Pediatric Pulmonary Neoplasia: Current Perspectives

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Pediatric Neoplasia: Background

Primary Lung Tumors in Neonates, Infants, Children and Adolescents

- Rare Tumors
  - 0.2% of All Childhood Tumors
  - Malignant Tumors (65-76%) More Common than Benign Tumors (24-35%)
    - Mortality for Benign Tumors 8% and Malignant Tumors 30-50%
- Metastatic Tumors 5-times More Common
- Benign Non-Neoplastic Tumors 60-times More Common Than Primary Tumors
  - Bronchogenic Cysts and Bronchial Atresia with Mucocoele
  - Pulmonary Sequestrations (intralobar, extralobar)
  - Congenital Cystic Adenomatoid Malformations.
- Pulmonary Infections, Inflammatory or Reactive Processes May Mimic Solid Tumors

Symptoms Associated with Pediatric Lung Tumors

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Benign (n=86)</th>
<th>Malignant (n=255)</th>
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<tbody>
<tr>
<td>None</td>
<td>28%</td>
<td>6%</td>
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<tr>
<td>Fever</td>
<td>16%</td>
<td>18%</td>
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<tr>
<td>Cough</td>
<td>14%</td>
<td>35%</td>
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<tr>
<td>Pneumonitis</td>
<td>10%</td>
<td>23%</td>
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<tr>
<td>Chest Pain</td>
<td>8%</td>
<td>7%</td>
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<tr>
<td>URT Infection</td>
<td>7%</td>
<td>2%</td>
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- Respiratory Distress 7% 12%
- Hemoptysis 6% 12%
- Dysphagia 6% 0%
- Wheezing 2% 4%
- Cyanosis 2% 1%
- Weight Loss 0% 1%

**Benign Primary Lung Tumors**
- Hamartoma (24%)
- Mature Teratoma (1%)
- Myofibroblastic Tumors (52%: myofibroma, inflammatory myofibroblastic tumor, congenital peribronchial myofibroblastic tumor)
- Lymphovascular (hemangioma, lymphangioma, Arteriovenous Malformation)
- Neurofibroma (10%)
- Smooth Muscle Tumor (7%; some associated with EBV)
- Chondroma
- Granular Cell Tumor (3%)
- Lymphoproliferative Disorder (some associated with EBV)
- Langerhans and non-Langerhans Cell Histiocytosis
- Squamous Papillomas (some associated with HPV)
- Adenomas of Minor Salivary/Mucin Glands (3%)
- Mesothelial Proliferation
- Fetal Lung Interstitial Tumor (FLIT)
- Lipoblastoma
- Solitary Fibrous Tumor

**Malignant Primary Lung Tumors**
- Pleuropulmonary Blastoma (20-27%: PPBs Types I-cystic; II-cystic/solid: and III-solid)
- Germ Cell Tumors, Immature Teratomas and Malignant Teratomas (1%)
- Lymphoproliferative Disorders with Monoclonality or Lymphomatous Transformation (most associated with EBV)
- Hodgkin and non-Hodgkin Lymphomas (1%)
- Carcinoid Tumor (17%)
- Minor Salivary/Mucin Gland Tumors
  - Mucoepidermoid Carcinoma (13%)
  - Adenoid Cystic Carcinoma (1%)
  - Other Salivary Gland Tumors
- Bronchial “Adenomas” (40%: Carcinoid Tumor, Mucoepidermoid Carcinoma, Adenoid Cystic Carcinoma)
- Squamous Cell Carcinoma (some associated with HPV)
- Adenocarcinoma, Bronchoalveolar Carcinoma, Small Cell Carcinoma, Neuroendocrine Carcinoma (16%)
- Bronchopulmonary Fibrosarcoma (10%)
- Myofibroblastic Sarcoma
- Rhabdomyosarcoma (4%; not associated with Pleuropulmonary Blastomas or Other Cystic Lung Lesions)
- Ewing Family of Tumors
- Synovial Sarcoma
• Leiomyosarcoma (4%: most associated with EBV)
• Angiosarcoma and Kaposi Sarcoma (HHV8 associated)
• Mesothelioma

Metastatic Tumors Involving Lung
• Secondary Involvement of Lung
  o Leukemic or Lymphomatous Infiltrates
    ▪ Lymphoproliferative Disorders, Monomorphous
    ▪ Hodgkin and Non-Hodgkin Lymphomas
    ▪ Leukemias: ALL, AML, CML
• Solid Tumors
  o Wilms Tumor, Osteosarcoma, Ewing Family of Tumors
  o Rhabdomyosarcoma, Germ Cell Tumors
  o Neuroblastoma, Hepatoblastoma, Hepatocellular Carcinoma
  o Rhabdoid Tumor, Clear Cell Sarcoma of Kidney
  o Cellular Mesoblastic Nephroma
  o Desmoplastic Small Round Cell Tumor
  o Undifferentiated Sarcoma, Synovial Sarcoma, Angiosarcoma
  o Clear Cell Sarcoma of Soft Tissue, Fibrosarcoma, Liposarcoma
  o Myofibrosarcoma, Pleomorphic Undifferentiated Sarcoma (MFH)
  o Alveolar Soft Part Sarcoma
  o Nasopharyngeal Carcinoma, Adenoid Cystic Carcinoma
  o Colon Adenocarcinoma, Clear Cell Carcinoma, Squamous Cell Carcinoma
  o Juvenile Secretory Carcinoma of the Breast

Selected Primary Pediatric Lung Tumors

Fetal Lung Interstitial Tumor (FLIT)
• Newly Recognized Lung Tumor of Infancy (1st Case Diagnosed as Atypical PPB)
• Currently Reported: 10 Infants (7 Females, 3 Males) with Tumor-Like Lung Masses
• Detected in Perinatal Period and up to 3 Months of Age (median 1 day-old)
• Often Detected by Prenatal Ultrasound
• Symptoms
  o Variable Respiratory Distress Shortly After Birth (mild to moderate to severe)
  o Progressive Feeding Difficulties
  o Low Grade Fever
  o Diminished Breath Sounds
  o Airway Obstruction with "Inspissated Mucin"
• Radiologic Imaging
  o Well Circumscribed, Solid or Mixed Solid/Cystic Lobar-Based Mass
  o Solid Masses in 8/10 Cases and Partially Cystic Masses in 2/10 Cases
• Pathologic Features
  o Gross Appearance:
    ▪ Tumor Size: 2 to 7 cm
    ▪ Well Circumscribed, Tan-Pink to Dark Red-Brown
    ▪ Solid to Spongy Mass
- Border Between Mass and Normal Lung Demarcated by Complete to Incomplete Fibrous Interface
  - Histopathologic Appearance:
    - Comprised of Immature Mesenchyme Associated with Irregular Airspace-Like Structures Resembling Abnormal Incompletely Developed Lung
    - Gestationally Inappropriate, Immature Airspaces Formed by Variably Widened Septa with Similarly Immature Interstitial Cells
    - Interstitial Compartment Comprised of Monotonous Immature Round to Oval Mesenchymal Cells.
    - Interstitial Cells Formed Uniform Monolayer of Polygonal Cells Without A Cambium Layer Beneath the Non-Ciliated, Low Cuboidal to Flattened Epithelium
    - Interstitial Cells Possessed Clear to Pale Eosinophilic Cytoplasm with PAS Granular Positivity that Digested with Diastase (glycogen) and Nuclei with Dispersed Chromatin and Inconspicuous Nucleoli
    - Membranous Bronchiolar and Small Airway Structures Modest in Number and Accompanied by Smooth Muscle.
    - Isolated Foci of Cartilage Similar to That in Small Bronchioles in 2 Cases
    - Less Frequent Pattern (2/10 Cases) of Immature Fibroblastic to Myofibroblastic Cells Replacing Polygonal Interstitial Cells with Focal Chronic Inflammatory Cells Including Plasma Cells
    - Normally Developed Lung Present in Immediate Vicinity to the Mass
    - Fibrous Border or Abrupt Interface Demarcated Normal Saccular Stage Lung From Masses Immature Airspace-Like Structure with Widened Cellular Septa
    - Resembles Fetal Lung at 20 to 24 Weeks Gestation Canalicular Stage
  - Immunocytochemistry:
    - Positive for Strong Diffuse Vimentin, Focal SMA and Focal Desmin For Interstitial Cells
    - Negative for Myogenin
    - Epithelial Lining of Airspaces: Positive for Cytokeratin, EMA and TTF-1
    - Mib1 (Ki-67): 15-25% of Interstitial and Epithelial Cells Positive
  - Electron Microscopy:
    - Plump Alveolar Epithelial Lining Cells with Abundant Cytoplasmic Glycogen and Some with Lamellar Bodies Consistent with Type II Alveolar Cell Differentiation
    - Interstitial Cells with Abundant Cytoplasmic Glycogen and Rare Fibronexus Structures Consistent with Myofibroblastic Differentiation
    - Smooth Muscle Cells Present Adjacent to Epithelial Basement Membranes
  - Cytogenetics:
    - Normal Karyotype in 2 Cases (Not Done in 8 Cases)
    - DICER1 Sequencing Negative in 1 Case
• Lobectomy or Wedge Resections in Each Case With Complete Excision in 8/10 Cases
• *Ex Utero* Intrapartum Surgical Resection at 37 Weeks Gestation in 1 Case with MRI Indicating Fetal Ascites Due to Inferior Vena Caval Obstruction
• Only 1 Case with Vincristine-Based Chemotherapy Initiated Although Diagnosis of FLIT was Made at Time of Resection and Not PPB.
• No Recurrences and No Metastatic Disease in All Cases on Follow-Up after 15-182 months
• Differential Diagnosis: Bronchogenic Cyst, Congenital Cystic Adenomatoid or Pulmonary Airway Malformation (CCAM-CPAM), Cystic Pleuropulmonary Blastoma (PPB Type I), Pulmonary Interstitial Glycogenosis (PIG), Congenital Peribronchial Myofibroblastic Tumor (CPMT)
  o FLIT
    ▪ Gross: Solid to Spongy Lobar Based Mass
    ▪ Microscopic:
      • Circumscribed Lesion with Partial Fibrous Interface with Adjacent Compressed Normal Lung
      • Small Airspace-Like Structures Lined by Single Layer of Flattened to Cuboidal Epithelium
      • Septal Interstitial Expansion by Uniform Polygonal Cells with Clear Cytoplasm (PAS Positive, Diastase-Digestion)
      • Network of Delicate Capillaries
    ▪ Lung Involvement: Limited to Single Lobe
  o Cystic Pleuropulmonary Blastoma (PPB Type I)
    ▪ Gross: Collapsible, Delicate Multicystic Structure Located at Periphery of Lobe
    ▪ Microscopic:
      • Transition from Normal Lung to Variable-Sized Cysts with Continuous or Discontinuous Population of Primitive Small Cells with or without Rhabdomyoblastic Differentiation Beneath Lining Epithelium (Cambium Layer)
      • Small Nodules of Primitive Cartilage (not all cases), Fibrous Interstitium with Prominent Vessels, Focal Necrosis and/or Hemorrhage
    ▪ Lung Involvement: Multifocal in 40% of Cases
  o Congenital Cystic Adenomatoid Malformation
    ▪ Gross: Dominant Lobar-Based Cyst or Variable-Sized Cysts Within Lung Parenchyma (Types I and 2)
    ▪ Microscopic:
      • Dominant Cyst Lined by Ciliated Respiratory Epithelium With Adjacent Compressed Lung (type I) or
      • Multiple Variable-Sized Cysts Lined by Respiratory Epithelium (type 2)
      • Background of Normal Lung Parenchyma
      • Immature But Differentiated Rhabdomyomatous Cells in Interstitium (type 2)
      • Microscopic Terminal Bronchiole-like Structures with Solid Gross Appearance (type 3)
    ▪ Lung Involvement: Rarely Multilobar in ≤1% of Cases
Pleuropulmonary Blastoma (PPB)

- Embryonal Malignant Tumor Derived from Mesenchyme of Lung and Pleura
- Rare Tumor with 20 to 25 Cases Per Year in USA
- First Described in 1988 as Distinct Entity
- Predominantly in Neonates, Infants and Young Children (single documented adult case reported)
- Rarely Reported After 12 years of Age
- Detection May Occur During Routine Ultrasound Prenatally
- Important to Distinguish from Adult Pulmonary Blastoma
  - Adult Pulmonary Blastoma: Biphasic Tumor with Both Malignant Mesenchymal and Epithelial (glandular) Components (Carcinosarcoma)
  - PPB: Only Malignant Mesenchymal Component and No Malignant Epithelial Component
- Equal Gender Ratio
- Laterality: Right Lung 54%; Left Lung 37%; Bilateral 9%

PPB Types (I, II, III and IR)

- Type I PPB (Purely Cystic Tumors): 27% of All PPBs
  - Occur in Youngest Affected Patients (median age 10 months, range newborn to 32 months)
  - Multilocular Cyst on Radiologic and Gross Examination
  - Respiratory Distress Due to Air-Filled Cysts or Pneumothorax
  - Usually Incidental Lung Cysts on Chest X-Ray - Often Confused with Congenital Cystic/Pulmonary Adenomatoid Malformation (CCAM/CPAM)
  - Pathology of Type I PPB
    - Single or Multiloculated Cysts with Thin Fibrous Septa
    - Cysts Lined by Ciliated Columnar Epithelium
    - Subepithelial Small "Buds"/Aggregates of Primitive Mesenchymal Cells and/or Nodules of Immature Cartilage
    - Subepithelial Cambium Layer- Continuous or Discontinuous Condensed Zone
      - Small Round to Spindled Immature/Primitive Mesenchymal Cells Forming Cambium Layer
      - Botryoid Appearance with Intermixed Polygonal and Strap Cell Rhabdomyoblasts
      - Myogenin, Desmin, MyoD1, MSA: Positive
      - Ultrastructure: Myofilaments, Rudimentary Z-bands
  - Differential Diagnosis
    - CCAM Types I, II and III
    - CPAM Type 4
    - FLIT (Fetal Lung Interstitial Tumor)

- Type II PPB (Solid and Cystic Tumors): 35% of All PPBs
  - Median Age 36 Months (range 15-64 months, single documented 36 year-old)
  - Dyspnea, Fever, Cough, Chest or Abdominal Pain, Pneumonia, Malaise, Anorexia
  - Pleural Effusion, Pneumothorax
  - Pathology: Cystic and Solid Tumors
    - Cystic Component of Type II PPB
Remnants of Cysts with Thin Fibrous Septa and Lined by Ciliated Columnar Epithelial Cells with Subepithelial Malignant Mesenchymal Cells

Predominantly Cystic PPBs with Plaque-Like Areas with Overgrowth of Rhabdomyoblasts, Spindle Cell Sarcoma or Blastematous Elements

- **Solid Tumor: Mixed Sarcomatous and Blastematous Features**
  - Cellular Islands of Small Primitive Blastematous Cells (oval nuclei, granular chromatin, inconspicuous nucleoli, minimal cytoplasm, numerous mitotic figures)
  - Stroma Blends with Spindle Cells Organized into Vague Fascicular Pattern of Fibrosarcoma or Pleomorphic Undifferentiated Sarcoma (MFH)
  - Stroma Resembling that Surrounding Blastema in Wilms Tumors
  - Foci of Skeletal Muscle and Chondroid Differentiation (resembles rhabdomyosarcoma or chondrosarcoma or fetal/immature cartilage)
  - Foci of Anaplasia with Giant Bizarre Pleomorphic Tumor Cells in Many Type II and III PPBs
  - "Cystic" Necrosis in Solid PPB Areas - Friable Empyema-like Tissue
  - Myxoid Degeneration
  - Pericytomatous or Liposarcomatous Pattern
  - Many Different Malignant Mesenchymal Tumor Patterns May Be Seen.

- **Type III PPB (Solid Tumors): 32% of All PPBs**
  - Median Age 44 Months (range 12-147 months)
  - Dyspnea, Fever, Cough, Chest or Abdominal Pain, Pneumonia, Malaise, Anorexia
  - Pleural Effusion
  - Pathology of Type III PPB (Solid Tumor)
    - Stroma Blends with Spindle Cells Organized into Vague Fascicular Pattern of Fibrosarcoma or Pleomorphic Undifferentiated Sarcoma (MFH)
    - Stroma Resembling that Surrounding Blastema in Wilms Tumors
    - Foci of Skeletal Muscle and Chondroid Differentiation (resembles rhabdomyosarcoma or chondrosarcoma or fetal/immature cartilage)
    - Foci of Anaplasia with Giant Bizarre Pleomorphic Tumor Cells in Many Type II and III PPBs
    - "Cystic" Necrosis in Solid PPB Areas - Friable Empyema-like Tissue
    - Myxoid Degeneration
    - Pericytomatous or Liposarcomatous Pattern
    - Many Different Malignant Mesenchymal Tumor Patterns May Be Seen.
Differential Diagnosis of Type II and Type III PPBs

- Primary or Metastatic Rhabdomyosarcoma
- Malignant Teratoma
- Synovial Sarcoma
- Undifferentiated Pleomorphic Sarcoma (MFH)
- Spindle Cell Sarcoma
- Fibrosarcoma
- Fibrous Histiocytoma
- Inflammatory Myofibroblastic Tumor
- Metastatic Wilms Tumor

Type IR PPB (regressed PPB): 5% of All PPBs

- Cystic Mass Similar to Type I PPB Recognized in 2008
- Delicate Septa with No Malignant Cells
- Small Spindle Cells Lacking Primitive Appearance
- Foci of Dystrophic Calcifications
- Histopathologically Distinct From CCAM/CPAMs
- Either Regressed from Type I PPB or Precursor Lung Cyst That Mesenchyme Did Not Become Dysplastic or Malignant
- May Present with Pneumothorax
- Recognized in Children and Adults

Progression of Type I to Type II to Type II: Well Recognized

- Occurs Over Time with As Noted With Recurrences
- Tumors Progress, but Do Not Regress from Type III to Type II or Type II to Type I
- "Benign" Lung Cysts Followed from Infancy and Into Early Childhood May Progress from Radiologic Pure Cystic Lesion (Type I) to Type II or Type III

Metastatic Disease

- Brain 15-25%
  - More Common in Type III PPBs with 54% CNS Involvement
  - Less Common in Type II PPBs with 11% CNS Involvement
- Bone 6-10%
- Liver 2-4%
- Rare Sites
  - Choroid of Eye, Iris, Ovary, Adrenal Glands
  - Spinal Cord, Leptomeninges
- Time to Metastases: 24 months from Diagnosis in Most

Treatment

- Surgical Excision of Type I, II and III PPBs and Lung Cysts Suspicious for PPB
- Type I PPB with Incomplete Excision - Adjuvant Chemotherapy
- Chemotherapy for Type II and Type III PPBs
  - Ifosfamide, Doxorubicin, Vincristine, Actinomycin D
    - Response Prompt with Maximum Response with 2-4 Courses
    - Prior Partial Resection, 2nd Look Surgery and Complete Resection after 2-4 Courses of Chemotherapy
    - Complete Response Rarely Reported and Recommend Complete Resection of Remainder of Primary Site
• Intracavitary Chemotherapy and/or Radiation Therapy With Tumor Spillage (Cis-Platinum with Systemic Chemotherapy and Radiation)
  • Intracavitary $^{32}$P for Residual Pleural Disease
  • Recurrent PPB
    • Individualized Therapy
  o Radiation Therapy
    • Residual Disease After Surgery
    • Intracavitary $^{32}$P for Residual Pleural Disease
  o High Dose Chemotherapy and Stem Cell Reconstitution (autologous bone marrow transplantation) in Recurrent or Metastatic PPB
    • 50% Success Rate in Limited Patients
• Surveillance in PPB
  o Lung Cysts in High Risk Children
    • Chest X-Ray Every 2 Months
    • Chest CT Every 4-6 months until 60 months of age
  o Type I PPB
    • Years 1 & 2 After Diagnosis:
      • Monthly Chest X-ray and Chest CT Every 3 months
    • 24 to 60 Months of Age: Chest CT Every 3 months
  o Type II and III PPB
    • Years 1 & 2 After Diagnosis:
      • Chest X-ray monthly
      • CT of Chest and Abdomen Every 3 Months
      • Bone Scan Every 3 Months
      • CNS/Head MRI Every 3 Months
    • Year 3 After Diagnosis
      • CT of Chest and Abdomen Every 3 Months
      • Bone Scan Every 3 Months
      • CNS/Head MRI Every 3 Months
• Five-Year Overall Survival Rates:
  o Type I PPBs: 85%
  o Type II PPBs: 58%
  o Type III PPBs: 42%
• Dicer 1 Germline Mutations in PPB Family Tumor and Dysplasia Syndrome (2009)
  o Autosomal Dominant Inheritance
  o Dicer 1 Required for Normal Branching Lung Morphogenesis
  o Dicer 1 Mutation Results in Loss of Dicer 1 Protein in Lung Epithelium in PPBs with Retention of Dicer 1 Protein in Sarcomatous/Mesenchymal Cells
  o Dicer 1 Mutant Lung Epithelium in Murine Model Leads to Impaired Branching and Cystic Dilatations Due to Lack of Epithelial-Mesenchymal Interaction
  o Postulated that Loss of Dicer 1 Function and Dysregulated Autocrine Signals from Lung Epithelium to Mesenchymal Cells Induce Cystic Formation and Lead to Malignant Transformation.
• PPB Family Tumors and Dysplasia Syndrome
  o Familial Distribution in 33%
  o Usually Occurs in First Two Decades of Life
- Associated with Dicer 1 Mutation
- Tumors/Dysplasias
  - Lung Cysts (Dicer 1 Mutation)
  - Cystic Nephroma (9-10%, Dicer 1 Mutation)
  - Wilms Tumor (Dicer 1 Mutation)
- Dysplasias
  - Intestinal Hamartomatous Polyps (ileal most common with intussusception)
  - Cystic Hepatic Hamartoma
- Nasal Chondromesenchymal Hamartoma (Dicer 1 Mutation)
- Ciliary Body Medulloepithelioma (Dicer 1 Mutation)
- Ovarian Fibroma (Dicer 1 Mutation)
- Childhood Cancers
  - Rhabdomyosarcoma (Dicer 1 mutation)
  - Other Sarcomas
  - Neuroblastoma, Medulloblastoma, Other CNS Tumors
  - Leukemias
  - Gonadal Tumors
    - Sertoli-Leydig Cell Tumors (Dicer 1 Mutation)
    - Dysgerminoma (Dicer 1 Mutation)
    - Seminoma (Dicer 1 Mutation)
    - Germ Cell Tumors
    - Uterine/Cervical Sarcoa Botryoides (Dicer 1 Mutation)
  - Thyroid
    - Nodular thyroid Hyperplasia (Dicer 1 Mutation)
    - Follicular and Papillary Thyroid Carcinomas (Dicer 1 Mutation)
- Cytogenetic Findings in PPB
  - Trisomy 2 and 8
  - 17p Deletions
  - P53 Mutations
  - Rearrangements in 11p
  - Chromosomal Instability
  - CGH Amplification at 5q33-34, 11q22.2-ter, 15q25-ter, 19q11-13.2
  - CGH Gains 8q11-22.2, 20q
  - CGH Losses 9p21-24, 11p14

**Mucoepidermoid Carcinoma (MEC)**
- Uncommon Tumor Characterized by Combination of Mucus Secreting, Squamous and Intermediate Cell Types
- Frequency of 0.1 to 0.2% of Primary Lung Tumors
- Wide Age Range from 3 to 78 Years with No Gender Bias
- Most Cases in Pediatric Age Group and Accounts for 10% of Primary Lung Tumors in This Group
- Clinical Symptoms
  - Cough, Hemoptysis, Bronchitis, Wheezing
  - Fever, Chest Pain, Clubbing of Fingers
- Clinical and Radiologic Differential Diagnosis
  - Asthma, Pneumonia, Atelectasis
Middle Lobe Syndrome, Pleural Effusion
- Conventional Chest X-ray and CT Not Helpful in Estabishing Diagnosis of Endobronchial MEC
  - Fiberoptic Bronchoscopy Usually Necessary

Pathology Features
- Gross Features
  - Tumor Arises in Large Airways (main and lobar bronchi, trachea)
  - Exophytic Luminal Mass: Sessile, Polypoid, Broad-Based or Pedunculated
  - Cut Surface: Gray-White-Tan with Glistening Mucoid Appearance and May Have Cystic "Degeneration"
  - Variable Size: up to 6cm.
  - Dilated Bronchus With Abundant Luminal Mucoid Substance in Distal Aspect
  - Adjacent Lung Atelectasis or Pneumonia

- Histopathologic Features
  - Mucus-Secreting, Squamous and Intermediate Epithelial Cells
  - Patterns: Glandular, Tubular, Cystic, Nested and Solid
  - Close Association with Adjacent Submucosal Bronchial Glands
  - Mucus-Secreting Cells: Large Light-Blue to Gray Mucinous Cytoplasm
    - Variants: Columnar, Goblet, Cuboidal, Clear Oncocytic
  - Mucus extravasation
  - Squamous Cells: Intercellular Bridges, Usually Lack Keratin Whorls or Pearls
  - Intermediate Cells Lack Specific Differentiation -Usually Polygonal with Bland Nuclei and Abundant Amphophilic to Slightly Eosinophilic Cytoplasm
  - Calcifications and Lymphoid Aggregates
  - Grading of Bronchial MECs
    - High Grade:
      - Necrosis, Nuclear Pleomorphism
      - Mitoses, Solid or Nested Pattern
      - About 50% of Tumors
      - Infiltrate Surrounding Lung Parenchyma
    - Low Grade: Lack of Above Features
      - Typically Confined to Bronchus
      - Not Involve Adjacent Lung Parenchyma

- Molecular & Cytogenetic Features
  - t(11;19)(q21;p13): MECT1-MAML2 (Most Common Translocation [40%])
    - Disrupts Notch Signaling Pathway
    - MECT1 (MEC Translocated 1)
      - Transducer of Regulated cAMP Response Elements Binding 1 (CREB1, TORC1) and Warthin-Mucoepidermoid Tumor Translocation Partner Gene 1 (WAMPT1)
    - MAML2 (Mastermind-Like 2)
      - Encode Fusion Transcript Acts as Co-activator for cAMP Signaling Pathway
      - Linked to Prognosis in Children with MEC
  - t(1;11)(p22;q13): Cyclin D1 Located at 11q13
- Increased Cyclin D1 Expression in 20-30% of MECs
  - Multiple Translocations Most Frequently Involving
    - Chromosomes 1, 5, 7 and 11
    - Reciprocal Translocations
      - t(11;19); t(1;16); t(6;8)
      - t(3;15); t(7;15)
  - Immunophenotype
    - Negative for TTF1 and CK30
    - Positive for CK7, CK5, CK6
- Differential Diagnosis
  - Adenocarcinoma
  - Adenosquamous Carcinoma
  - Metastatic Renal cell Carcinoma
  - PEComa
- Treatment and Prognosis
  - Surgical Resection: Sleeve Resection, Segmental or Localized Resection, Lobectomy, Endoscopic Resection
  - Overall and Disease-Free Survival in Pediatrics
    - 5 Year Survival 100%
    - 10 Year Survival 100%

**Pulmonary Carcinoid (Neuroendocrine Tumors, Well-Differentiated)**

- Although Rare in Children, Pulmonary Carcinoid Diagnosis May Be Delayed Due to Low Clinical Suspicion
- Considered As Low-Grade Neuroendocrine Carcinoma
  - Potential for Aggressive Local Growth
  - Low Potential for Metastatic Disease
- Arise from Kulchitsky Cells in Normal Basal Cell Layer of Bronchial Epithelium
  - Carcinoids Prevalence by Location
    - Foregut
      - Thymus 0.4%
      - Lung, Bronchi, Trachea 29.8%
      - Stomach 4.9%
    - Midgut
      - Small Intestine 30.4%
      - Gallbladder, Pancreas 1.0%
    - Hindgut
      - Appendix 5.1%
      - Colon 9.2%
      - Rectum 14.5%
- Endobronchial Obstructive Mass in Preadolescents and Adolescents
- Symptoms
  - Wheezing, Cough, Hemoptysis, Pneumonia, Pleuritic Pain, Dyspnea
  - Carcinoid Syndrome Rare in Absence of Metastatic Disease and Rare in Bronchial Carcinoid
  - Cushing's Syndrome in 4% (hypertension, cushingoid habitus, muscle weakness, hypokalemic alkalosis)
- Arise Within Lobar (75%) or Mainstem (10%) Bronchi & Lung Parenchyma (15%)
- Pathology Features
  - Cut Surface Firm, Homogenous Tan with Foci of Hemorrhage
- Average Size of 2-4cm
- Infiltrate Underlying Bronchial Wall and Adjacent Lung Parenchyma in "Iceberg" Pattern
- Sheets, Nests, Cords of Bland Small Cells with Finely Granular (Salt and Pepper) Chromatin, Eosinophilic Cytoplasm and Central Round Nuclei
- Tumor Cells in Background of Fine Vascular Network
- Atypical Carcinoid Associated with >2 mitoses per 10 HPFs
- Metastatic Disease to Regional Lymph Nodes, Liver, Bone and Brain

- **Bronchial Carcinoids May Be Associated with MEN Syndromes- Most Often with Pituitary Tumors**
- **Genomic Alterations**
  - Chromosomal Loss (Deletions): 11p (18%), 11q (36%, MEN1 at 11q13)
  - Chromosomal Gains: 5p (18%), 5q (18%), 7p (9%), 7q (9%), 9q (18%), 16q (18%), 20q (9%)
- **Localized Tumor Invasion or Metastatic Disease in Pediatric Cases: 27%**
- **Survival with Carcinoids ()**
  - Series Including Adults and Children 5 Year 10 Year
    - Typical Carcinoid 87-100% 87-93%
    - Atypical Carcinoid 40-59% 31-59%
    - Metastatic Disease 14-25% NA
  - Survival in Children
    - Overall Survival 94% 92%
    - Disease-Free Survival 97% 97%
- **Treatment**
  - Surgical Resection Treatment of Choice
    - Lobectomy/Pneumonectomy (60-75%)
    - Wedge or Segment Resection & Sleeve Resection
  - Radiation and Chemotherapy Adjuncts in Incomplete Resection, or Unresectable Tumors, Metastatic Disease or Recurrences
  - Chemotherapy with or without Radiation Response Rate of 22%
  - Molecular Targeted Agents
    - Angiogenesis (VEGF, PDGF, mTOR)
    - Bevacizumab, Everolimus, Sunitinib (Advanced Disease)

### Spindle Cell Tumors
- **Congenital Peribronchial Myofibroblastic Tumor**
  - Rare Benign Tumor Occurring in Fetus, Neonate and Infant
  - Other Terminologies: Congenital Mesenchymal Hamartoma of Lung, Bronchopulmonary Leiomyosarcoma, Primary Bronchopulmonary Fibrosarcoma
  - Arise from Pluripotent Mesenchyme Adjacent to Developing Bronchi at 12 weeks Gestation
  - Smooth Muscle and Cartilaginous Differentiation
  - Presents on Ultrasound In Utero or in Neonatal Period
    - Large 5-7 cm Unilateral Mass
    - Mediastinal Shift
    - Polyhydramnios, Hydrops, Respiratory Failure
  - Gross Features
    - Firm, Rubbery Mass
    - Cut Surface Yellow-Tan to Gray Whorled Surface with Fibrous Bands
Histopathologic Features
- Bland Spindle Cells with Large Fascicles That Surround, Displace and Distort Airways
- Irregular Cartilage Adjacent to Entrapped Airways
- Uniform Cellularity

Immunohistochemistry: Diffuse Vimentin and Focal Desmin, MSA, and SMA.

Cytogenetics: Complex Rearrangement of Chromosomes 4, 9, 10 (1 case studied)

Electron Microscopy: Features of Myofibroblastic Origin - Spindled Cells with Dilated Rough Endoplasmic Reticulum, Infrequent Cytoplasmic Filaments, Dense Bodies and Attachment Plaques

Treatment and Outcome
- Complete Surgical Excision
- Respiratory and/or Hemodynamic Compromise Due to Large Tumor Size
- Mortality About 50% in Single Series

Inflammatory Myofibroblastic Tumor (Inflammatory Pseudotumor, Plasma Cell Granuloma)
- Reactive and Neoplastic Tumor Features with Slow Growth
- Presents with Cough and/or Fever (75%) and Asymptomatic in 25%
- Most Children >5 Years of Age
- Radiology: Solitary, Well-Circumscribed Mass (1-12cm)
- Location: Parenchymal (80%) or Endobronchial (20%)
- Histopathology:
  - Proliferation of Bland Spindled Cells with Abundant Cytoplasm
  - Scattered Lymphocytes, Plasma Cells and Eosinophils
- Immunohistochemistry: SMA, MSA, ALK1, P80 (some associated with HHV-8)
- Electron Microscopy: Features of Myofibroblastic Origin - Spindled Cells with Dilated Rough Endoplasmic Reticulum, Infrequent Cytoplasmic Filaments, Dense Bodies and Attachment Plaques
- Cytogenetics/Genetics:
  - Translocation of ALK with Several Partners (TPM3, TPM4, CLTC, RANBP2 [epithelioid variant-aggressive], CARS, ATIC, SEC31L1)
- Treatment:
  - Primarily Surgical Excision
  - Local Recurrence with Incomplete Excision
  - Recurrence and Metastatic Disease May Occur: Re-excision and Oncologic Management

Smooth Muscle Tumors
- EBV-associated in Children with Immune Dysregulation, Auto-Immune Diseases, Immune Suppression, Solid Organ Transplantation, Primary and Secondary Immunodeficiency
- Respiratory Tract and Gastrointestinal Tract Involvement as Single or Multifocal Tumors
- Circumscribed Tumors with Pushing Borders
- Spindle Cell Tumors with Variable Cellularity
- Range from Benign to Atypical to Malignant
EBV (EBER-1) Nuclear Reactivity in All Smooth Muscle Tumor Cells
- CD21 Receptor Infection of Cells

Treatment:
- Excision of Symptomatic Tumors
- Optimize Immune Status - Induce Regression

References:


International Pleuropulmonary Blastoma Website http://www.ppbregistry.org/


