

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 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, claudin-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

Plexiform Fibromyxoma

Benign tumors that arise in the stomach antrum/pylorus

Multinodular, centered in muscularis propria composed of bland spindled cells in myxoid stroma

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

Basic Mesenchymal GI tumor Immunohistochemistry Panel

First Round:

CD117 (ckit)
DOG1 } → GIST

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*

Group	Tumor Parameters		Patients With Progressive Disease During Follow-Up and Characterization of Malignant Potential, %			
	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.