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Mesenchymal Tumors of the Gastrointestinal Tract

Gastrointestinal Stromal Tumors (GISTs)

Derived from interstitial cells of Cajal
Stains: (+) CD117 (cKit), DOG1, CD34
Most common in Stomach (60%) followed by Small Bowel (30%)
Most often spindled, but can be epithelioid or pleomorphic
Mutually exclusive cKIT (80%) or PDGFRA (10%) receptor tyrosine kinase mutations→ often shrink pre-operatively with receptor tyrosine kinase inhibitors (e.g., imatinib)
Increased in NF1 patients
Can estimate risk of progressive disease (see table at end of guide)

SDH-mutated type (without a cKit mutation)→ pediatric/familial
- Carney-Stathakis syndrome→ paraganglioma and GIST with germline SDH mutation
- Carney's Triad→ GIST, pulmonary chondroma, paraganglioma, somatic SDH mutation
- Epithelioid, multinodular, metastasize to lymph nodes, don't respond to RTK inhibitor therapy (no Ckit mutations!), but overall more indolent; Characterized by loss of SDHB IHC staining

Neural Origin (arise from myenteric plexus or other nerves)

Schwannoma
Benign nerve sheath tumor with Schwannian differentiation
Most common in stomach in muscularis propria. Well-circumscribed. Unencapsulated.
Spindle cell proliferation with varying cellularity. Often have a lymphoid cuff, but Verocay bodies and hyalinized vessels often absent (unlike elsewhere)
Stains: (+) S100 (strong, diffuse)

Mucosal Schwann cell hamartoma
Small, sporadic, benign, presenting as a colon polyp
Uniform bland spindled cells expanding lamina propria between crypts.
Stains: (+) S100

Granular cell tumor
Benign neoplasm with neuroectodermal differentiation.
Often esophagus, submucosal→ look out for pseudoepitheliomatous hyperplasia (SCC mimic)
Epithelioid to spindled cells with abundant eosinophilic granular cytoplasm highlighted by PASd
Full of lysosomes due to inactivating mutations in ATP6AP1 or 2 (makes it so can't break down lysosomes)→ granular appearance
Stains: (+) S100, CD68, Inhibin, Calretinin

Perineurioma
Benign peripheral nerve sheath tumor composed of cells with perineurial differentiation
Typically, colonic, small, and solitary. Can be associated with a serrated polyps.
Bland spindled cells expanding lamina propria and distorting glands.
Stains: (+) EMA (weak), GLUT1, clauidin-1

Ganglioneuroma
Benign neoplasm composed of mature ganglion cells and nerves (unmyelinated axons with Schwann cells). Usually in the colorectum.

When multiple/diffuse and/or syndrome-related (MEN 2b, Cowden, and NF1)→ Ganglioneuromatosis
Usually sporadic, small mucosal polyps detected incidentally.
Diffuse mural involvement strongly associated with MEN2B (RET mutation)
Stains: Schwann cells (+) S100, Ganglion cells (+) Synaptophysin, neurofilament

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

Muscle Origin

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

Leiomyoma
Benign smooth muscle tumors, 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 smooth muscle tumors, aggressive. Spindle cell neoplasms with atypia, mitoses, and/or necrosis.

If multiple smooth muscle tumors in an immunosuppressed patient→ consider an EBV-associated smooth muscle tumor

Rhabdomyosarcoma
Malignant tumors with skeletal muscle differentiation.
Stains: (+) Myogenin, MyoD1
Multiple subtypes (see small round blue cell tumor guide)

Fibroblastic Origin

Fibromatosis ("Desmoid fibromatosis" or "Mesenteric fibromatosis")
Most common in small bowel mesentery; usually large
Bland, spindled cells in long, sweeping fascicles. Infiltrative growth.
Locally aggressive, non-metastasizing.
Stains: + nuclear β-catenin (80%), may stain with smooth muscle actin
WNT/ β-catenin signaling dysregulation due to somatic CTNNB1 or germline APC mutations (so see with Familial Adenomatous Polyposis)

Inflammatory fibroid polyp
Benign. Most common in stomach, proximal duodenum, or ileum→ can cause intussusception
Centered in submucosa but extend to mucosa
Spindled to plump cytologically bland spindled cells and associated eosinophils and lymphocytes; often myxoid background. Cells proliferate/circle around vessels→"onion-skinning"
Stains: (+) CD34
Molecular: PDGFRA mutations

Inflammatory myofibroblastic tumor ("IMT")
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
Molecular: ~60% have ALK rearrangements; ~5% show ROS1 fusions
Low risk for recurrence; very rare metastases

Solitary Fibrous Tumor ("SFT")
Adults with slow-growing mass in any anatomic site
Bland ovoid to spindled cells with "patternless pattern" (haphazard), "Stag-horn vessels," variable cellularity and collagen.
Stains: (+) STAT6, CD34
Molecular: NAB2-STAT6 rearrangement→ best seen with STAT6 IHC

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 polygonal cytoplasm arranged in sheets and nests
Richly vascular, hyalinized stroma. Can be mistaken for NET morphologically.
Stains: (+) Smooth muscle actin

Lymphangioma
Benign, lymphatic tumor.
Most common in small intestine. Often congenital, presenting in childhood.
Thin-walled, dilated spaces with a single layer of endothelial-lined lymphatic spaces containing chylous or serous material.
Lymphangiomatosis—multicentric or extensively infiltrating lymphangioma.
Stains: (+) CD31, D2-40

Hemangioma
Can be in any organ. Benign, but can bleed. Varying morphologies with different caliber vessels (e.g., Cavernous)
Should NOT see: Papillary growth, multilayering, cellular atypia, mitoses, and necrosis
Stains: (+) ERG, CD31, CD34

Kaposi Sarcoma
HHV8-associated vascular neoplasm often occurring in immunocompromised patients (classically AIDS)
Infiltrating small, irregular vascular channels and fascicles of non-pleomorphic spindled epithelioid cells.
Erythrocyte containing clefts. Hyaline globules. Associated inflammation.
Stains: (+) CD31, CD34, ERG, HHV8 (LANA-1)
Often asymptomatic, can bleed

Angiosarcoma
Malignant vascular tumor with endothelial differentiation. Aggressive.
Often high-grade malignant tumors with nuclear atypia, mitoses, and necrosis. Can be epithelioid.
Variably vasoformative, with anastomosing vessels to solid sheet-like growth

Stains: (+) ERG, CD31, CD34; Epithelioid angiosarcomas can stain with CK

Adipocytic differentiation

Lipoma
Benign tumor composed of mature adipocytes.
Can occur anywhere. Most common in colon in submucosa. If mucosal→ possible Cowden's syndrome

Well-differentiated liposarcoma/Atypical lipomatous tumor
Malignant adipocytic tumor.
Often lipoblasts or atypical cells with smudged nuclei in fibrous septae
MDM2 amplifications by FISH

Rare/Other

Plexiform Fibromyxoma
Benign tumors that arise in the stomach antrum/pylorus.
Multinodular, centered in muscularis propria composed of bland spindled cells in myxoid stroma.
Non-specific, mostly negative IHC profile.

Synovial Sarcoma
Malignant spindle cell ("monophasic"), possibly with epithelioid to glandular component ("biphasic")
Uniform spindle cells with almost no matrix and somewhat vesicular nuclei.
Characteristic SS18 gene rearrangements.
Patchy keratin and EMA.

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

Perivascular epithelioid cell tumor ("PEComa")
Mostly epithelioid cells with some spindled component. Cytoplasm granular, eosinophilic to clear.
Admixture of adipocytes, epithelioid cells, and intimately associated thick-walled blood vessels.
Variable expression of smooth muscle and melanocytic markers
Stains: HMB-45, also often Melan-A, MITF (and smooth muscle markers)
Marked nuclear atypia and mitoses→ risk of metastatic behavior

Sclerosing Mesenteritis
Idiopathic fibroinflammatory tumefactive lesion (likely non-neoplastic)
Includes a combination of: 1)Fibrosis, 2)Fat necrosis, and 3)Chronic inflammation (lymphocytes, histiocytes, and occasional germinal centers)
Usually self-limited and cured by surgery

Calcifying Fibrous Tumor
Benign neoplasms composed of hypocellular dense stromal collagen with psammomatous and dystrophic calcifications and patchy chronic inflammation. Well-circumscribed, unencapsulated.
Usually affects children and young adults.
IHC: (+)CD34

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Basic Mesenchymal GI tumor Immunohistochemistry Panel

First Round:

CD117 (ckit) } →GIST
DOG1 }

Desmin → Smooth Muscle tumors

S100 → Neural Tumors (and other, rarer, neural crest tumors)

Second Round (less common tumors):

EMA→ Perineurioma

Nuclear β–Catenin→ Fibromatosis

ALK→ Inflammatory myofibroblastic tumor

Melan-A→ GNET, PEComa

Calretinin, CD68→ Granular cell tumor

SMA→ Myofibroblastic or muscle differentiation (or Glomus)

CD31 or ERG → Vascular tumors

CD34→ 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*

	Tumor Parameters		Patients With Progressive Disease During Follow-Up and Characterization of Malignant Potential, %	
Group	Size, cm	Mitotic Rate per 50 HPFs	Gastric GISTs	Small Intestinal GISTs
1	≤2	≤5	0 Very low if any	0 Very low if any
2	>2 ≤5	≤5	1.9 Low	4.3 Low
3a	>5 ≤10	≤5	3.6 Low	24 Intermediate
3b	>10	≤5	12 Intermediate	52 High
4	≤2	>5	0 Low†	50 High†
5	>2 ≤5	>5	16 Intermediate	73 High
6a	>5 ≤10	>5	55 High	85 High
6b	>10	>5	86 High	90 High

* Note significantly worse prognosis in small intestinal GISTs. Based on data from Miettinen et al.[28,29] 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