Mesenchymal Tumors of the Gastrointestinal Tract

Gastrointestinal Stromal Tumors (GISTs)
Derived from interstitial cells of Cajal
Stains: (+) CD117, DOG1, CD34
Most common in Stomach (60%) followed by Small Bowel (30%)
Most often spindled, but can be epithelioid
Mutually exclusive cKIT (80%) or PDGFRA (10%) receptor tyrosine kinase mutations → Rx target
SDH-mutated → pediatric/familial → Carney-Stratakis syndrome/Carney’s Triad
Epithelioid, multinodular, metastasize to lymph nodes, don’t respond to RTK inhibitor therapy,
but overall more indolent; Characterized by loss of SDHB staining

Neural Origin (arise from myenteric plexus or other nerves)

Schwannoma
Most common in stomach, Stains: (+) S100
Often have a lymphoid cuff, but Verocay bodies and hyalinized vessels often absent (unlike elsewhere)

Mucosal Schwann cell hamartoma
Small, sporadic, benign, colonic polyps
Uniform bland spindled cells expanding lamina propria; Stains: (+) S100

Granular cell tumor
Most common in esophagus, submucosal
Epithelioid to spindled cells with abundant eosinophilic granular cytoplasm highlighted by PASd
Stains: (+) S100, CD68, Inhibin, Calretinin

Mucosal Perineurioma
Typically, colonic, small, and solitary
Bland spindled cells expanding lamina propria and distorting glands; associated with serrated polyps
Stains: (+) EMA (weak), GLUT1

Ganglieneuroma
Benign, can get diffuse/multiple with MEN 2b, Cowden, and NF1
Admixture of Schwann cells and Ganglion cells in lamina propria

Gangliocytic paraganglioma
Most common in second part of the duodenum, mostly benign
3 characteristic elements: 1)Epithelioid neuroendocrine cells (think paraganglioma), 2)Ganglion cells,
3)Spindled Schwann cells
Stains: (+) S100 in Schwann cells, (+) Synaptophysin in neuroendocrine cells

Smooth Muscle Origin
Stains: (+) Desmin, Caldesmon, Actin; (-) Neural markers and GIST markers

Leiomyoma
Benign, Most common in colorectum (< 1 cm, polypoid arising from muscularis mucosae, pedunculated,
asymptomatic) and esophagus (Larger, arising from muscularis propria, symptomatic)
Bland, spindled cells, fascicular architecture
Minimal mitotic activity (<1 per 50 HPF) and no tumor-type necrosis
Leiomyosarcoma
Malignant, similar to leiomyomas, but have necrosis, mitoses, and/or atypia

**Fibroblastic Origin**
**Mesenteric fibromatosis**
Most common in small bowel mesentery; usually large; Can be associated with FAP (APC mutations)
Bland, spindled cells in long, sweeping fascicles
Stains: (+ nuclear) β-catenin, may stain with smooth muscle actin

**Inflammatory fibroid polyp**
Most common in stomach or proximal duodenum; centered in submucosa but extend to mucosa
Spindled to plump cytologically bland stromal cells and associated eosinophils; often myxoid background
Cells proliferate/circle around vessels \(\rightarrow\) “onion-skinning”
Stains: (+) CD34  Often associated PDGFRA mutations

**Inflammatory myofibroblastic tumor**
Usually in children and young adults
Bland, spindled to stellate cells in myxoid to collagenous stroma with associated lymphoplasmacytic inflammation.
Stains: \(~50\%\) stain with ALK (also detect with FISH), variable staining with myoid markers

**Vascular Origin**
**Glomus Tumor**
Derived from modified smooth muscle cells of the perivascular glomus body
Most common in stomach, usually benign
Round, uniform nuclei with pale eosinophilic cytoplasm arranged in sheets and nests
Richly vascular, hyalinized stroma
Stains: (+) Smooth muscle actin

**Hemangioma** \(\rightarrow\) Like in other organs
**Kaposi Sarcoma** \(\rightarrow\) Associated with AIDS and HHV-8
**Angiosarcoma** \(\rightarrow\) Malignant vascular tumor, Stains: (+) ERG, CD31, CD34

**Adipocytic differentiation**
**Lipoma**
**Liposarcoma** \(\rightarrow\) MDM2 amplifications by FISH

**Rare**
**Plexiform Fibromyxoma**
Seem to be limited to stomach and benign
Multinodular tumor centered in muscularis propria composed of bland spindled cells in myxoid stroma

**Gastrointestinal Clear Cell Sarcoma-like tumor (GNET)**
Alveolar/nested architecture; epithelioid to spindled cells with eosinophilic to clear cytoplasm, vesicular chromatin, and prominent nucleoli; scattered multinucleated giant cells; Malignant
Stains: (+) S100, HMB-45, MelanA, and MiTF  FISH: EWSR1 translocation

**Perivascular epithelioid cell tumor (“PEComa”)**
Stains: HMB-45, also often Melan-A (MART-1)
Basic Mesenchymal GI tumor Immunohistochemistry Panel

First Round:

\[
\text{CD117 (c-kit)} \quad \text{DOG1} \\
\text{Desmin} \rightarrow \text{Smooth Muscle tumors} \\
\text{S100} \rightarrow \text{Neural Tumors (and other, rarer, neural crest tumors)}
\]

Second Round (less common tumors):

\[
\text{EMA} \rightarrow \text{Perineurioma} \\
\text{Nuclear } \beta\text{-Catenin} \rightarrow \text{mesenteric fibromatosis} \\
\text{ALK} \rightarrow \text{Inflammatory myofibroblastic tumor} \\
\text{Melan-A} \rightarrow \text{GNET, PEComa} \\
\text{Calretinin, CD68} \rightarrow \text{Granular cell tumor} \\
\text{SMA} \rightarrow \text{if only positive stain with good morphology = Glomus} \\
\text{CD31 or ERG} \rightarrow \text{Vascular tumors} \\
\text{CD34} \rightarrow \text{Vascular tumors, GIST, Inflammatory fibroid polyp, some NF cells}
\]
Gastrointestinal stromal tumor prognosis

Table 1. Prognosis of Gastrointestinal Stromal Tumor (GIST) Based on Long-Term Follow-Up of Observation of 1684 Patients in Armed Forces Institute Studies Prior to Imatinib*

<table>
<thead>
<tr>
<th>Group</th>
<th>Size, cm</th>
<th>Mitotic Rate per 50 HPFs</th>
<th>Gastric GISTS</th>
<th>Small Intestinal GISTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤2</td>
<td>≤5</td>
<td>0 Very low if any</td>
<td>0 Very low if any</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2 ≤5</td>
<td>≤5</td>
<td>1.9 Low</td>
<td>4.3 Low</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;5 ≤10</td>
<td>≤5</td>
<td>3.6 Low</td>
<td>24 Intermediate</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;10</td>
<td>≤5</td>
<td>12 Intermediate</td>
<td>52 High</td>
</tr>
<tr>
<td>4</td>
<td>≤2</td>
<td>&gt;5</td>
<td>0 Low†</td>
<td>50 High†</td>
</tr>
<tr>
<td>5</td>
<td>&gt;2 ≤5</td>
<td>&gt;5</td>
<td>16 Intermediate</td>
<td>73 High</td>
</tr>
<tr>
<td>6a</td>
<td>&gt;5 ≤10</td>
<td>&gt;5</td>
<td>55 High</td>
<td>85 High</td>
</tr>
<tr>
<td>6b</td>
<td>&gt;10</td>
<td>&gt;5</td>
<td>86 High</td>
<td>90 High</td>
</tr>
</tbody>
</table>

* Note significantly worse prognosis in small intestinal GISTs. Based on data from Miettinen et al.26,27 HPFs indicates high-power fields.
† Denotes tumor categories with very small numbers of cases insufficient for prediction of malignant potential.

Miettinen and Lasota, Arch Pathol Lab Med—Vol 130, October 2006