Gastrointestinal Clear Cell Sarcoma-Like GI Tumor

- EWS-CREB1
  \[t(2;22)(q32.3;q12)\]
- EWS-ATF1
  \[t(12;22)(q13;q12)\]
Gastrointestinal Stromal Tumor
- Arises from Interstitial Cells of Cajal – Peristalsis Control
- Resemble Smooth Muscle & Schwann Cells
- 95% C-KIT, 98% DOG1, 70% CD34 Positive; C-Kit Mutation
- Carney’s Triad (gastric GIST, paraganglioma, pulmonary chondroma), Neurofibromatosis Type 1, Carney-Stratakis (paraganglioma, GIST), Familial GIST (germline mutation KIT/PDGFRA)
- STI-571: PDGFRA & c-Kit Mutated Tumors
- BRAF (13%), IGF1R (Most), HIF-1A Targets (Carney-Stratakis) - Also EGFR, MET, NY-ESO

Gastrointestinal Stromal Tumors in Pediatrics
- Represent About 1-2% of GISTs
- Age:
  - >10 yrs 60%
  - <1 yr 20%
  - 1-5yr 12%
  - 6-10yr 8%
- F:M Gender Ratio 1.5:1.0
- Stomach (antrum) 52%
- Small Intestine 20%
- Colon/Rectum 20%
- Size
  - <5cm 20%
  - >5-10 cm 28%
  - >10 cm 24%
- Symptoms
  - GI Bleeding, Abdominal Palpable Mass, Abdominal Distention, Intestinal Obstruction
### TABLE 1. Number and Frequencies of Histologic Features in Both Sexes. Overall Epitheloid Cell Tumors are Most Frequent, but Spindle-cell Tumors are More Frequent in Boys

<table>
<thead>
<tr>
<th>Feature</th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
<th>Σ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Spindle cells</td>
<td>9</td>
<td>23.1</td>
<td>7</td>
<td>43.8</td>
<td>16</td>
<td>27.1</td>
</tr>
<tr>
<td>Epitheloid cells</td>
<td>20</td>
<td>51.3</td>
<td>4</td>
<td>25.0</td>
<td>24</td>
<td>40.7</td>
</tr>
<tr>
<td>Mixed-cell type</td>
<td>10</td>
<td>25.6</td>
<td>5</td>
<td>31.3</td>
<td>15</td>
<td>25.4</td>
</tr>
</tbody>
</table>

### Mimickers of GIST

- **A** Fibromatosis
- **B** Granular Cell Tumor
- **Leiomyoma**
- **Spindle Cell Melanoma**
### TABLE 1. Marker Positivity (%)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD117</td>
<td>95</td>
</tr>
<tr>
<td>CD34</td>
<td>70</td>
</tr>
<tr>
<td>SMA</td>
<td>40</td>
</tr>
<tr>
<td>S100</td>
<td>5</td>
</tr>
<tr>
<td>Desmin</td>
<td>2</td>
</tr>
<tr>
<td>Bcl2</td>
<td>80</td>
</tr>
<tr>
<td>PKCtheta</td>
<td>72–100</td>
</tr>
<tr>
<td>DOG1</td>
<td>98</td>
</tr>
<tr>
<td>WT1</td>
<td>98</td>
</tr>
<tr>
<td>Calretinin</td>
<td>95</td>
</tr>
</tbody>
</table>

### TABLE 2. Electron Microscopic Features of GISTs in Children and Young Adults

<table>
<thead>
<tr>
<th>Case #</th>
<th>Type</th>
<th>Cell Processes</th>
<th>Skinoid Fibers</th>
<th>Cell Junctions</th>
<th>Actin Filaments</th>
<th>Neurosecretory Granules</th>
<th>Microtubules</th>
<th>Intermediate Filaments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>Long filopodia “axenome”-like</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>S</td>
<td>ICP ++ neural-like</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>Long filopodia “axenome”-like</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>E</td>
<td>ICP, rare short microfilament type</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>S</td>
<td>ICP ++ neural-like</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>S</td>
<td>ICP ++ neural-like</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>S</td>
<td>ICP ++ neural-like</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>S</td>
<td>ICP ++ neural-like</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Case number corresponds to the case number in Table 1. ICP = interdigitation cell process; CR cell process.*
Sporadic GIST
- C-Kit & PDGFRA Mutations
  - Rare (10-15%; Most Adults)
  - Gastric & Epithelioid
  - Worse Prognosis
- Carney’s Triad (GIST, Pulmonary Chondroma, Paraganglioma)
  - C-Kit, PDGFRA & SDH Mutations Absent
  - Multicentric GIST
- NF1-Related GIST
  - C-Kit & PDGFRA Mutations Absent
  - Usually Intestinal and Spindled
  - Better Prognosis

C-Kit & PDGFRA Mutations

Table 4. IC<sub>50</sub> values obtained by proliferation inhibition studies

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (nmol/L)</th>
<th>Dasatinib (nmol/L)</th>
<th>Sorafenib (nmol/L)</th>
<th>Nilotinib (nmol/L)</th>
<th>Sunitinib (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS590</td>
<td>63</td>
<td>27</td>
<td>66</td>
<td>44</td>
<td>276</td>
</tr>
<tr>
<td>WT KIT</td>
<td>3,132</td>
<td>316</td>
<td>910</td>
<td>35</td>
<td>245</td>
</tr>
</tbody>
</table>

KIT & PDGFRA Mutations: All GISTS

- KIT Mutations 70-75%
  - Exon 11 deletions 45%
    - Gastric GIST More Aggressive
  - Exon 11 Substitutions 10-15%
    - Codons 557, 559, 560, 576
  - Exon 11 Duplications 5%
    - Gastric GIST, Favorable Prognosis
  - Exon 9 Duplications 5%
    - ALA-TYR 502-503 Duplication
    - Intestinal GIST – Rare in Gastric GIST
  - Exon 13 Substitutions 1%
  - Exon 17 Substitutions 1%
KIT & PDGFRA Mutations: All GISTs

- PDGFRA Mutations 10-15% (Gastric & Duodenal GISTs; Epithelioid Pattern GISTs)
  - Exon 12 Deletions/Substitutions <5%
  - Exon 14 Substitutions 1%
  - Exon 18 Substitutions/Deletions 10%
    - Majority of PDGFRA GISTs
    - Most Common Variant D842V; Imatinib Resistant
- No Kit or PDGFRα Mutation 15-20%
  - Typical Finding in NF1 GISTS, Carney Triad, Carney-Stratakis Syndrome and Pediatric GISTS

Pediatric Vs Adult GIST
### Table 2. Differentially expressed genes in pediatric GISTs in comparison with adult WT GISTs

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene title</th>
<th>Fold change</th>
<th>Chromosomal location</th>
<th>Gene ontology biological process</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRLF1</td>
<td>Cytokine-receptor-like factor 1</td>
<td>186.2</td>
<td>19p12</td>
<td>Antimicrobial humoral response</td>
</tr>
<tr>
<td>BAALC</td>
<td>Brain and acute leukemia, cytoplasmic</td>
<td>40.93</td>
<td>8q22.3</td>
<td></td>
</tr>
<tr>
<td>FGFR4</td>
<td>Fibroblast growth factor 4</td>
<td>18.88</td>
<td>11q33.3</td>
<td>Cell proliferation</td>
</tr>
<tr>
<td>PLAG1</td>
<td>Pleomorphic adenoma gene 1</td>
<td>16.63</td>
<td>8q12</td>
<td></td>
</tr>
<tr>
<td>IGFR1</td>
<td>Insulin-like growth factor 1 receptor</td>
<td>10.06</td>
<td>15q25</td>
<td>Positive regulation of cell proliferation</td>
</tr>
<tr>
<td>FGFR3</td>
<td>Fibroblast growth factor 3</td>
<td>9.913</td>
<td>11q13</td>
<td>Cell proliferation</td>
</tr>
<tr>
<td>GJB8</td>
<td>Glycine receptor, p</td>
<td>17.94</td>
<td>4q31.3</td>
<td>Receptor linked signal transduction</td>
</tr>
<tr>
<td>NEFL</td>
<td>Neurofilament, light polypeptide 68 kDa</td>
<td>15.84</td>
<td>8p21</td>
<td></td>
</tr>
<tr>
<td>NRCAM</td>
<td>Neuronal cell adhesion molecule</td>
<td>14.95</td>
<td>7q21.1</td>
<td>Neuronal migration</td>
</tr>
<tr>
<td>NELL1</td>
<td>NEL-like 1 (chicken)</td>
<td>12.67</td>
<td>11p15.2</td>
<td>Cell adhesion, neurogenesis</td>
</tr>
<tr>
<td>RTN1</td>
<td>Reticulin 1</td>
<td>11.87</td>
<td>14q21</td>
<td>Neuron differentiation</td>
</tr>
<tr>
<td>MAGF4J</td>
<td>Human MAGF-6 antigen (MAGE6)</td>
<td>11.51</td>
<td>Xq28</td>
<td></td>
</tr>
<tr>
<td>RELN</td>
<td>Reelin</td>
<td>8.74</td>
<td>7q22</td>
<td>Cell adhesion, development</td>
</tr>
<tr>
<td>FGFR18</td>
<td>Fibroblast growth factor 18</td>
<td>5.999</td>
<td>5p14</td>
<td>Regulation of transcription</td>
</tr>
</tbody>
</table>

### Table 3. Validation by quantitative reverse transcription-PCR of selective overexpressed genes

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene title</th>
<th>Reverse transcription-PCR</th>
<th>Microarray</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGFR1</td>
<td>Insulin-like growth factor 1 receptor</td>
<td>6.9</td>
<td>10.9</td>
</tr>
<tr>
<td>BAALC</td>
<td>Brain and acute leukemia, cytoplasmic</td>
<td>29.1</td>
<td>40.0</td>
</tr>
<tr>
<td>FGFR4</td>
<td>Fibroblast growth factor 4</td>
<td>5.8</td>
<td>18.9</td>
</tr>
<tr>
<td>PLAG1</td>
<td>Pleomorphic adenoma gene 1</td>
<td>13.5</td>
<td>16.6</td>
</tr>
<tr>
<td>NELL1</td>
<td>NEL-like 1 (chicken)</td>
<td>32.6</td>
<td>12.7</td>
</tr>
</tbody>
</table>

*Fold change is the expression in pediatric GISTs relative to that in the adult WT tumors.

### Table 4. Genes Expressed Differentially in Children and Young Adults Versus the Older Adult Control Group

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>P Value</th>
<th>FC</th>
<th>Location</th>
<th>Molecular Function (GO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIKK1</td>
<td>Phosphatidylinositol 4-kinase, alpha 1 (muscle)</td>
<td>4.6E-09</td>
<td>3.76</td>
<td>Chr:1q21.2</td>
<td>phosphatidylinositol 4-kinase, alpha 1 (muscle)</td>
</tr>
<tr>
<td>ABCG2</td>
<td>ATP-binding cassette, sub-family G, member 2</td>
<td>4.3E-07</td>
<td>-12.25</td>
<td>Chr:1q21.1</td>
<td>ATP-binding cassette, sub-family G, member 2</td>
</tr>
<tr>
<td>RAB3B</td>
<td>RAB3B, member RAS oncogene family</td>
<td>5.0E-07</td>
<td>-22.28</td>
<td>Chr:1q14</td>
<td>RAB3B, member RAS oncogene family</td>
</tr>
<tr>
<td>MTF2</td>
<td>Microphthalmia-associated transcription factor</td>
<td>5.0E-07</td>
<td>2.04</td>
<td>Chr:1q44</td>
<td>Microphthalmia-associated transcription factor</td>
</tr>
<tr>
<td>FZD2</td>
<td>Frizzled homolog 2 (Drosophila)</td>
<td>2.0E-06</td>
<td>12.22</td>
<td>Chr:1q21.1</td>
<td>Frizzled homolog 2 (Drosophila)</td>
</tr>
<tr>
<td>ASGR1</td>
<td>Asialoglycoprotein receptor 1</td>
<td>2.0E-06</td>
<td>14.89</td>
<td>Chr:1q21.3</td>
<td>Asialoglycoprotein receptor 1</td>
</tr>
<tr>
<td>NRG4</td>
<td>Nerve growth factor 4</td>
<td>9.0E-06</td>
<td>16.71</td>
<td>Chr:1q21.1</td>
<td>Nerve growth factor 4</td>
</tr>
<tr>
<td>GPRC5B</td>
<td>G protein-coupled receptor, family C, alpha 5</td>
<td>5.0E-05</td>
<td>2.22</td>
<td>Chr:1q21.1</td>
<td>G protein-coupled receptor, family C, alpha 5</td>
</tr>
<tr>
<td>CDKN3A</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
<td>5.0E-05</td>
<td>2.50</td>
<td>Chr:1q21.1</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
</tr>
<tr>
<td>FOXD1</td>
<td>Forkhead box D1</td>
<td>6.0E-05</td>
<td>13.13</td>
<td>Chr:1q21.1</td>
<td>Forkhead box D1</td>
</tr>
<tr>
<td>DPT</td>
<td>Dermatopontin</td>
<td>8.0E-04</td>
<td>-36.19</td>
<td>Chr:1q21.2</td>
<td>Dermatopontin</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Platelet-derived growth factor receptor alpha</td>
<td>1.0E-05</td>
<td>-39.39</td>
<td>Chr:1q21.1</td>
<td>Platelet-derived growth factor receptor alpha</td>
</tr>
<tr>
<td>IGFR1</td>
<td>Insulin-like growth factor 1 receptor</td>
<td>1.39E-03</td>
<td>14.22</td>
<td>Chr:1q21.1</td>
<td>Insulin-like growth factor 1 receptor</td>
</tr>
<tr>
<td>GPR30</td>
<td>G protein-coupled receptor B</td>
<td>0.00E-03</td>
<td>-16.32</td>
<td>Chr:1q21.3</td>
<td>G protein-coupled receptor B</td>
</tr>
<tr>
<td>ANK3</td>
<td>Ankyrin 3, member of Rassf family</td>
<td>0.00E-05</td>
<td>10.56</td>
<td>Chr:1q21.1</td>
<td>Ankyrin 3, member of Rassf family</td>
</tr>
<tr>
<td>GLI1</td>
<td>GLI1, generator-related 1 (glioma)</td>
<td>0.00E-04</td>
<td>-6.00</td>
<td>Chr:1q21.1</td>
<td>GLI1, generator-related 1 (glioma)</td>
</tr>
</tbody>
</table>

*Selective discriminatory genes are listed according to their gene designation, p value, fold change (FC) pediatric and young adult vs. older adult group, and molecular function.
GIST Pathway

- **Stable genome** (Very few cytogenetic changes)
- **Overexpression of** KIT, PDGFRA, FGFR1, PLCγ1, NTRK1, NTRK3
- **Loss of chromosome 1p, 14q, 22q (early events)**
- **Multiple additional chromosomal aberrations** (including CNVs in chromosomes 2, 4, 6, 8, 10, 15, 18)

**Characteristics**
- Greater % Female
- Epithelioid Morphology
- Gastric
- Multi Focal

**KIT/PDGFRα Wild-type**

**KIT/PDGFRα Mutation**

- Greater % Male
- Spindle Morphology
- Equal Male: Female
- Spindle Morphology
- Single Primary Tumor

---

**GIST**

<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12.4 y</td>
<td>&gt; 40 y</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>2.7:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Most frequent cell type</td>
<td>Epitheloid 40.7%</td>
<td>Spindle 70%</td>
</tr>
<tr>
<td>Receptor mutations</td>
<td>Rare, suggestive of syndromal occurrence</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Chronic anemia 86.4% palpable tumor 11.9% abdominal pain 15.3%</td>
<td>GI-bleeding 40% palpable tumor 40% abdominal pain 20%</td>
</tr>
<tr>
<td>Risk category</td>
<td>Size (cm)</td>
<td>Mitoses (HPF)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>---------------</td>
</tr>
<tr>
<td>Very low risk</td>
<td>&lt;2</td>
<td>≤ 5/50</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5</td>
<td>≤ 5/50</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>≤ 5</td>
<td>5–10/50</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>≤ 5/50</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;5</td>
<td>&gt;5/50</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>Any size</td>
</tr>
</tbody>
</table>

- **Recurrence**
  - Local: 20%
  - Metastatic: 4%

- **Survival**
  - Alive: 80%
  - DOD: 4–13%
  - DOC: 4%
  - Unknown: 12%

---

**Case History**

- 6 Month Old Boy
- Recent Onset of Vomiting, Abdominal Pain & Cramping
- Intermittent Rectal Bleeding
- Diagnostic Imaging:
  - Intussusception
Hamartomatous Polyp??
Wait A Minute.....
- No Mucocutaneous or Nailbed Pigmentation
- LKB1/STK11 Genetic Mutation Testing Negative

Diagnosis:
- Hamartomatous Polyp
- Cystic Nephroma
- ???
PPB Family Tumor Susceptibility Syndrome

- PPB Family Tumor Susceptibility Syndrome: Multiple Tumors Exist or Develop.
  - Bilateral and/or Multifocal Lung Cysts in 15% of children
  - Bilateral Type I PPB In Several Cases
  - Cystic nephroma: Most Common Non-Pulmonary Neoplasm (~10% in PPB Patients or Relatives)
  - *Small Subset: PPB, Cystic Nephroma and Small Bowel Polyps
  - Several PPB Patients with Sertoli-Leydig Cell Ovarian Tumors or Nasal Chondromesenchymal Hamartoma
  - Unique Set of Diseases Different than Other Familial Neoplasia Syndrome

PPB Family Tumor Susceptibility Syndrome

- Treatment-Related Second Malignant Neoplasms
  - Not Different from Other Cancer Survivors
  - 3 PPB Children With Apparent Treatment-Related Malignancies:
    - Glioblastoma Multiforme (radiation PPB brain metastasis)
    - Thyroid Carcinoma After Chest Radiation
    - AML After Chemotherapy for PPB (Alkylation Agents & Etoposide)
Burkitt Lymphoma

- Aggressive B-cell NHL with Extremely High Proliferation Index & Characteristic Tranlocation (8q24- MYC)
- Endemic (most cases) Associated with Early EBV Infection and Increased EBV Viral Loads
  - Promoters: Plasmodium Falciparum, Arbovirus and Plant Tumor Promoters
- Sporadic: EBV in 20-30% of Cases
  - Low Socioeconomic Status and Early EBV Infection
- Immunodeficiency: EBV in 30-40%
  - More Common in HIV: May Occur with High CD4 T-Cell Counts in HIV
  - Polyclonal B-Cell Activation in HIV and Malaria

Burkitt Lymphoma

- Endemic BL
  - 4-10/100,000 Children; 2M:1F
  - Most <15 Years of Age
  - Equatorial Africa & New Papua-Guinea
- Sporadic BL
  - 40% of All Childhood Lymphomas
  - 0.3/100,000 Children, 3M:1F
  - Industrialized Nations
  - Caucasian>Asian or African-American
- Immunodeficiency BL: Low Incidence
  - Decreasing Lymphoma Incidence in HIV Children: Highly Active Anti-Retroviral Therapy
Burkitt Lymphoma

- **Endemic BL:**
  - Jaw/Facial Bones (50-60%), Breast, Abdomen, Bone Marrow (10%)
  - Typically Lack Leukemic Presentation

- **Sporadic BL:**
  - Abdominal Mass (Ileocecal Region)
  - Ovaries, Kidneys, Breasts
  - Jaws Rarely

- **Immunodeficiency BL:**
  - Nodal and Bone Marrow

---

Burkitt Lymphoma

- Often Present with Bulkly Disease (Stage III/IV)
- Symptoms Present for Few Weeks
- Immunophenotype: IgM, B-Cell Antigens (CD19, CD20, CD22, CD79a), CD10, CD38, CD45, Bcl-6, Ki-67 >95%
- Rarely Weak Bcl-2, MUM1/IRF-4 in Subset, Lack TdT
- Recommended IHC Panel: CD10, CD20, Bcl-6, Bcl-2, Ki67, EBER-1 (in situ), EBV-LMP
Burkitt Lymphoma

- Molecular and Cytogenetics
  - MYC Translocations (8q24) with IgH (80%, 14q32), Kappa light Chain (15%, 2p11), Lambda Light Chain (5%, 22q11), NonIg Partners Rare
  - 10% Lack MYC Translocation by FISH Alone
  - Other Genetic and Epigenetic Alterations
    - BAX, P16, p53, p73, p130/Rb2, Bel-6
  - Complex Cytogenetics More Common in Adults
  - Additional Abnormalities Correlate with Poor Prognosis

- Differential Diagnosis:
  - Diffuse Large B Cell Lymphoma
  - Lymphoblastic Leukemia Lymphoma
  - Unclassified B Cell Lymphoma
  - Small Round Cell Tumor: (Ewing Tumor, Neuroblastoma, Rhabdomyosarcoma)
  - Myeloid Sarcoma

- Prognosis: Highly Aggressive, But Curable
  - Better Prognosis for Children than Adults

- Treatment: Intensive Chemotherapy and Intrathecal Prophylaxis
  - Anti-CD20 (Rituximab)
  - Cure Rate Up To 90% Low Stage & 60-80% in Advanced Stage
  - Relapses Typically Occurs 1 Year from Diagnosis

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Carcinoid Tumors: What’s The Big Deal?

- Incidence: 2 per 100,000 per Year
- Pernicious Anemia & Atrophic Gastritis: Carcinoid Tumors (11%)
- Zollinger-Ellison Disease & MEN 1
  - LOH on chromosome 11q13 (MENIN)
  - 26-78% Carcinoid Tumors
- Associated with Other Tumors (13%)

Carcinoid Tumors

- GI carcinoids:
  - Incidental Finding at Appendectomy (1 in 200-300)
  - Recurrent Abdominal Pain
  - Melena and Bleeding (Rectal)
- Bronchopulmonary carcinoids:
  - Hemoptysis, Pneumonia
  - Cough Only
- 76% of Carcinoids Found at Autopsy
Carcinoid Syndrome

- Occurs in 2-20%
  - Flushing Attacks (23-65%)
    - Erythema Upper Body Associated with Other Symptoms
    - Spontaneous or Triggered by Stress, Foods, Exercise
    - May last for minutes or hours
  - Diarrhea (32-75%)
  - Cardiac Manifestations (11-66%)
    - Fibrosis of Endocardium (Heart Failure)
  - Other Symptoms (Asthma-Like Attack, Skin Lesions, Arthralgias, Mental Status Changes)

Pediatric Carcinoid Tumors

- Most Common Tumor of Appendix
- Second Most Common GI Tract Tumor After Lymphoma
- 1:100,000 in Children Per Year
- Acute Appendicitis Common Presenting Symptom
- Usually Localized at Appendix Tip
- Small Localized Tumors: 100% EFS
- Locally Invasive Tumors: Ileocecal Resection Adequate Most Children, No Long-Term Follow-Up Available
Prognostic factors:

Carcinoids

- Tumor Site
  - Appendix > Small Intestine > Colorectal > Liver/Pancreas
- Tumor Size (survival)
  - <1 cm: 100%; 1.1-2.0 cm: 82%; >2 cm: 39%
- Depth of Invasion
- Metastases
  - (Liver Metastases, Unfavorable)
- Mitotic Index
  - <10/10 HPF, Favorable
Appendicæal Carcinoids: Survival

- Small Tumors (<1cm): 100% Event Free Survival (EFS)
- Localized Tumors (regardless of size): 94% EFS
- Regional Metastases: 84.6% EFS
- Distant Metastases: 33.7% EFS
- Slowly Growing Tumor
  - 5-Yr Survival Rate May Not Be Indicative of True Risk for Recurrence
**Carcinoid Treatment**

- Tumor Size < 1 cm
  - Appendectomy Alone
- Tumor Size 1 to 2 cm
  - Unclear
  - Aggressive Surgery With Serosal Invasion
- Tumor Size > 2 cm
  - Full Cancer Surgery
  - Right Hemicolectomy
  - Lymph Nodes

**Smooth Muscle Tumors**

- Arise in Association with Muscularis Mucosae or Propria
- Most Common in Esophagus and Colon
  - Adults: Esophagus with Tiny Seedling Leiomyomas In Inner Muscularis Propria on about 50% of Gastroesophageal Carcinoma Resections
  - Colonic Leiomyomas Typically Found with Screening for Colorectal Adenomas
- Well-Circumscribed, Whorled Cut Surface Similar to Leiomyomas at Other Sites
Smooth Muscle Tumors

- Smooth Muscle Differentiation
- Spindle Cells with Eosinophilic Cytoplasm and Blunt Nuclei
- “Perpendicularly” Oriented Fascicles (Herring Bone-Like)
- Minimal Mitotic Activity
- Immunophenotype:
  - SMA, Desmin, h-Caldesmon >70%
  - Focal: Keratin, EMA, CD34, S100
  - Negative: CD117

Smooth Muscle Tumors

- Pediatric Leiomyomas
  - HIV, Immune Suppression, Immunodeficiency Disorders, Solid Organ Transplantation
  - EBV-Association: CD21 Receptor on Smooth Muscle Cells
  - Tumors Tend To Be Multicentric – Not Mets
  - Involve Parenchyma Organs Rather than Soft Tissue
  - Bland But with Primitive Round Cell Component
  - Variable Mitotic Activity & Lymphocytic Infiltrate
  - May Have Perivascular Myopericytoma Growth Pattern
  - Better Behavior Than Conventional Type
Smooth Muscle Tumors

Differential Diagnosis:
- Gastrointestinal Stromal Tumor, GI Schwannoma, Benign Fibroblastic Polyp (perineurioma), Granular Cell Tumor, Leiomyosarcoma

Prognostic Factors In Pediatrics
- Improvement in Immune Status
  - Highly Active Anti-Retrovirals
  - Decreased Immunosuppression
  - Bone Marrow Transplantation
  - Gene Therapy
- Location, Size, Resectability