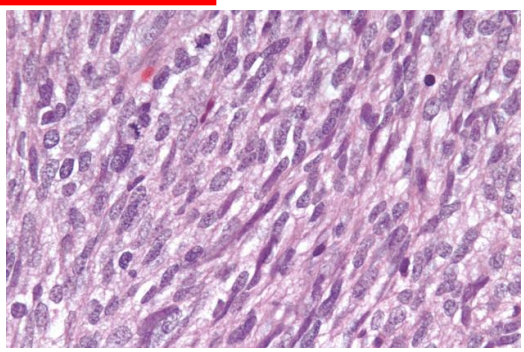
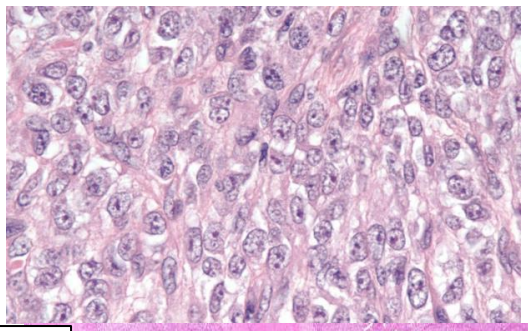
Mesenchymal tumors of the GI Tract

Gastrointestinal Stromal Tumor (GIST)



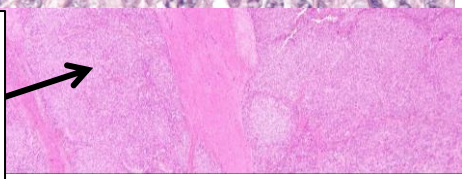


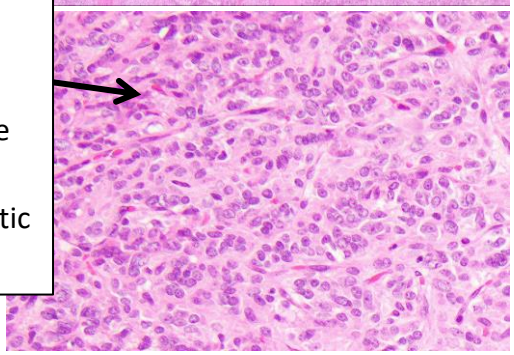
Derived from **interstitial cells of Cajal** (pacemaker cells of GI tract)
Most common in Stomach (60%) followed by Small Bowel (30%)
Most often **spindled**, but can be epithelioid or pleomorphic
Intramural, submucosal, or subserosal location

Molecular: Mutually exclusive **cKIT** (80%) or **PDGFRA** (10%) receptor tyrosine kinase mutations→ Can shrink pre-operatively with receptor tyrosine kinase inhibitors (e.g., imatinib)
Mainstay therapy = surgery, but can use RTK inhibitors if metastatic/recurrent
Increased in NF1 patients

IHC: **(+) CD117 (cKit), DOG1**, CD34

Variable behavior→ estimate risk of progressive disease based on size, mitoses, location (see table below)





SDH-mutated GIST (without a cKit mutation)→ **pediatric**/familial
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**

Carney-Stathakis syndrome→ paraganglioma and GIST with germline SDH mutation
Carney's Triad→ GIST, pulmonary chondroma, paraganglioma, somatic SDH mutation

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

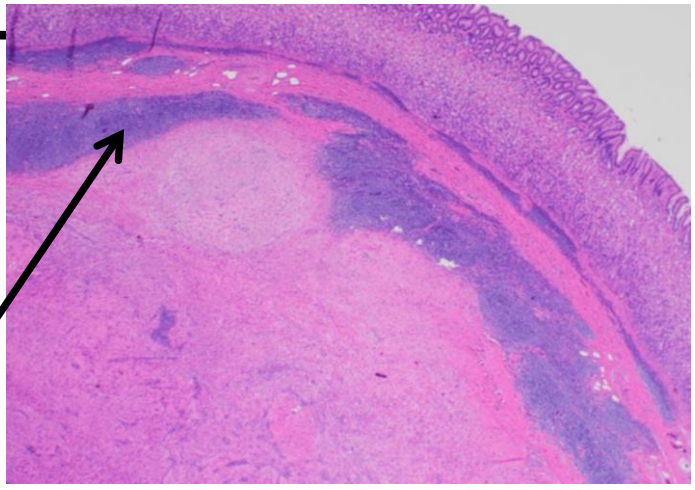
* Note significantly worse prognosis in small intestinal GISTs. Based on data from Miettinen et al.[28,29] HPFs indicates high-power fields.
† Denotes tumor categories with very small numbers of cases insufficient for prediction of malignant potential.

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

Neural Origin

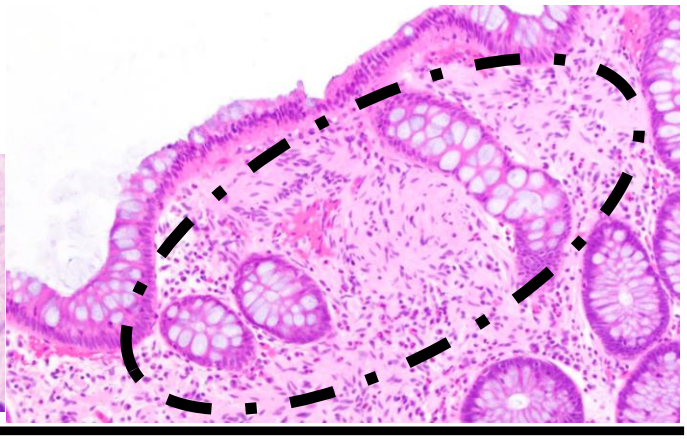
Arise from myenteric plexus or other nerves

Schwannoma

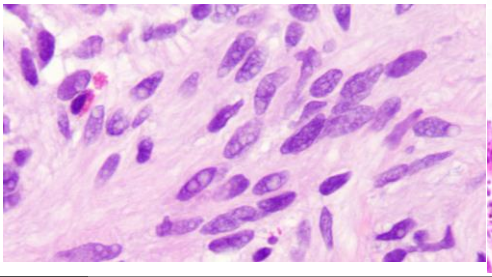


Benign nerve sheath tumor.
Schwannian differentiation
Most common in **stomach** in submucosa or muscle.
Well-circumscribed. Unencapsulated.
Spindle cell proliferation with varying cellularity.
Often have a **lymphoid cuff,** but Verocay bodies and hyalinized vessels often *absent* (unlike elsewhere).
Rare subtype: Microcystic/reticular
IHC: **(+) S100** (strong, diffuse), Often (+) GFAP

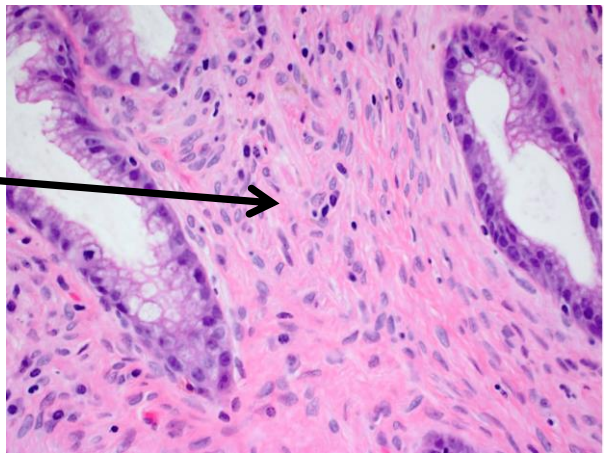
Mucosal Schwann cell hamartoma



Small, sporadic, benign. Present as a colon **polyp**
Uniform bland spindled cells expanding lamina propria between crypts.
IHC**: (+) S100**



Perineurioma

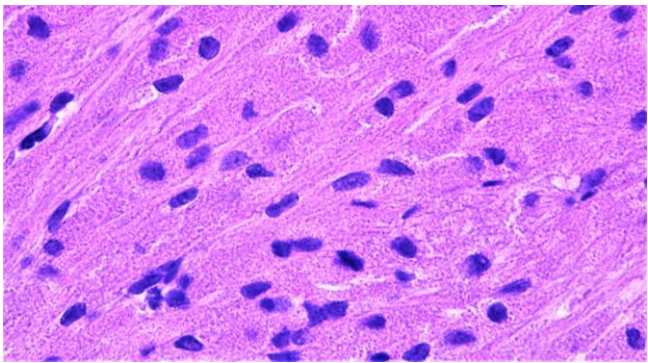


Benign peripheral nerve sheath tumor composed of cells with **perineurial differentiation.**
Typically, colonic, small, and solitary **polyp**.
Bland spindled cells expanding lamina propria and distorting glands. Can have whorls.
IHC: (+) EMA (weak), GLUT1, claudin-1

Perineurial-*like* proliferations can be associated with a serrated polyps (these are likely reactive changes)

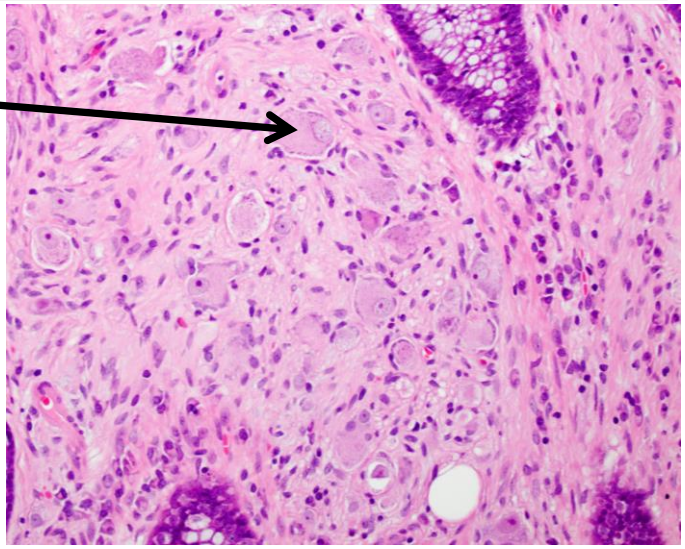
Sometimes tumors with this morphology don't express any markers→ can call **"Benign fibroblastic Polyp"**

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
ATP6AP1 or 2 mutations
IHC**: (+) S100, CD68,** Inhibin, Calretinin

Ganglioneuroma

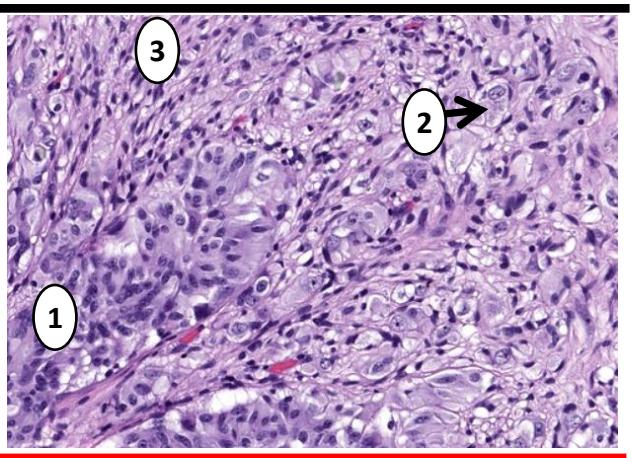


Benign neoplasm composed of **mature ganglion cells** and **nerves** (unmyelinated axons with Schwann cells).
Usually in the colorectum.
IHC: **Schwann cells (+) S100,**
Ganglion cells (+) Synaptophysin, calretinin

Usually sporadic, small mucosal polyps detected incidentally.

When multiple/diffuse and/or syndrome-related (MEN 2B, Cowden, and NF1)→ ***Ganglioneuromatosis***

Gangliocytic paraganglioma

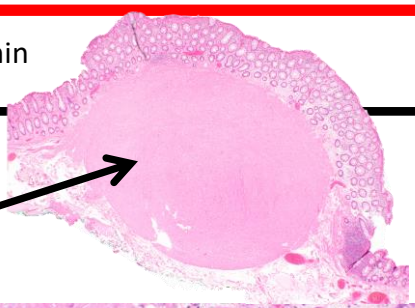


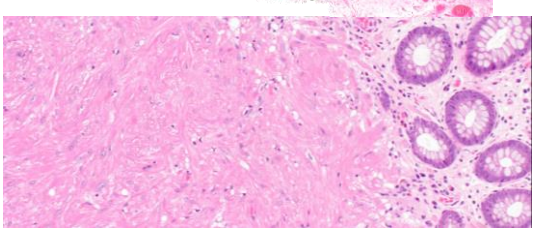
Most common in second part of the **duodenum**,
mostly benign
3 characteristic elements:
1) **Epithelioid neuroendocrine cells** *(like paraganglioma)*,
2) **Ganglion cells,**
3) **Spindled Schwann cells**
Stains: (+) S100 in Schwann cells, (+) Synaptophysin in neuroendocrine cells

Muscle Origin

Stains: (+) Desmin, Caldesmon, SMA, Calponin

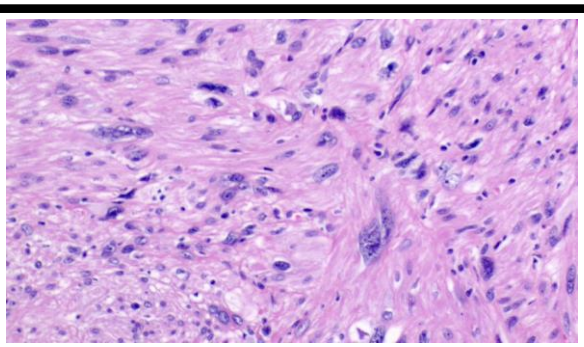
Leiomyoma





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

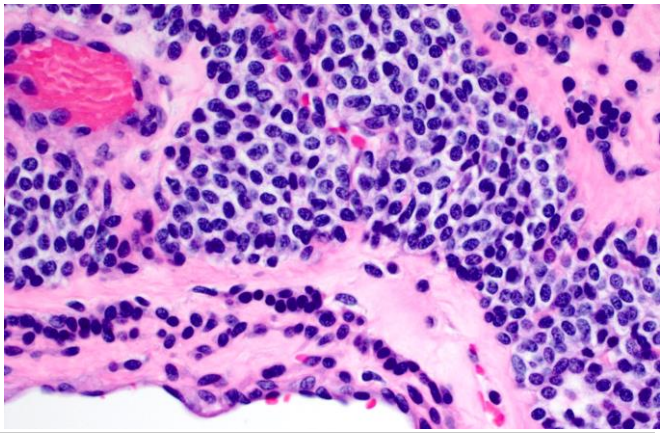
Leiomyosarcoma



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

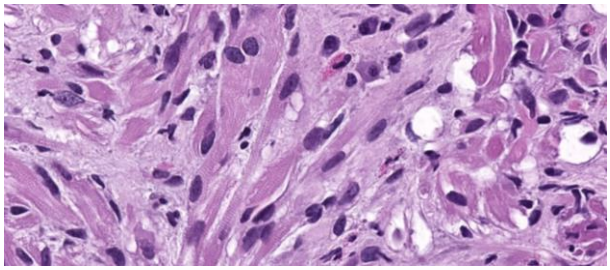
If multiple smooth muscle tumors in an immunosuppressed patient→ consider an EBV-associated smooth muscle tumor

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: **(+) SMA,** (+/-)Caldesmon;
Focal synaptophysin is a potential pitfall!

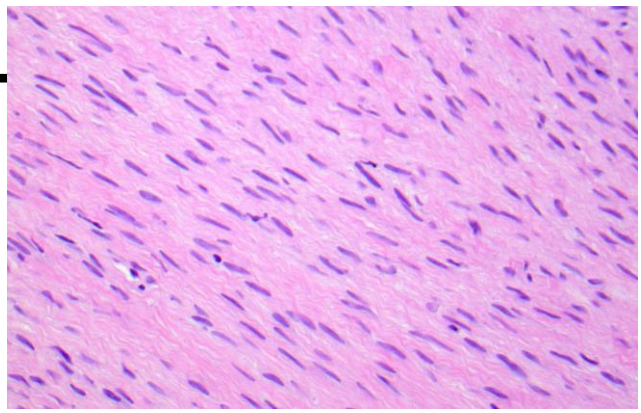
Rhabdomyosarcoma

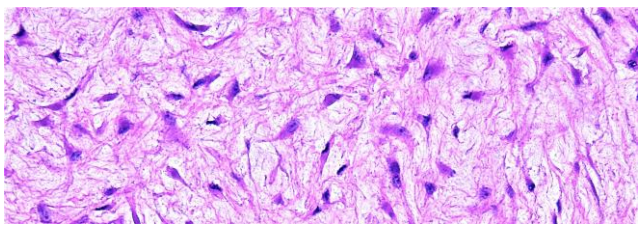


Malignant tumors with **skeletal muscle differentiation**.
Stains: **(+) Myogenin, MyoD1**
Multiple subtypes (Embryonal pictured here with striated "strap" cells; see soft tissue handout for more)

Fibroblastic Origin

Desmoid Fibromatosis





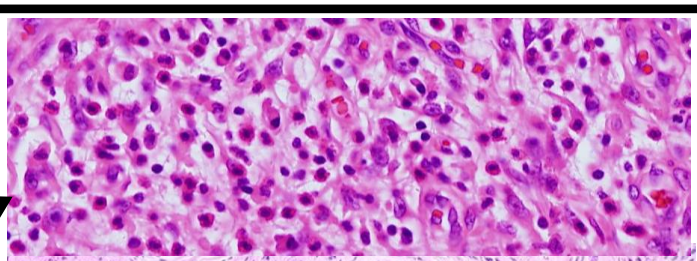
Bland, spindled to stellate cells. Pale chromatin.
Sweeping fascicles. **Infiltrative growth**. Few mitoses.
Most common in small bowel mesentery; usually large.

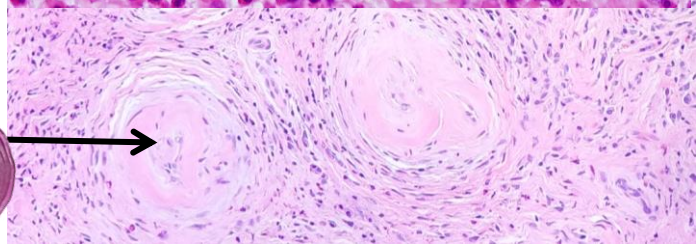
Locally aggressive, non-metastasizing.

IHC: (+) SMA, **nuclear β-catenin (80%),**

WNT/ β-catenin signaling dysregulation due to somatic CTNNB1 or germline APC mutations (so see with Familial Adenomatous Polyposis)

Inflammatory fibroid polyp

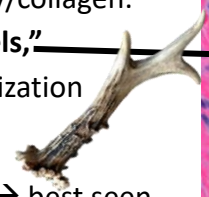




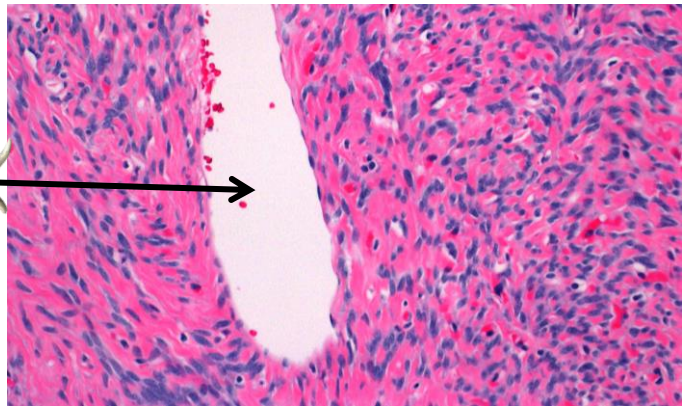
Benign. Most common in stomach, proximal duodenum, or ileum→ can cause intussusception
Centered in submucosa but extend to mucosa
Spindled to plump cytologically bland cells and associated **eosinophils** and lymphocytes;
often myxoid background. Cells proliferate/circle around vessels, whorled→ **"onion-skinning"**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

Solitary Fibrous Tumor *"SFT"*

Bland ovoid to spindled cells with "patternless pattern" (haphazard), variable cellularity/collagen.
thin-walled, branching **"Stag-horn vessels,"**
Variable stromal and perivascular hyalinization

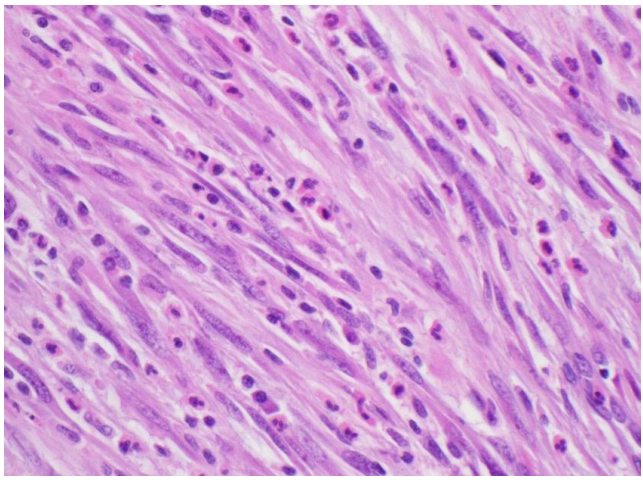


IHC: (+) **STAT6**, CD34
Molecular: NAB2-STAT6 rearrangement→ best seen with STAT6 IHC



Inflammatory Myofibroblastic Tumor *"IMT"*

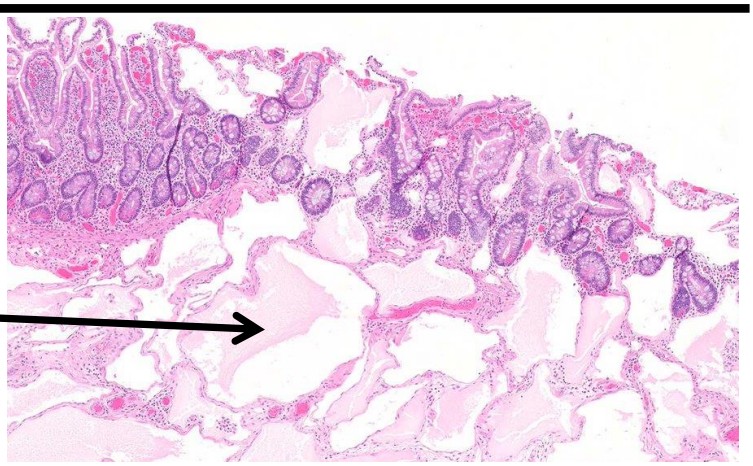
Usually in children and young adults
Plump spindled to stellate cells in myxoid to collagenous stroma with associated **lymphoplasmacytic inflammation**. Fibroblastic/myofibroblastic.
Vesicular chromatin, small nucleoli.
IHC: (+)SMA, **~60% stain with ALK**; (-/+) Desmin
Molecular: ~60% have ALK rearrangements;
~5% show ROS1 fusions
Low risk for recurrence; very rare metastases



Vascular Origin

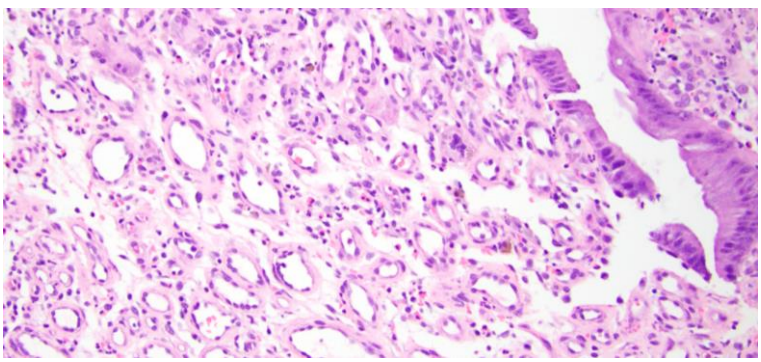
Lymphangioma

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,

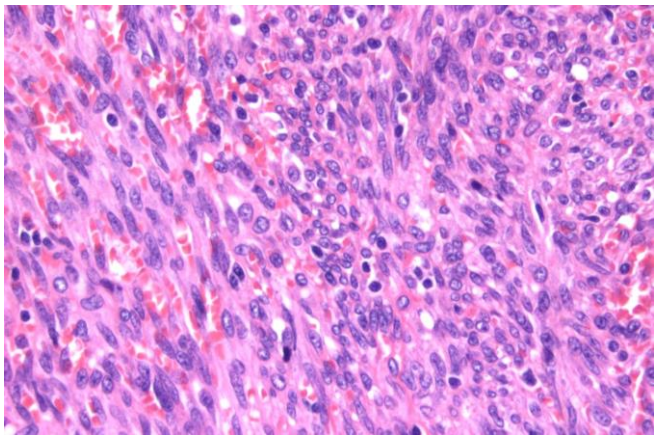


Hemangioma

Benign vascular tumor, 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, FLI1; Ki67<10%

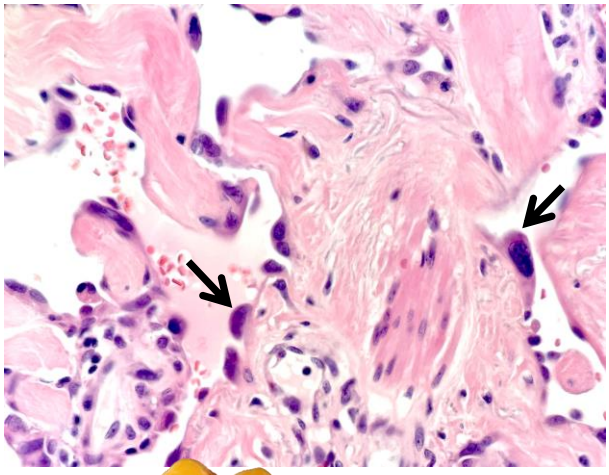


Kaposi Sarcoma



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.
IHC: (+) CD31, CD34, ERG, **HHV8** (LANA-1)
Often asymptomatic, can bleed

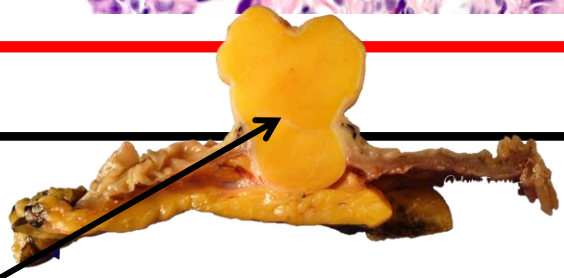
Angiosarcoma



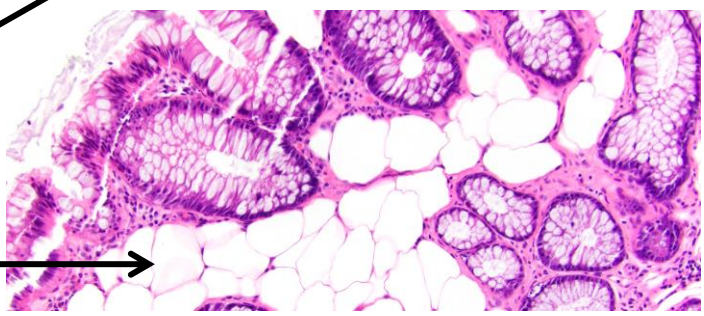
Malignant vascular tumor with endothelial differentiation. **Aggressive**.
Often high-grade tumors with nuclear atypia, mitoses, and necrosis. Hobnailed (→) or papillary projections
Variably vasoformative, with anastomosing vessels to solid sheet-like growth. Infiltrative, dissecting, complex growth.
IHC: (+) ERG, CD31, CD34; High Ki67 (usu. >40%)
Epithelioid angiosarcomas can stain with CK

Adipocytic Origin

Lipoma

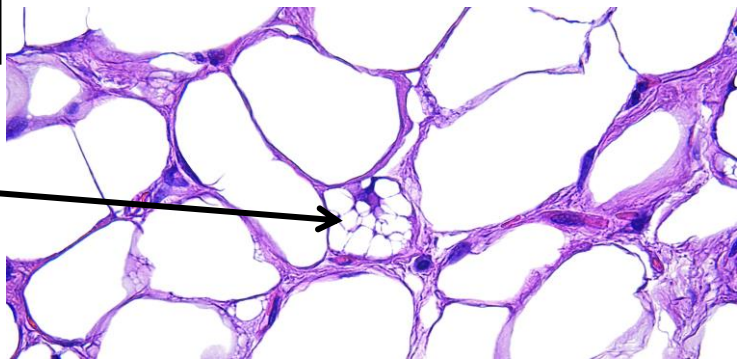


Benign tumor composed of mature adipocytes.
No cytologic atypia. Can occur anywhere. Most common in colon in submucosa. Often grossly recognizable. "Pillow sign" on endoscopy.



If mucosal→ associated with Cowden's syndrome (but easy to confuse with pseudolipomatosis, so consider doing S100 to confirm it's fat)

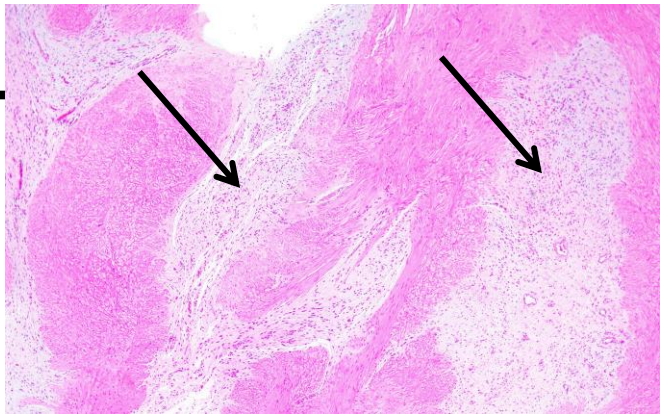
Well-differentiated liposarcoma



Malignant adipocytic tumor.
Often lipoblasts or atypical cells with smudged nuclei in fibrous septae
MDM2 amplifications by FISH.
Relatively common in retroperitoneum, but rare in GI tract proper.

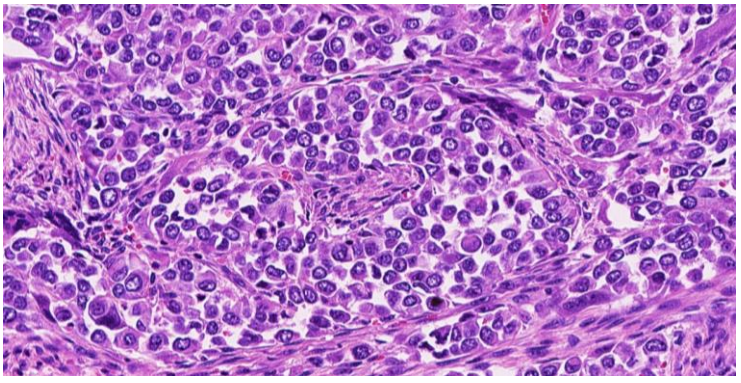
Rare/Other

Plexiform Fibromyxoma



Benign tumors that arise in the **stomach** antrum/pylorus.
Multinodular, centered in muscularis propria composed of bland spindled cells in myxoid stroma.
IHC: Non-specific, mostly negative. (+) SMA
Molecular: MALAT1-GLI1 fusion

Gastrointestinal Clear Cell Sarcoma / GNET

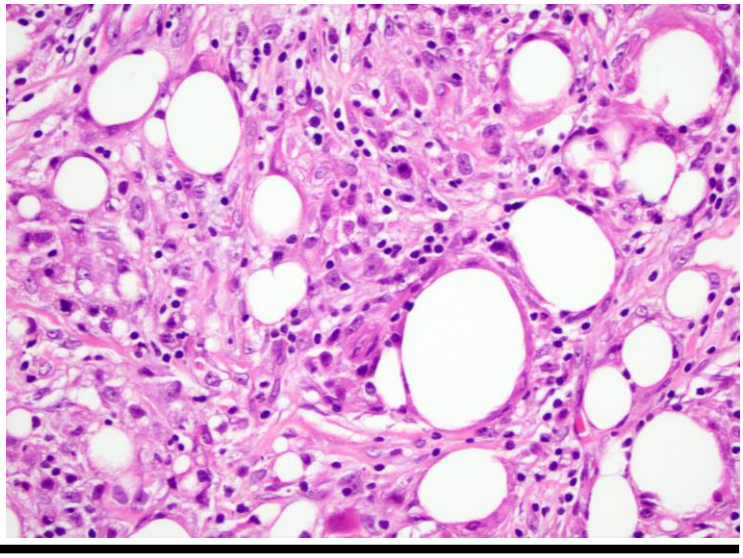


Malignant. Neuro*ec*todermal differentiation → so "GNET" for GI neuroectodermal tumor

Alveolar/nested architecture; epithelioid to spindled cells with eosinophilic to clear cytoplasm, vesicular chromatin, and scattered multinucleated giant cells.

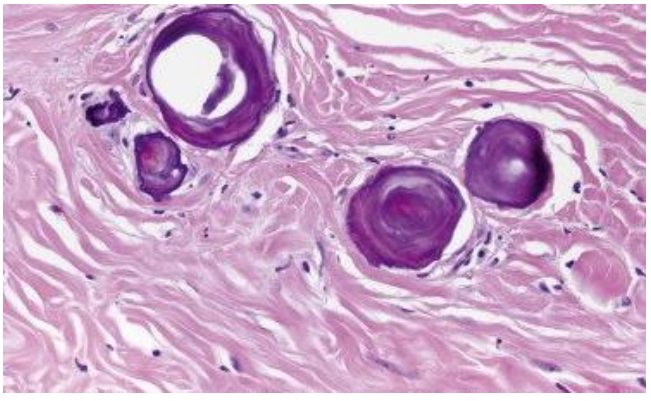
IHC: **(+) S100, SOX10**, CD56, Synaptophysin
(-) HMB-45, MelanA, and MiTF (unlike usual CCS)
FISH: EWSR1 translocation (with ATF1 or CREB1)

Sclerosing Mesenteritis



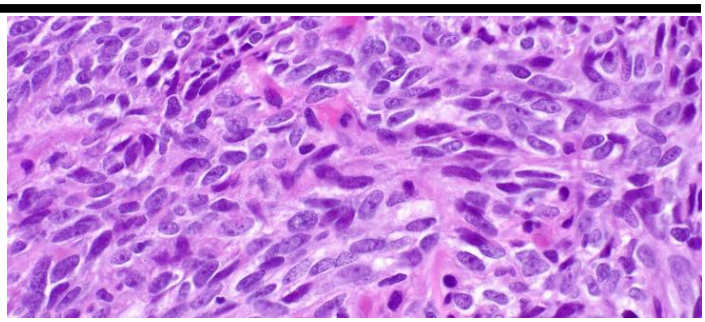
Idiopathic fibroinflammatory tumefactive lesion (likely non-neoplastic)
Includes a combination of:
1)Fibrosis,
2)Fat necrosis, and
3)Chronic inflammation (lymphocytes, histiocytes, and occasional germinal centers)
Usually self-limited and cured by surgery

Calcifying Fibrous Tumor



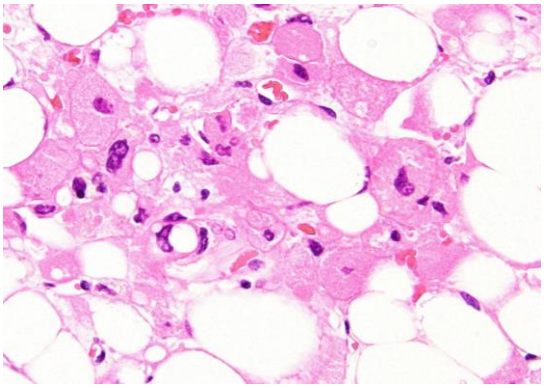
Benign neoplasms composed of hypocellular dense stromal collagen with psammomatous and dystrophic calcifications and patchy chronic inflammation.
Well-circumscribed, unencapsulated.
Usually affects children and young adults.
IHC: (+)CD34

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.
IHC: Patchy keratin and EMA.

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
IHC: (+) HMB-45 & Cathepsin K, also often Melan-A, MITF (and smooth muscle markers)
Marked nuclear atypia and mitoses→ risk of metastatic behavior

IHC Panels

First Round (most common DXs):

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 and HMB45 → 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