

# Mesenchymal tumors of the GI Tract

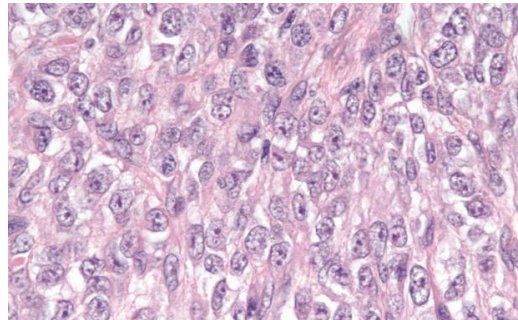
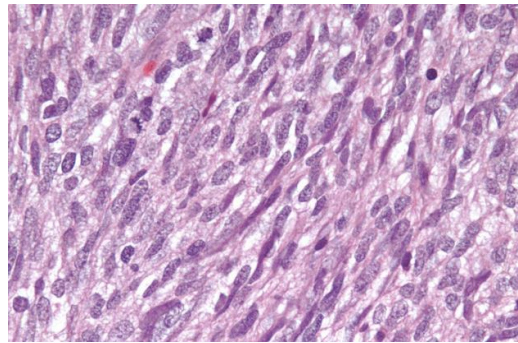
## Gastrointestinal Stromal Tumor (GIST)

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)

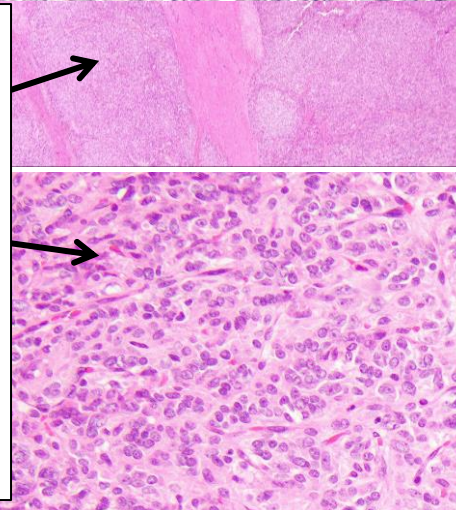


**SDH-mutated GIST** (without a cKit mutation) → **pediatric/familial**  
**Epithelioid, multinodular, metastasize to lymph nodes**, don't  
 respond to RTK inhibitor therapy (no cKit mutations!), but overall  
**more indolent**;

Characterized by **loss of SDHB IHC staining**  
 (CAP recommends screening all gastric GIST with SDHB)

**Carney-Stathakis syndrome** → paraganglioma and GIST with germline  
 SDH mutation

**Carney's Triad** → GIST, pulmonary chondroma, paraganglioma, somatic  
 SDH mutation



### Guidelines for Risk Assessment of Primary GIST (on resection, therapy-naïve)

Tumor Parameters		Risk of Progressive Disease (metastases/death) (%)			
Mitotic Rate	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5 per 5 mm <sup>2</sup>	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (12%)	High (34%)	High (52%)	High (57%)
>5 per 5 mm <sup>2</sup>	≤2 cm	None	(Insufficient data)	High	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Adapted from: CAP Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST) Version: 4.3.0.0

# Neural Origin

Arise from myenteric plexus or other nerves

## Schwannoma

### Benign nerve sheath tumor.

Schwannian differentiation

Most common in **stomach** in submucosa or muscle.

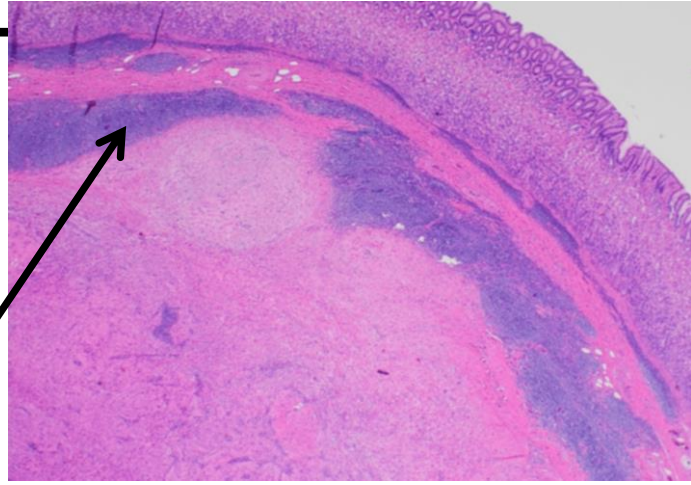
Well-circumscribed. Unencapsulated.

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

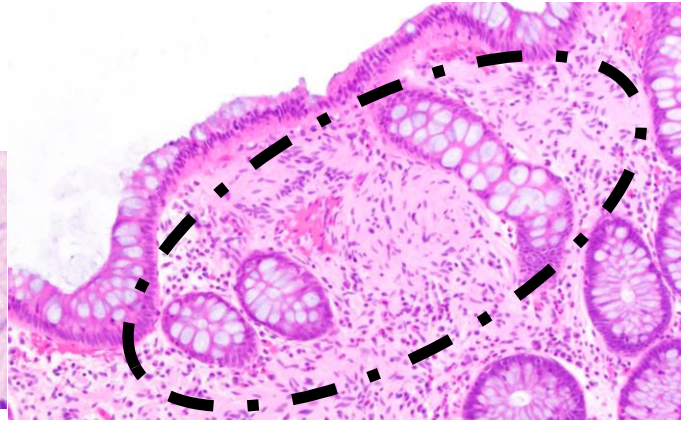
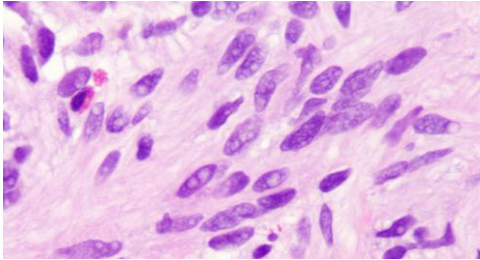


## Mucosal Schwann cell hamartoma

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**.

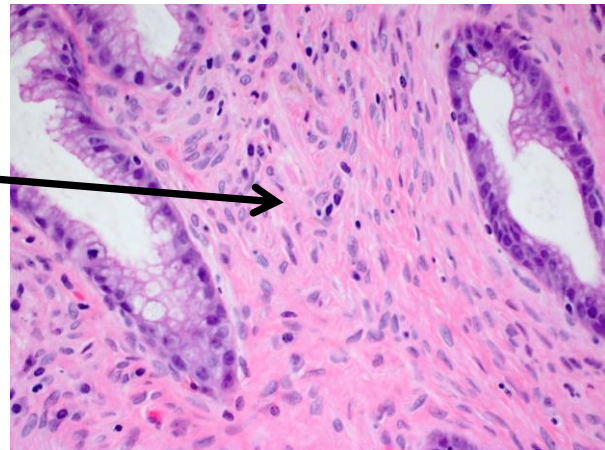
Typically, colonic, small, and solitary **polyp**.

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.

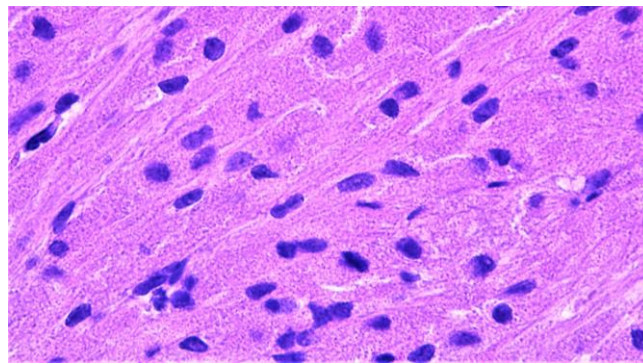
Often **esophagus**, submucosal → look out for

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**





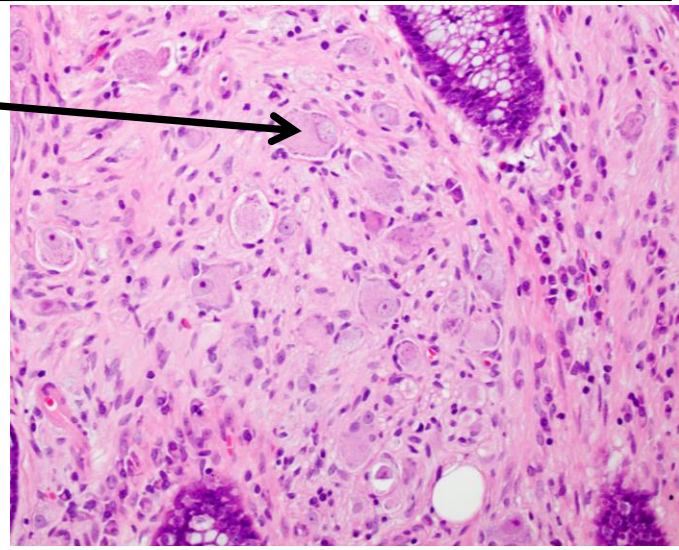
## Ganglioneuroma

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**



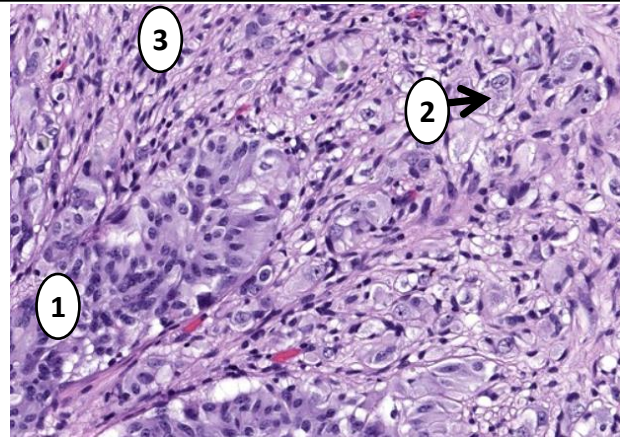
## Gangliocytic paraganglioma

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

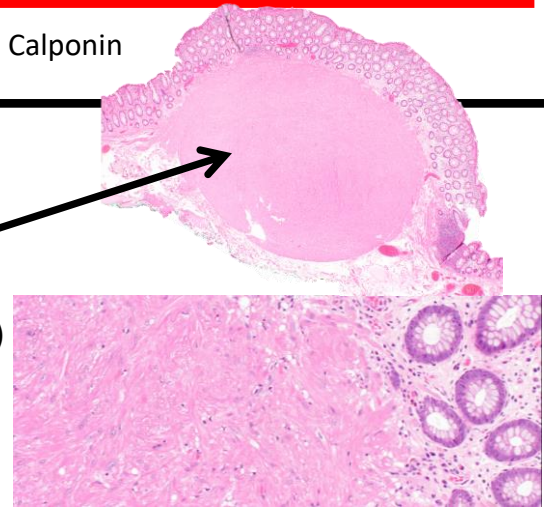
## Leiomyoma

**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**

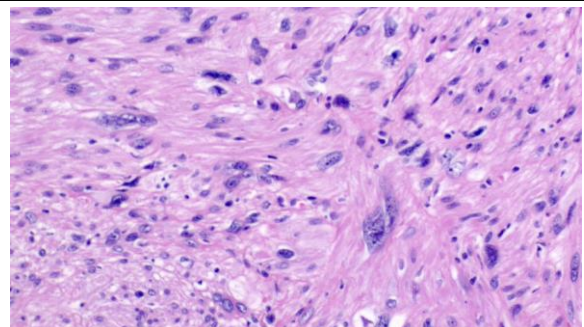
Minimal mitotic activity (<1 per 50 HPF) and no tumor-type necrosis



## 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**

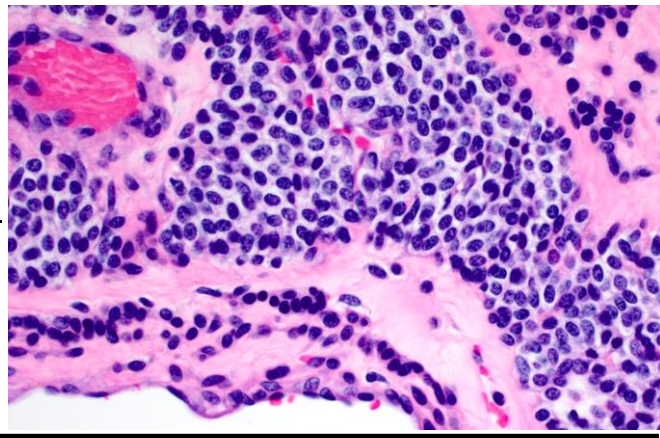
cytoplasm arranged in sheets and nests

Richly vascular, hyalinized stroma.

Can be *mistaken* for NET morphologically.

Stains: **(+) SMA**, (+/-)Caldesmon;

Focal synaptophysin is a potential pitfall!

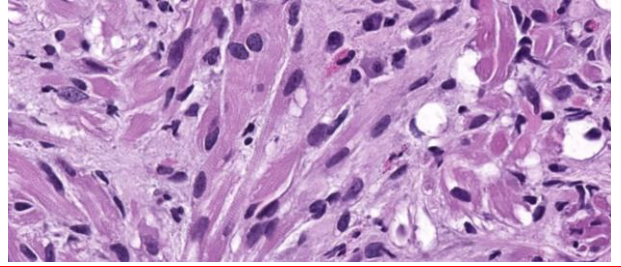


## Rhabdomyosarcoma

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.

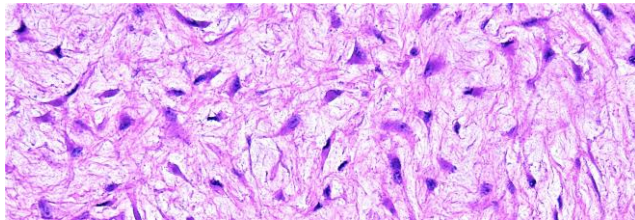
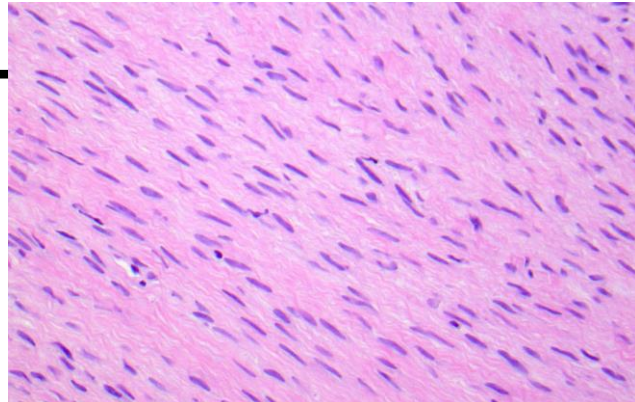
**Sweeping fascicles. Infiltrative growth.** Few mitoses.

Most common in small bowel mesentery; usually large.

**Locally aggressive, non-metastasizing.**

IHC: (+) SMA, **nuclear  $\beta$ -catenin (80%)**,

WNT/  $\beta$ -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  $\rightarrow$  can cause intussusception

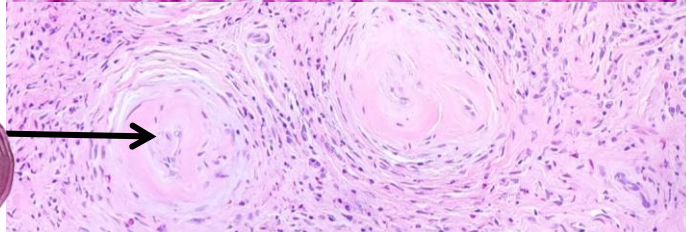
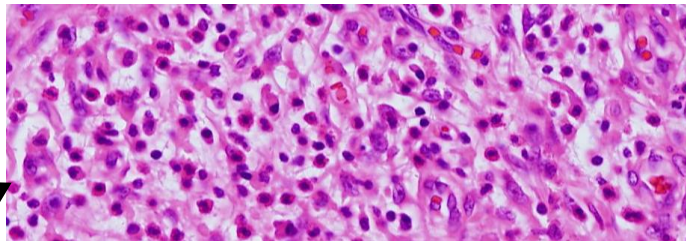
Centered in submucosa but extend to mucosa

Spindled to plump cytologically bland cells and associated **eosinophils** and lymphocytes;

often myxoid background. Cells proliferate/circle around vessels, whorled  $\rightarrow$  "**onion-skinning**"

IHC: (+) CD34

Molecular: PDGFRA mutations



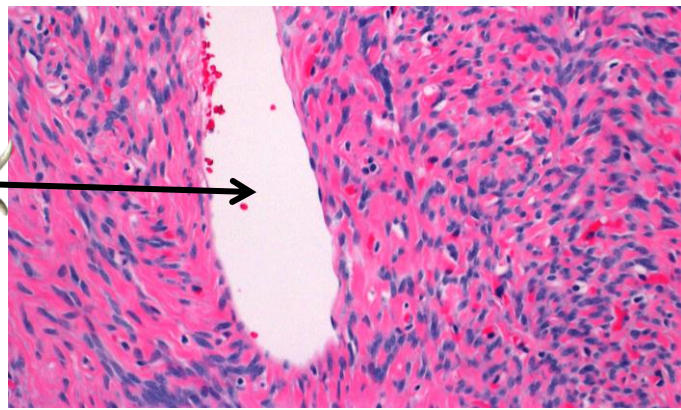
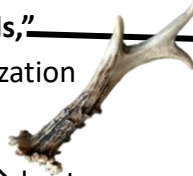


## Solitary Fibrous Tumor "SFT"

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

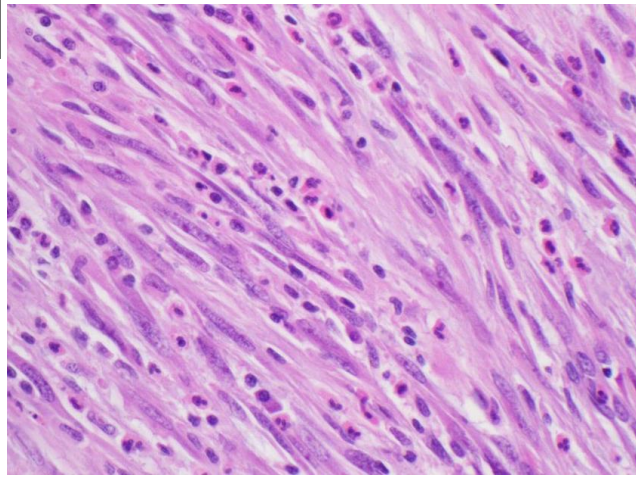
IHC: (+) **STAT6**, CD34

Molecular: NAB2-STAT6 rearrangement → best seen with STAT6 IHC



## Inflammatory Myofibroblastic Tumor

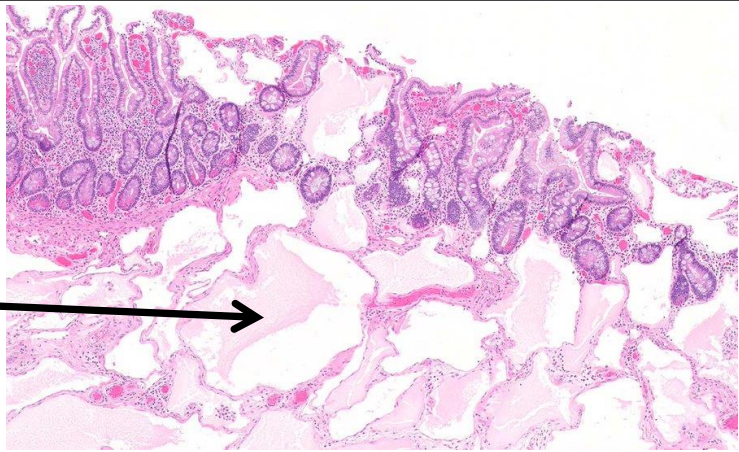
Usually in children and young adults "IMT"  
Plump spindle to stellate cells in myxoid to collagenous stroma with associated **lymphoplasmacytic inflammation**. Fibroblastic/myofibroblastic.  
Vesicular chromatin, small nucleoli.  
IHC: (+)SMA, ~60% stain with **ALK**; (-/+)  
Desmin  
Molecular: ~60%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



## Vascular Origin

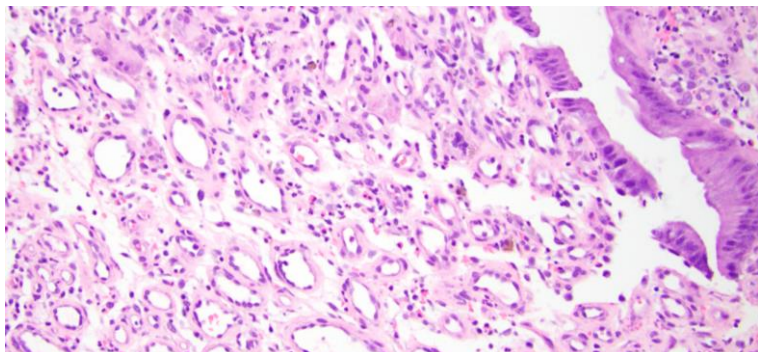
### Lymphangioma

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

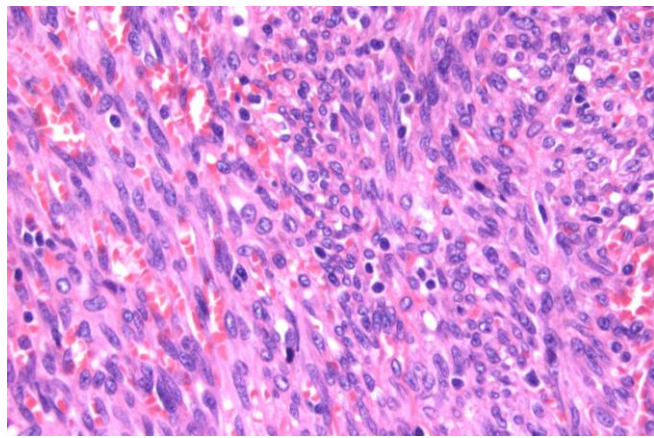
Benign vascular tumor, but can bleed.  
Varying morphologies with different caliber vessels (e.g., Cavernous)  
Should **NOT** see: Papillary growth, multilayering, cellular atypia, mitoses, and necrosis  
Stains: (+) ERG, CD31, CD34, FLI1; Ki67<10%





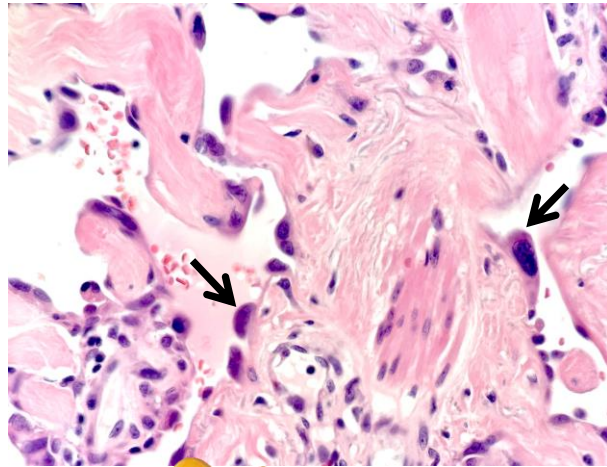
## Kaposi Sarcoma

**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

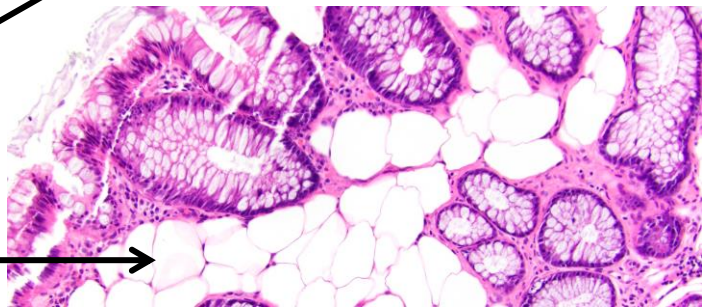
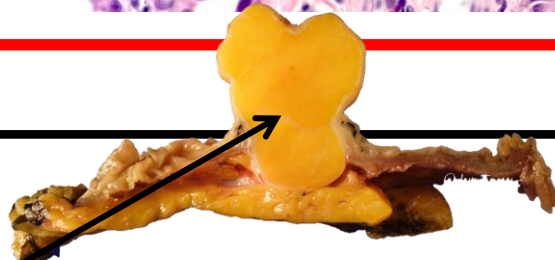


## Adipocytic Origin

### Lipoma

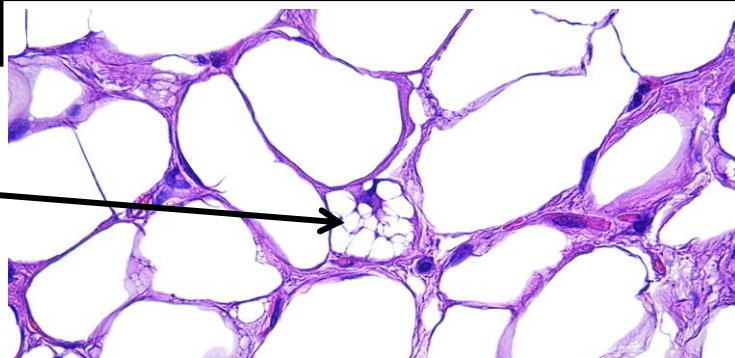
**Benign tumor** composed of mature adipocytes.  
No cytologic atypia. Can occur anywhere. Most common in colon in submucosa. Often grossly recognizable. "Pillow sign" on endoscopy.

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.





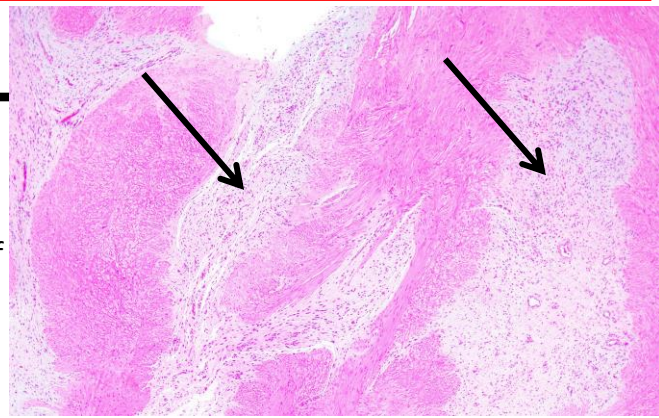
## Rare/Other

### 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

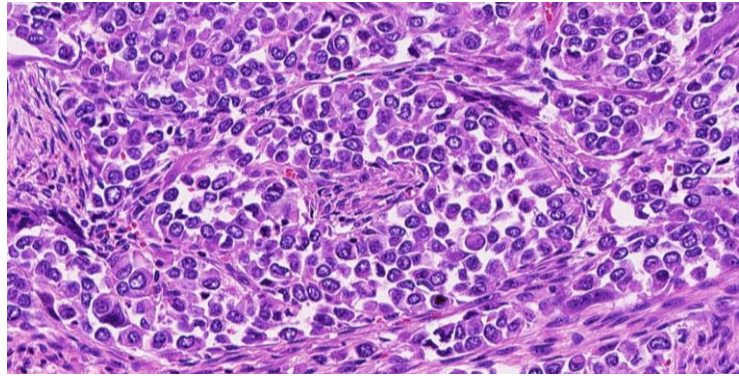


### Gastrointestinal Clear Cell Sarcoma / GNET

Malignant. Neuroectodermal 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)



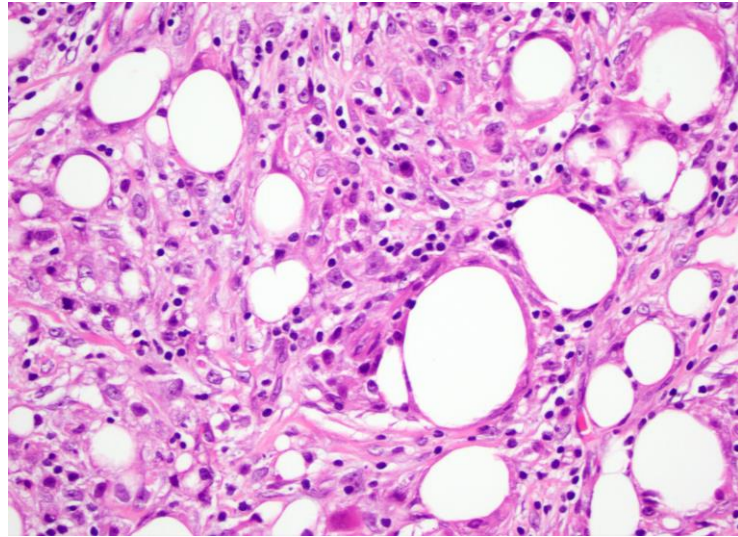
### Sclerosing Mesenteritis

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



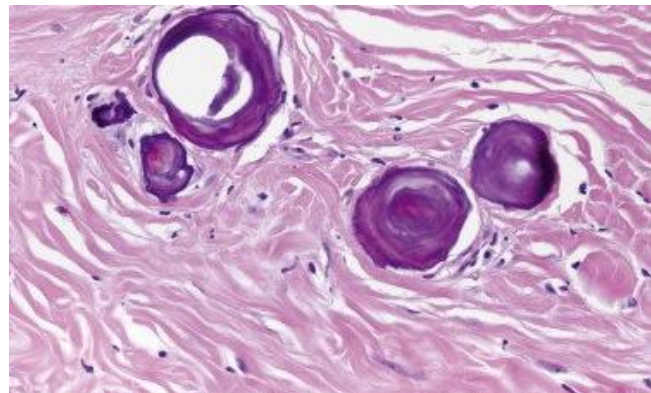
### Calcifying Fibrous Tumor

Benign neoplasms composed of hypocellular dense stromal collagen with psammomatous and dystrophic calcifications and patchy chronic inflammation.

Well-circumscribed, unencapsulated.

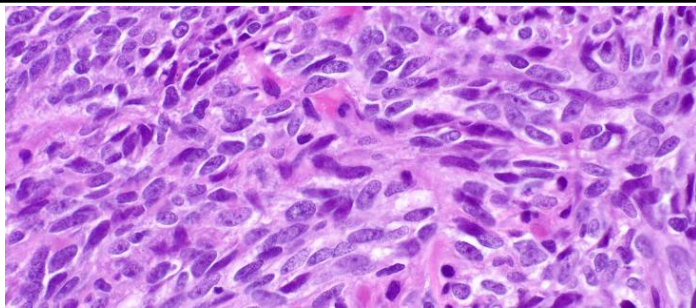
Usually affects children and young adults.

IHC: (+)CD34



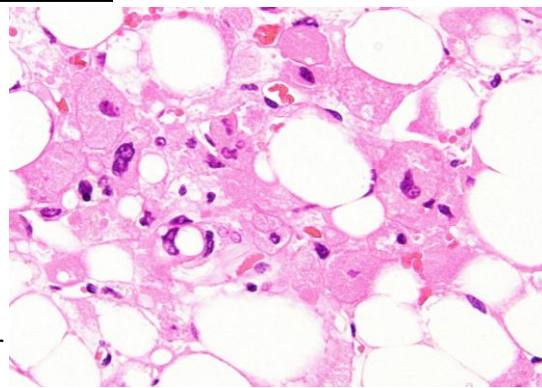
## Synovial Sarcoma

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



## Gastroblastoma

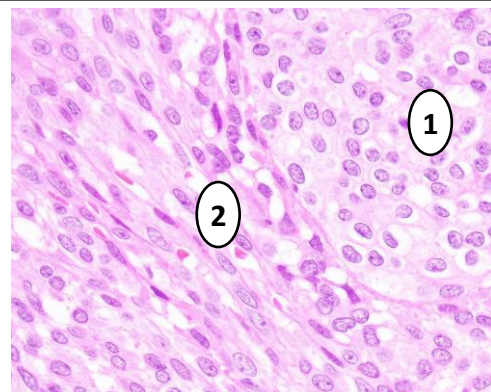
### Biphasic nested tumor

1) Uniform epithelioid cells that look vaguely neuroendocrine, round nuclei. 2) Uniform spindled cells

Mostly in stomach antrum muscularis propria of young boys/men.

IHC: (+) CD56, (±) CK, CD10, SMA, Desmin

Molecular: MALAT1-GLI1 fusion



## IHC Panels

### First Round (most common DXs):

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 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