyperplasia and related lesions</td>
<td>Laryngeal atresia</td>
</tr>
<tr>
<td></td>
<td>Solid or adenomatoid cystic adenomatoid malformation (Stocker type 3)</td>
</tr>
<tr>
<td></td>
<td>Polyalveolar lobe</td>
</tr>
<tr>
<td>Congenital lobar overinflation</td>
<td></td>
</tr>
<tr>
<td>Other cystic lesions</td>
<td>Lymphatic/lymphangiomatous cysts</td>
</tr>
<tr>
<td></td>
<td>Enteric cysts</td>
</tr>
<tr>
<td></td>
<td>Mesothelial cysts</td>
</tr>
<tr>
<td></td>
<td>Simple parenchymal cysts</td>
</tr>
<tr>
<td></td>
<td>Low-grade cystic pleuropulmonary blastome</td>
</tr>
<tr>
<td>Age range, months</td>
<td>All data (n=50)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>0-180</td>
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<tr>
<td></td>
<td>Mean 14.2</td>
</tr>
<tr>
<td></td>
<td>Median 7</td>
</tr>
<tr>
<td>Sex</td>
<td>25 M (51%)</td>
</tr>
<tr>
<td></td>
<td>24 F (49%)</td>
</tr>
<tr>
<td>Site</td>
<td>Right 27 R (55%)</td>
</tr>
<tr>
<td></td>
<td>Left 22 L (45%)</td>
</tr>
<tr>
<td></td>
<td>1 N/A (para-oesophageal)</td>
</tr>
<tr>
<td>Lobe</td>
<td>Right Upper Lobe 4</td>
</tr>
<tr>
<td></td>
<td>Right Middle 6</td>
</tr>
<tr>
<td></td>
<td>Right lower lobe 14</td>
</tr>
<tr>
<td></td>
<td>Right (NOS) 2</td>
</tr>
<tr>
<td></td>
<td>Left Upper Lobe 3</td>
</tr>
<tr>
<td></td>
<td>Left Lower Lobe 18</td>
</tr>
<tr>
<td></td>
<td>Left (NOS) 1</td>
</tr>
</tbody>
</table>

Acknowledgment: Sophie Stenton
Interesting patterns @SCH

• Sequestrations: > Left sided (74%) and in the LLL (63%)
• CPAMs: > right sided (72%) and in the RLL 50%.
• Atresia (without sequestration or CPAM) were all in the lower lobes (though small numbers)
• CLOs in youngest patients (median 2.5 months) and right-sided and represented over 50% of all RML lesions (small numbers though)
• 58% of sequestrations showed CPAM related change in keeping with the literature (not shown on this table)
• Of CPAMS: Type 1 (14), Type 2 (3), type 3 (1), Type 4 (0)
• Two type 0 (acinar dysplasia) presented at autopsy rather than as surgical specimens

Acknowledgment: Sophie Stenton
MOLECULAR ASPECTS CPAM: Congenital lung lesion transcriptome

A biplot of principal component analysis of gene expression data from 28 paired samples (from 14 patients: 6 microcystic, 5 hybrid, 1 bronchopulmonary sequestration [BPS], and 2 macrocystic lesions) demonstrates that microcystic and hybrid/BPS lesions cluster together, separate from macrocystic lesions, and from paired unaffected lung.

Novel Molecular and Phenotypic Insights into Congenital Lung Malformations

Daniel T. Swarr¹*, William H. Peranteau²*, Jennifer Pogoriler³, David B. Frank⁴,⁵,⁶, N. Scott Adzick², Holly L. Hedrick², Mike Morley⁶, Su Zhou⁶, and Edward E. Morrissey⁵,⁷

American Journal of Respiratory and Critical Care Medicine Volume 197 Number 10 | May 15 2018
Molecular aspects of CPAM

• Cysts lined by bronchial or bronchiolar epithelium showed upregulated transcripts for genes known to be expressed in the normal airway epithelium

• Genes within the Ras, P13k-AKT-mTOR (phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin) signalling pathways were demonstrated, suggesting an epithelial intrinsic role in the pathogenesis of congenital lung lesions.
Proposed model diagram:

A defect occurs during branching morphogenesis of the lung (a somatic mutation or alteration in chromatin state), that results in dysregulation of a key developmental signalling pathway such as Ras/MAPK or PI3K–AKT–mTOR signalling. This impaired epithelial population expands as development proceeds and remains “proximalized,” forming an abnormal collection of cystic airway structures seen in the mature congenital lung lesion. Disrupted epithelial–mesenchymal interactions arising from these epithelial cells occasionally result in abnormal vascular development or may even “recruit” a systemic feeding vessel.

CPAM = congenital pulmonary airway malformation; MAPK = mitogen-activated protein kinase; PI3K–AKT–mTOR = phosphatidylinositol 3-kinase–AKT–mammalian target of rapamycin.
Acinar dysplasia

• Very rare form of primary interstitial lung disease
• Diffuse bilateral impairment of pulmonary acini (the respiratory bronchioles, alveolar ducts, and alveoli) development
• Appearance of lung at term resembles the 16-week pseudoglandular phase with no alveolar spaces for gas exchange
• Always fatal
Acinar Dysplasia

- 38 WGA
- RSD at birth
- Bronchial-like structures surrounded by cartilage and mesenchyme
CPAM type 1

10 months old girl. RLL. 
?CCAM  ? sequestration

95% one lobe only. Few or single cyst (1 - 10 cm). “Lined” by smooth membrane.
CPAM type 1

CPAM 1 Axial CT aged 2 months (lung windows) Shows solid and cystic components in the right lower lobe.
CPAM Type 1

- Young infants
- 65% cystic lesions
- Larger cysts: Ciliated epithelium
- Smaller cysts: cuboidal
- 5-10% cartilage
- Mucous cells
Diagnosis:
CPAM associated with ILS
CPAM 1

Epithelium: cilia and mucous cells

- ? association of CPAM 1 with bronchioalveolar carc
- Case reports of BAC having occurred in older children who, as infants, had had a CPAM-1 partially or totally resected
- Similar genetic abnormalities (gains in chromosomes 2 and 4) in both CPAM-1 “goblet cells” and the cells of BAC
- 19 cases of mucinous adenocarcinoma reported in children (newborn-14 years) with CPAM Type 1
CPAM type 2

1.5 to 2 cm cysts lined by “smooth” membrane.

Axial CT (Lung windows) shows a part solid part multicystic mass in the left lower lobe.

14 months old girl. LLL

- 15-20% lung cysts

- Often associated with other severe malformation (renal agenesis, diaphragmatic hernia, C-V).
“back to back” dilated bronchioles with alveolar duct-like structures. Most frequent type in ELS.

Smooth muscle or rhabdomyomatous component in the cyst’s wall

No cartilage or mucous cells
CPAM 2 and ILS

Feeding vessel
Case of mucinous adenocarcinoma of the lung associated with congenital pulmonary airway malformation in a neonate

Junyeong Koh, MD, Euisook Jung, MD, Se Jin Kang, MD, Dae Won Kwon, MD, Byung Sap Lee, MD, Ki-Soo Kim, MD, Eileen Al-Rham Kim, ND

Departments of Pediatrics, Pathology, and Thoracic Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

- 10-day-old male
- LLL cyst: type II CPAM complicated by multifocal mucinous adenocarcinoma
- \( \text{KRAS} \) sequencing: somatic mutation in Codon12 (GGT \( \rightarrow \) GAT), suggesting the development of a mucinous adenocarcinoma in the background of mucinous metaplasia
CPAM type 3

1 12 years male. LUL. ? Lymphatic malformation

Bulky lesion or small cysts (0.5 to 1.5 cm)

5 to 10% cysts cases. Bronchiolar-alveolar duct origin. Newborn, > males, large size = 80% associated with polyhydramnios and fetal anasarca

Low cuboidal epithelium

Ciliated epithelium
CPAM type 3

Axial CT sections at lung apex and base (lung windows) shows solid areas of lung with microcystic change, left greater than right. The left lingula and lower lobe are compressed but normal.

There is a small area of microcystic change RUL. This case is unusual as the disease is bilateral and apical. It is more commonly unilateral and basal.
16 weeks fetal lung. Glandular stage

23 weeks. Canalicular stage

CAM 3 Bronchiolar/alveolar duct structures.

Mucous cells, cartilage or rhabdomyomatous elements are absent
CPAM & bronchial atresia

54 years old female with cough and blood stained sputum

RML: Bronchial atresia and a cystically dilated bronchus lined by pseudostratified ciliated columnar epithelium

Opacity is seen in the RLL (arrow).

Multiple large air-filled cysts consistent with a CPAM in RLL (arrow).

Oval-shaped opacity of the distal RML bronchus with no clear connection between the lesion and T- bronchial tree

RML bronchus not seen on bronchoscopy

Suspicious dimpling lesion (arrow) in the proximity of RML bronchus
So-called: CPAM Type 4

- Peripheral acinar type
- Males= females
- Newborn to 4 years
- 10-15% lung cysts
- X rays: large cysts, mediastinal shift, may be a tension pneumothorax

Stocker & Dehner’s Pediatric Pathology. 3rd edition
Current understanding

• “Type 4” CPAM: Overlaps with Type I pleuropulmonary blastoma (PPB)
• Three pathologic subtypes of PPB:
  - Type I: purely cystic (91% survival)
  - Type II: combined cystic solid (71% survival)
  - Type III: purely solid (53% survival)
• 112 Type I PPB retrieved from the International PPB Registry
• Comparison with an institutional cohort of children undergoing resection of CPAM (2002–2013)
• 6 c (5%) detected in prenatal USS
• Others presented with respiratory symptoms at 11.5 months
• 8 c with PPB Familial Tumour syndrome had cystic nephroma. > DICER I germline mutation
• CT: cystic lesion (97.5%) (5 cm diameter)
• 16 c (10.7%) had a recurrence of PPB.
• 11/16 c evidence of progression to type II, II/III PPB
DD PPB Vs CPAM

- Features most strongly associated with CPAM:
  - Prenatal diagnosis
  - Hyperinflated lung
  - Systemic feeding vessel on CT
  - Simple as opposed to a complex cyst on CT.

- Features most strongly associated with PPB
  - Multisegment involvement,
  - Complex cyst
  - Germline mutation in the DICER1 gene (2/3 PPB)
**PPB**

- Most common tumour in children associated to CPAM
- 66% of PPBs in the registry were associated with lung cysts, either discovered at diagnosis or predating it
- PPB Type I: Dx feature may be subtle, > localized in a collapsed multilocular cyst, > from the periphery of the lung.
- Air-filled cysts w primitive mesenchymal cells beneath an intact, benign-appearing epithelium
- Foci of dense subepithelial or septal spindle cell proliferation: highly suggestive of type I PPB
PPB cystic type 1

Multiple loculated cysts with delicate septal walls with a fibrous stroma

Cystic walls were lined with a high cylindrical epithelium, often ciliated, standing on a stroma with a cellular cambium layer, composed of blastematosus cells

dulti-loculated cystic tumour measuring \(13 \times 10 \times 7\) cm.
PPB solid: chondroid, sarcoma features, anaplasia
New study suggests IHC may aid DD

- Potential role of fibroblast growth factor (FGF) 10 in pathogenesis CPAM
- FGF10: mesenchymal growth factor. May act on the epithelium through its receptor FGFR2b to control pulmonary morphogenesis
- Mesenchymal FGF10 expression inhibited by Sonic Hedgehog (SHH), a diffusible factor secreted by epithelial cells
- Induction of localized lung FGF10 overexpression in fetal rats: macrocystic or microcystic lung malformations, depending on the developmental stage and the site of overexpression
FGF10 Signaling differences between type I pleuropulmonary blastoma and congenital cystic adenomatoid malformation

- HIC to compare the expression of FGF10, FGFR2b, and SHH in type I and type II CPAM and in type I PPB
- All very strong in CPAM

Figure 1 Immunostaining with FGF10. From left to right, original magnification x5 (A, C, E, G), x10 (B, D, F, H). The x10 magnified area is identified by a rectangle. Counterstain: hematoxilin. A-B: Control lung, strong FGF10 expression in both the epithelium and the underlying mesenchyme of normal bronchi. C-D: CCAM; the expression of FGF10 is strong and continue within the epithelium lining cysts, and within the underlying mesenchyme. E-F: multiloculated cysts in type I PPB, G-H: large cyst in a type I PPB, nearly absence of FGF10 expression in type I PPB.
Mechanisms involved in malignant transformation of CPAM

- KRAS gene mutated at high frequency in AC. KRAS missense mutations observed in the mucinogenic foci of CPAM, confirming the malignant nature of the mucinous cell proliferations.
- Mucogenic cells of CPAM1: implicated in the pathogenesis of mucinous BACs.
- Preneoplastic alterations in mucogenic cells genomic imbalances, decreased apoptosis & dysregulated paracrine growth of cells and matrix.
CPAM & Dx age Lung cancer

**Children with CPAM**
- PPB, RMS, others: mean ages ~ 3 yr
- BAC: mean age: 6 yr

**Adults with CPAM**
- AC: mean age 53 yr
- BAC: mean age 34.5 yr
- Squamous cell carc, bronchial carcinoid, others: mean age, 47; 43 and 46 yr, respectively.
Take-home message:

• CPAMs should be followed up and never underestimated because they may conceal a tumour

• The risk for malignant transformation of CPAMs might happen at any age
Bronchogenic cysts

- Consequence of a supernumerary lung bud/ aberrant foregut development
- Mediastinum, > above tracheal bifurcation
- Near pulmonary hilum
- Unusual locations like the retroperitoneum
- > asymptomatic
- 1 -10 cm diameter
- Not connected to T-bronchial tree
- Histology: unilocular cyst, lined by ciliated, cuboidal or pseudostratified epithelium overlying fibromuscular tissue containing seromucinous glands and cartilage
- No distal lung parenchyma.

https://basicmedicalkey.com/bronchogenic-cyst-5/
Congenital lobar emphysema (congenital large hyperlucent lobe)

- 1:20,000 and 1:30,000 births
- > LUL or RML
- May show very few primitive alveoli or even a polyalveolar lobe.
- Mechanisms proposed to explain the air-trapping include:
  - dysplastic or deficient bronchial cartilage
  - thick mucus
  - extensive mucosal proliferation
  - bronchial torsion / atresia/ compression by cardiopulmonary vessels, lymph nodes, cysts
  - polyalveolar lung
  - focal pulmonary hypoplasia.
Congenital Lobar Emphysema

- A 6 m old with respiratory distress.
- Chest X ray: gross over-expansion of the right lung and
DON'T WORRY  BE PROUD!