Mesenchymal syndromic polyposis/tumors

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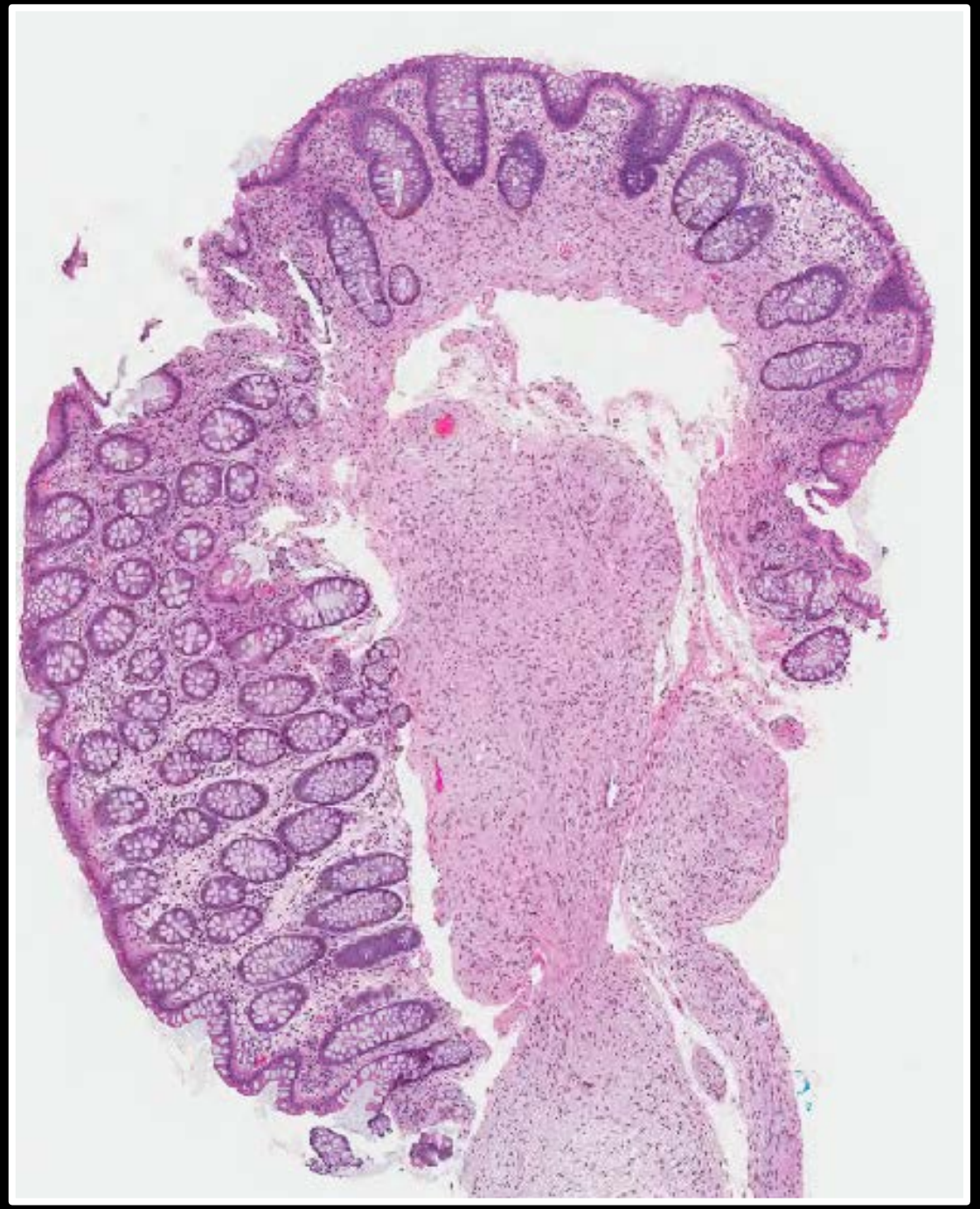
Disclosures/Objectives

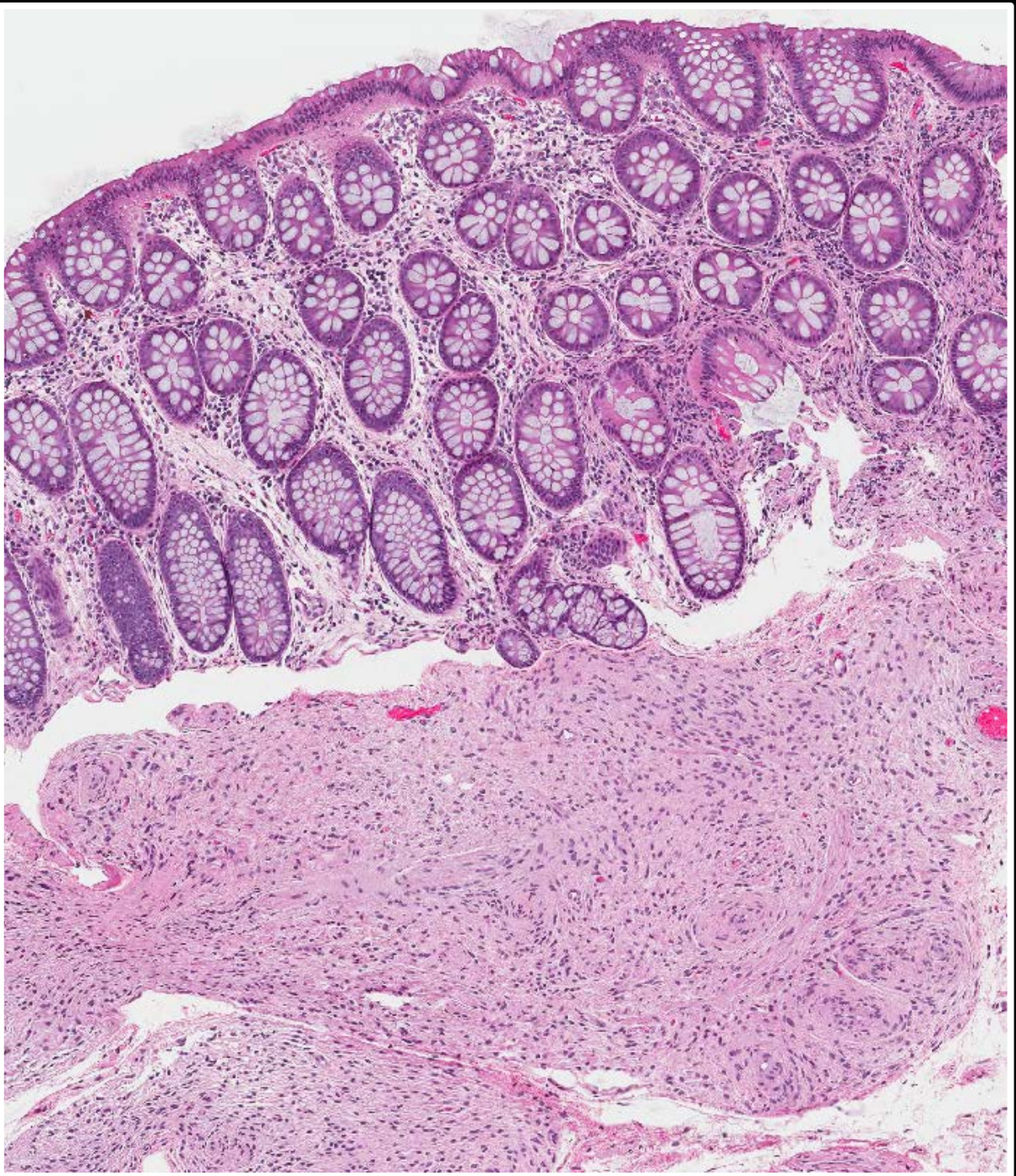
- No Disclosures

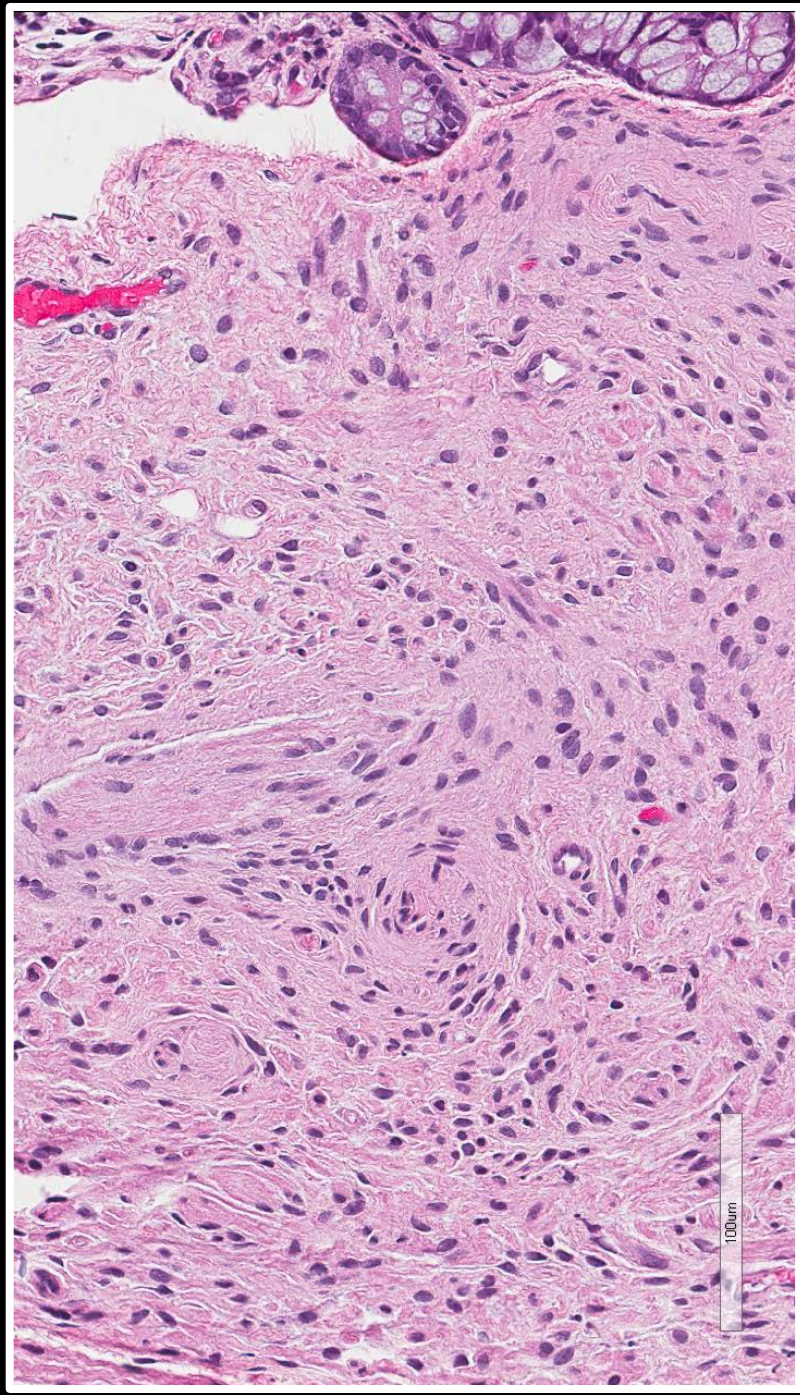
- Objectives
  - Review several different syndromes leading to polyps and other tumors of the GI tract
  - Describe why recognition of these syndromes is important for proper patient management

Case 1

- 28 y.o. female, initial colonoscopy for hematochezia
- Findings: Numerous (dozens) of polyps throughout colon and terminal ileum; multiple polyps biopsied



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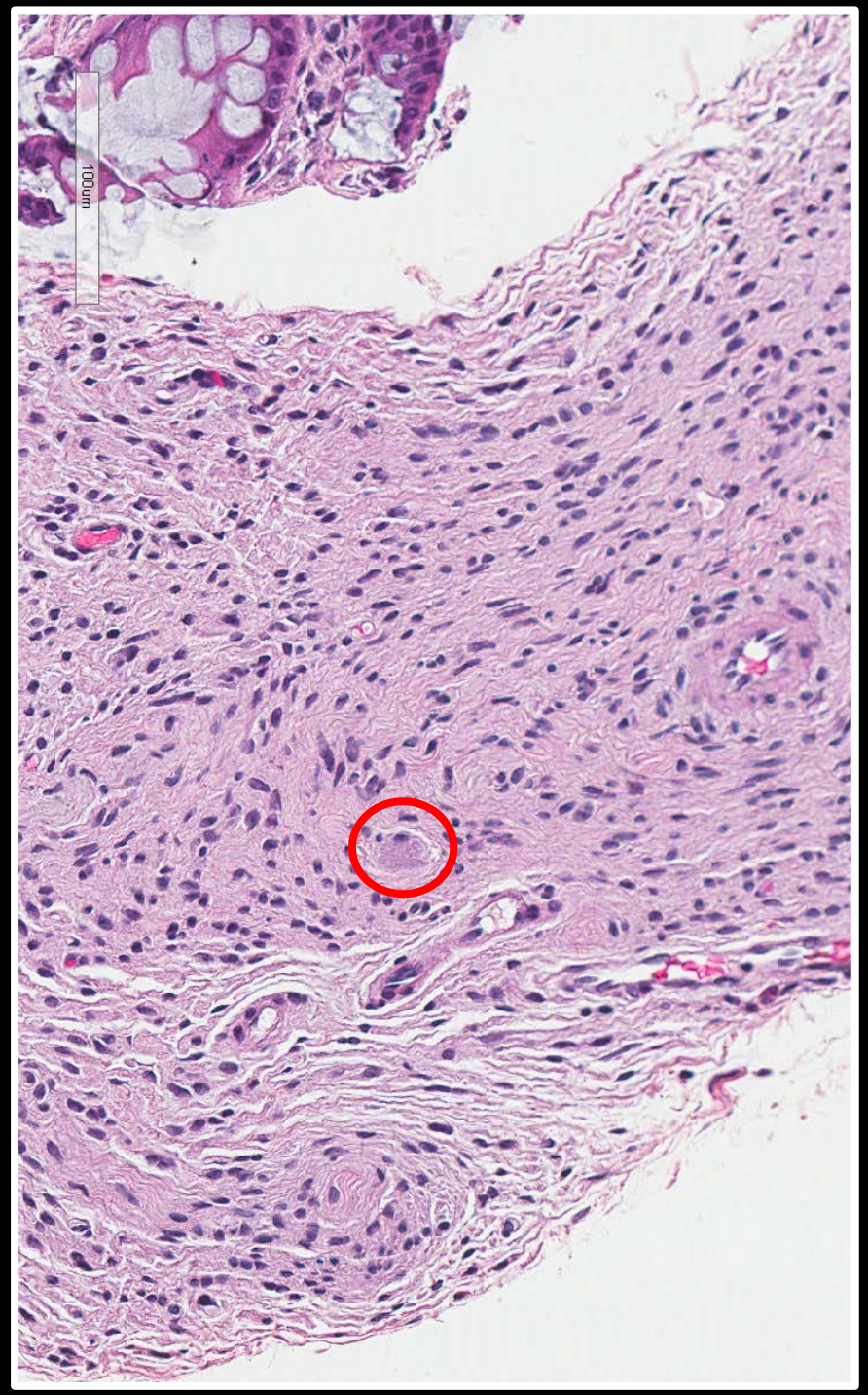
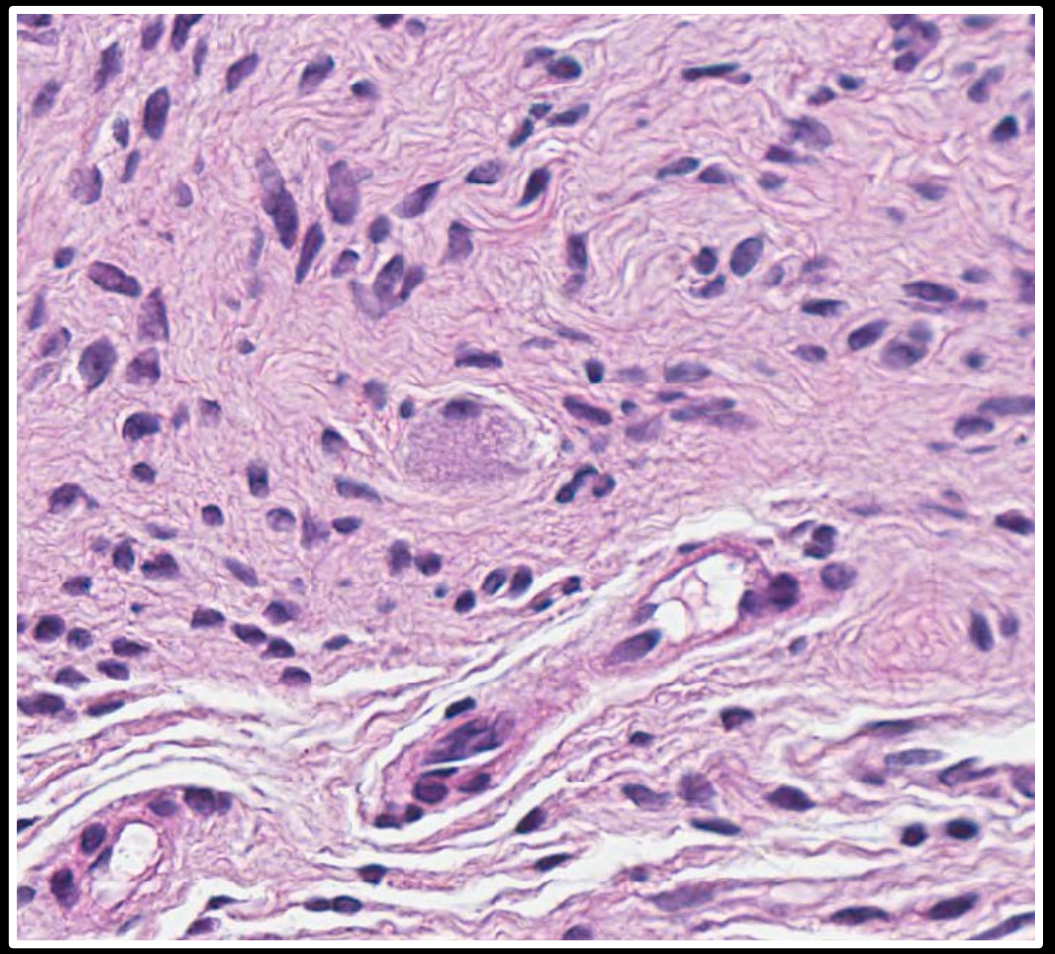




Diagnosis: Ganglioneuroma

Case, continued

- Other biopsies showed hyperplastic polyps, 1 additional ganglioneuroma and 1 tubular adenoma
- Based on pathology findings, upper endoscopy was performed
  - Numerous polyps: duodenum, stomach
  - Hyperplastic polyps, 1 tubular adenoma (duodenum)

- Case diagnosis: Probable Cowden syndrome (PTEN hamartoma syndrome)

GI ganglioneuromatous proliferations

- Sporadic (solitary) polyps
  - Incidental finding
  - Colon
  - Adults
  - Benign
- Ganglioneuromatous polyposis
- Diffuse ganglioneuromatosis

Ganglioneuromatous polyposis

- Associated with Cowden (adults) and Bannyan-Riley-Ruvalcaba (pediatric)
  - “PTEN hamartoma syndrome”
    - Mixed polyposis syndrome
      - Hyperplastic polyps, hamartomatous polyps
      - Ganglioneuromatous polyps, inflammatory/juvenile polyps, adenomas
    - Polyps (all types) focal or diffuse
    - Upper and lower GI tract affected

PTEN Hamartoma Syndrome

- Mutations in PTEN* gene
- Autosomal dominant or de novo mutation
- 1:200,000
- Other clinical features:
  - Macrocephaly
  - Mucocutaneous benign tumors, including hamartomas
- Increased cancer risk for breast, colorectal (early-onset), endometrial, kidney, melanoma, thyroid

Cancer Risk in PTEN Hamartoma Syndrome

General population

- Breast: 12%
- Thyroid: 1%
- Renal cell: 1.5%
- Endometrial: 2.5%
- Colorectal: 5%
- Melanoma: 2%

Patients with PTEN-HS

- Breast: 85%
- Thyroid: 35%
- Renal cell: 34%
- Endometrial: 28%
- Colorectal: 9%
- Melanoma: 6%

https://my.clevelandclinic.org/health/diseases/17397-pten-hamartoma-tumor-syndrome-cowden-syndrome-and-bannayan-riley-ruvalcaba-syndrome

Cowden/PTEN Hamartoma Syndrome

- Consider when
  - no other relevant history AND
  - multiple/mixed polyps present in upper and lower GI tract of young patient OR
  - colonic adenocarcinoma along with multiple polyps in patient under 50
- *Alert clinician to possibility of Cowden/PTEN Hamartoma Syndrome

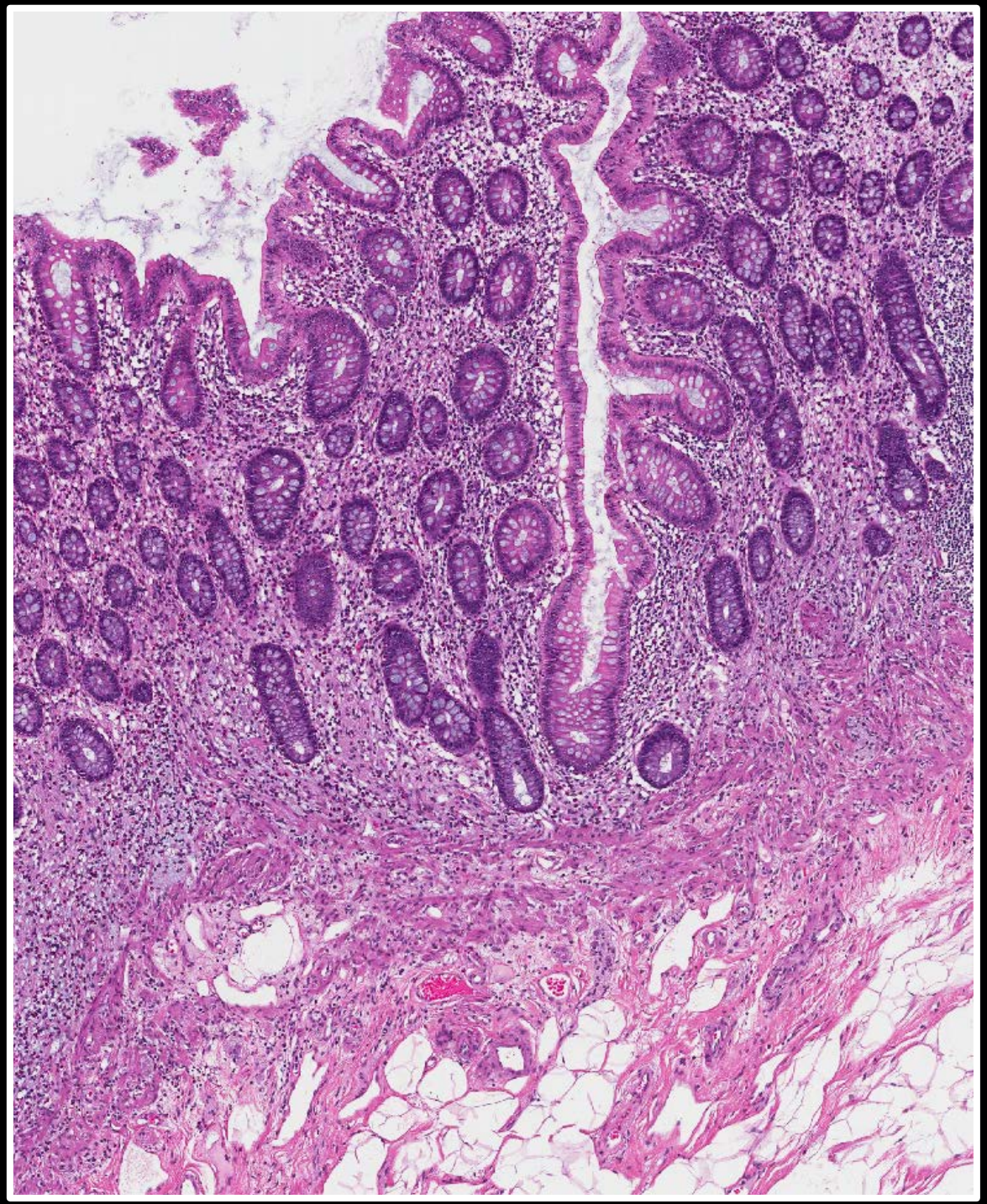
Diffuse Ganglioneuromatosis

- Diffuse, not polypoid, involvement of the bowel
- MEN2B most common associated syndrome; NF1 less commonly
  - MEN2B: Medullary thyroid carcinoma, pheochromocytoma, ganglioneuromatosis
- MEN2B: intestines or esophagus
- NF1: Colon=Ileum > rectum > jejunum
- Symptoms:
  - Abdominal pain, constipation, diarrhea common
  - Obstruction and megacolon may occur
  - 75-90% of patients report GI symptoms
- “Benign”, but symptoms may necessitate excision

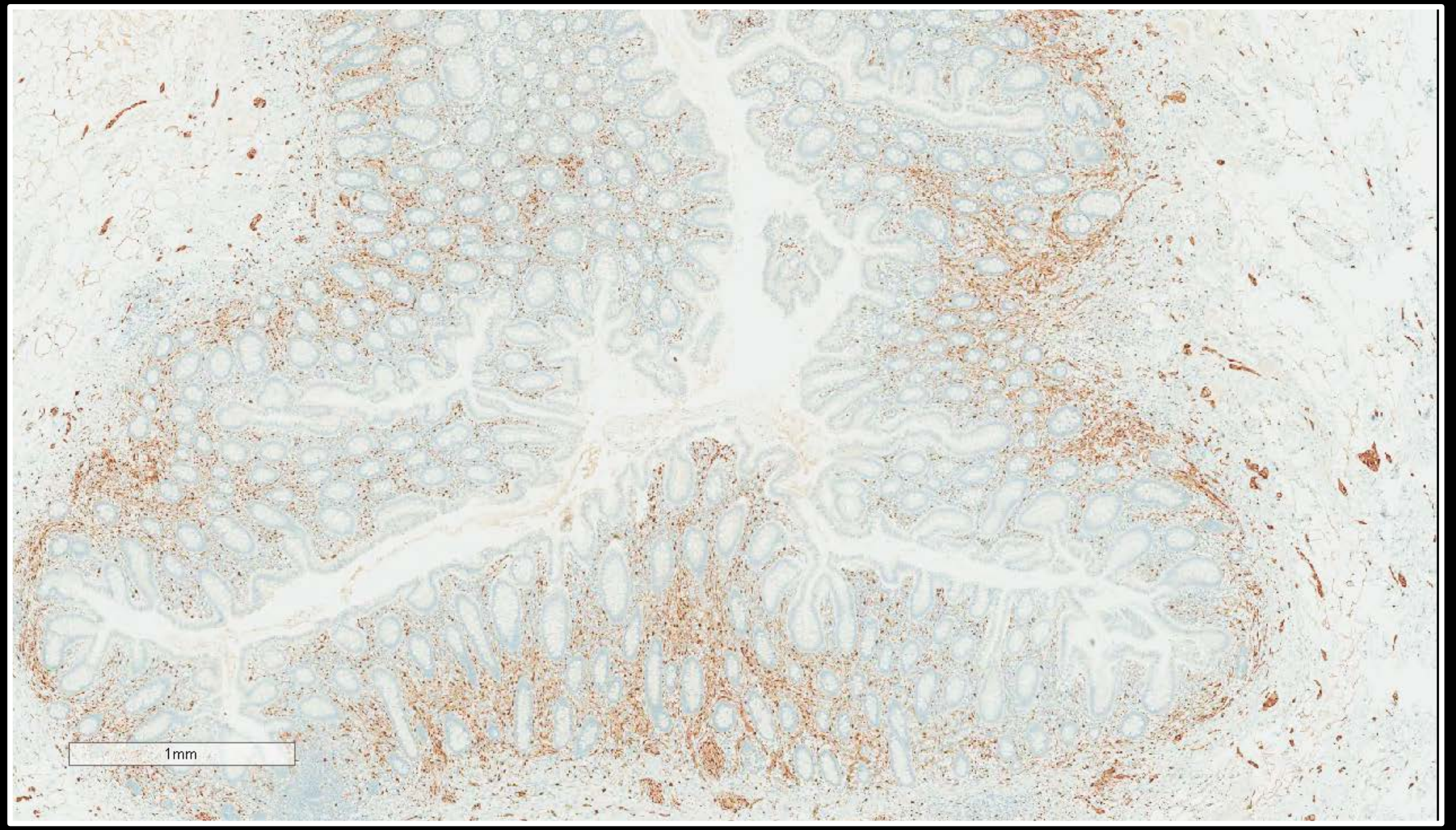
Diffuse Ganglioneuromatosis – histology

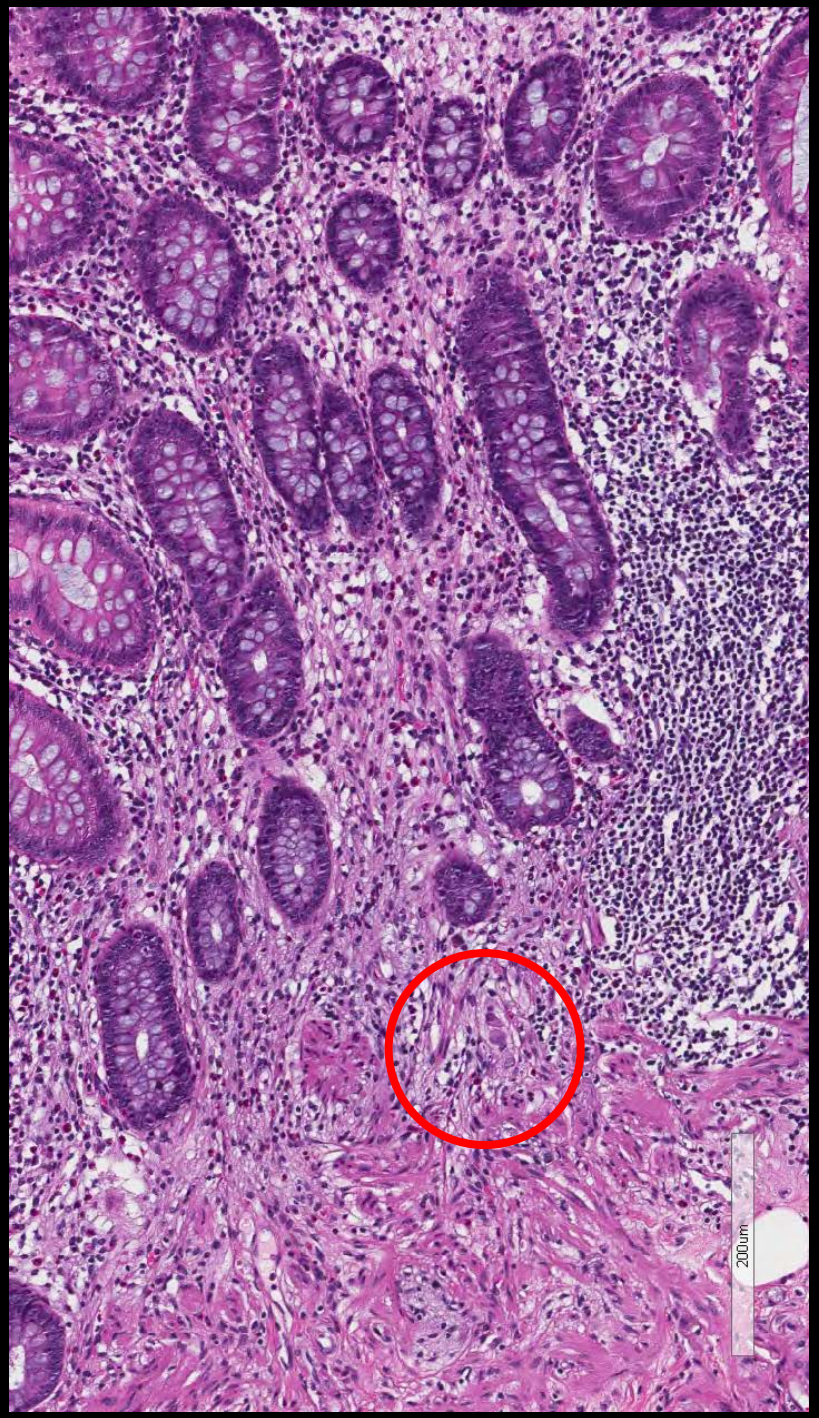
- Schwann cells and ganglion cells
- Infiltrative and diffuse rather than polypoid
- In NF1, affects mucosa and submucosa
- In MEN2B, affects submucosa and muscularis propria, with minimal mucosal involvement

Ganglioneuromatosis – histology (NF1)



S100

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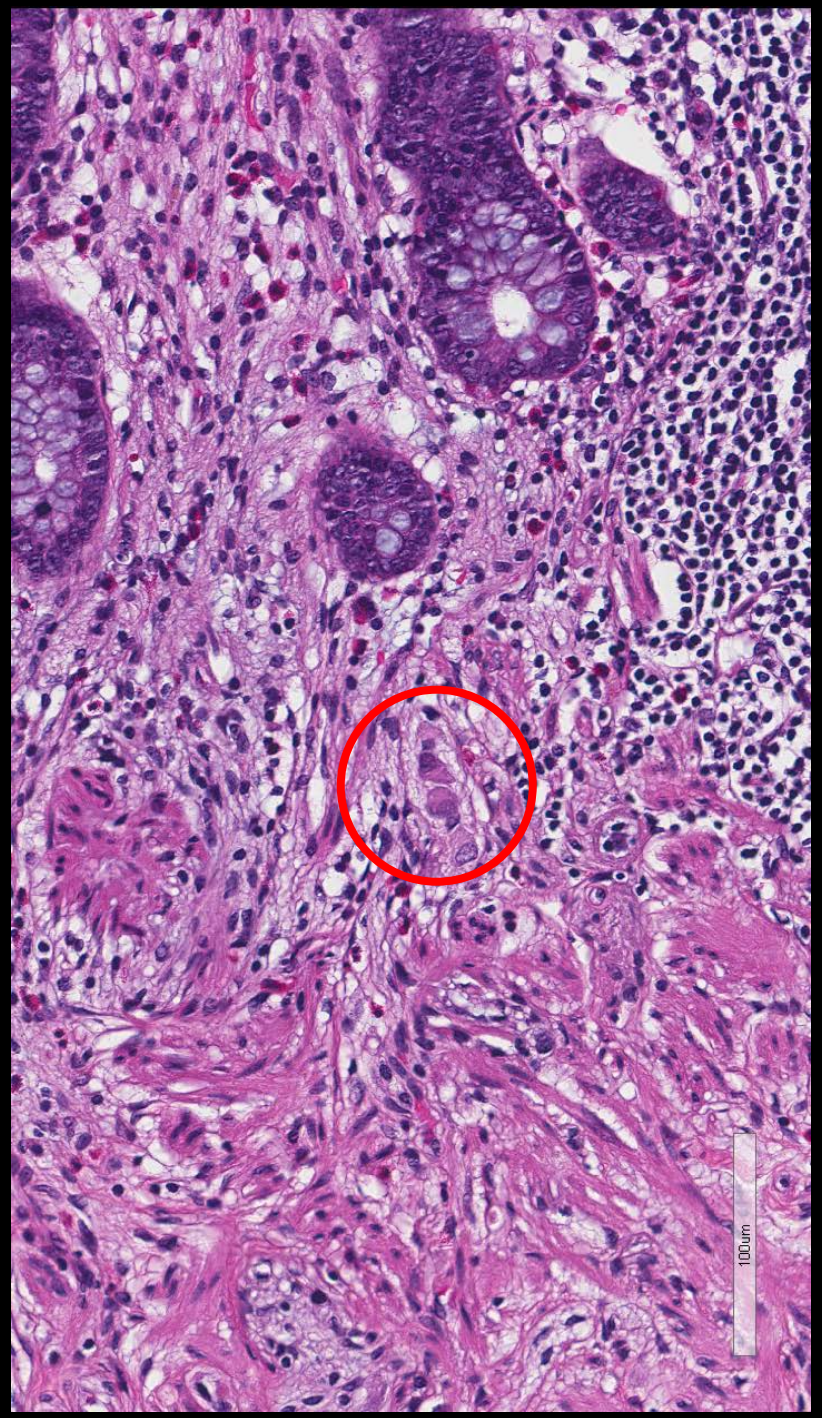
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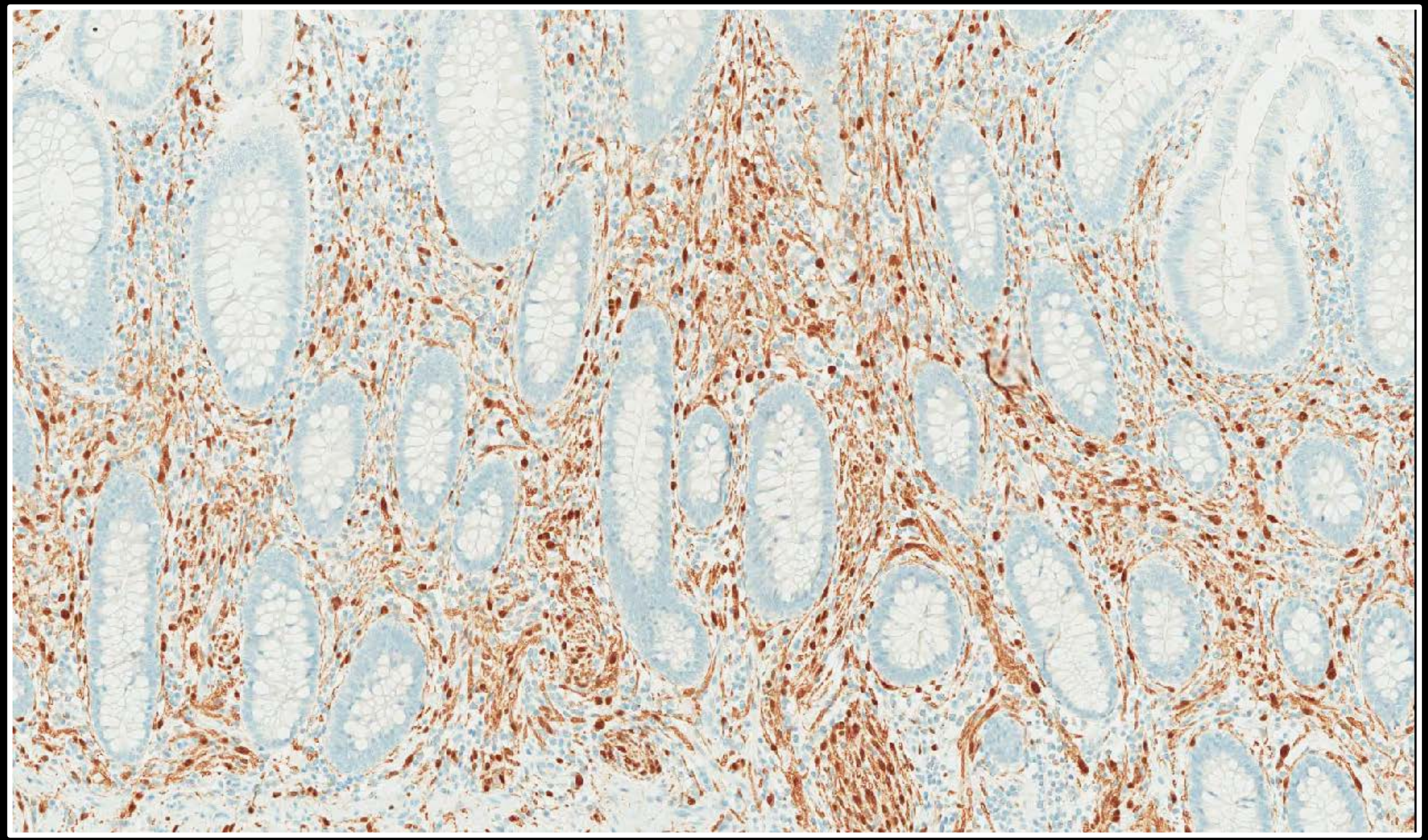


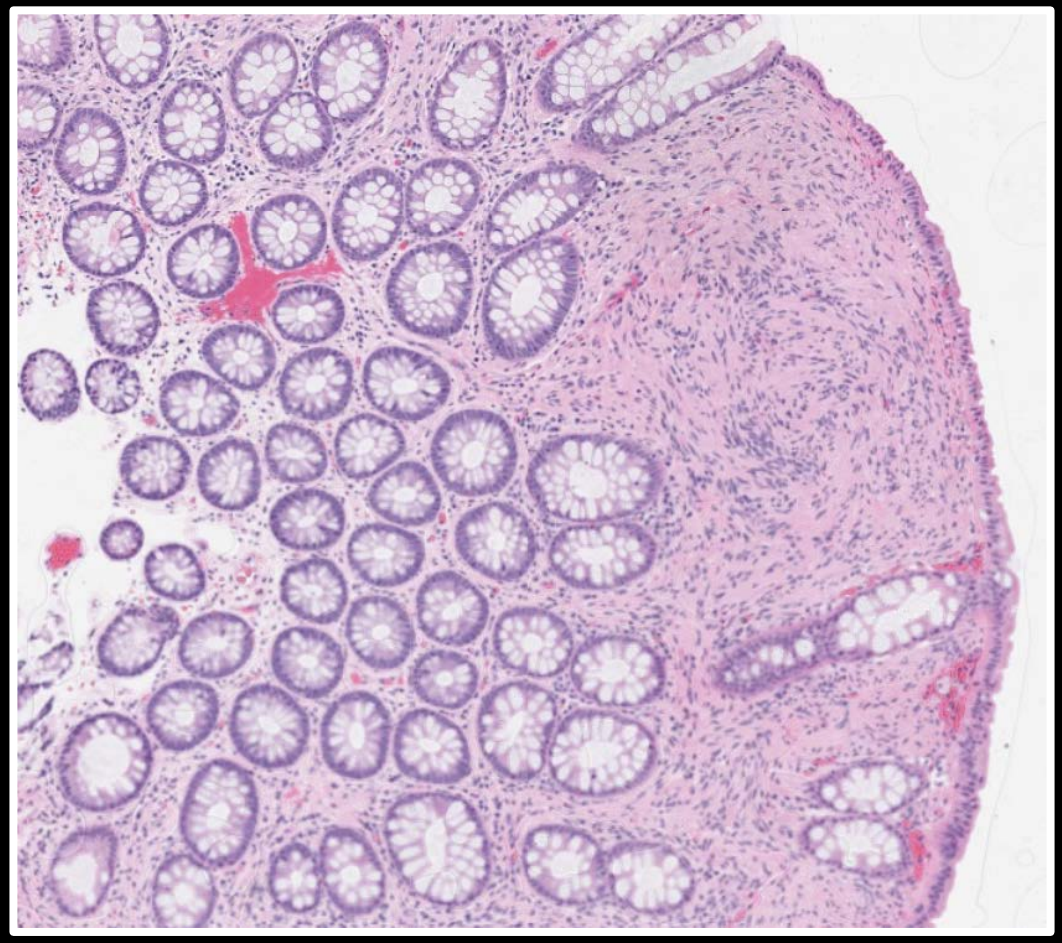
Differential diagnosis on biopsy** for ganglioneuroma and ganglioneuromatosis

- Mucosal schwann cell hamartoma
- Mucosal perineurioma
- Schwannoma
- Neurofibroma

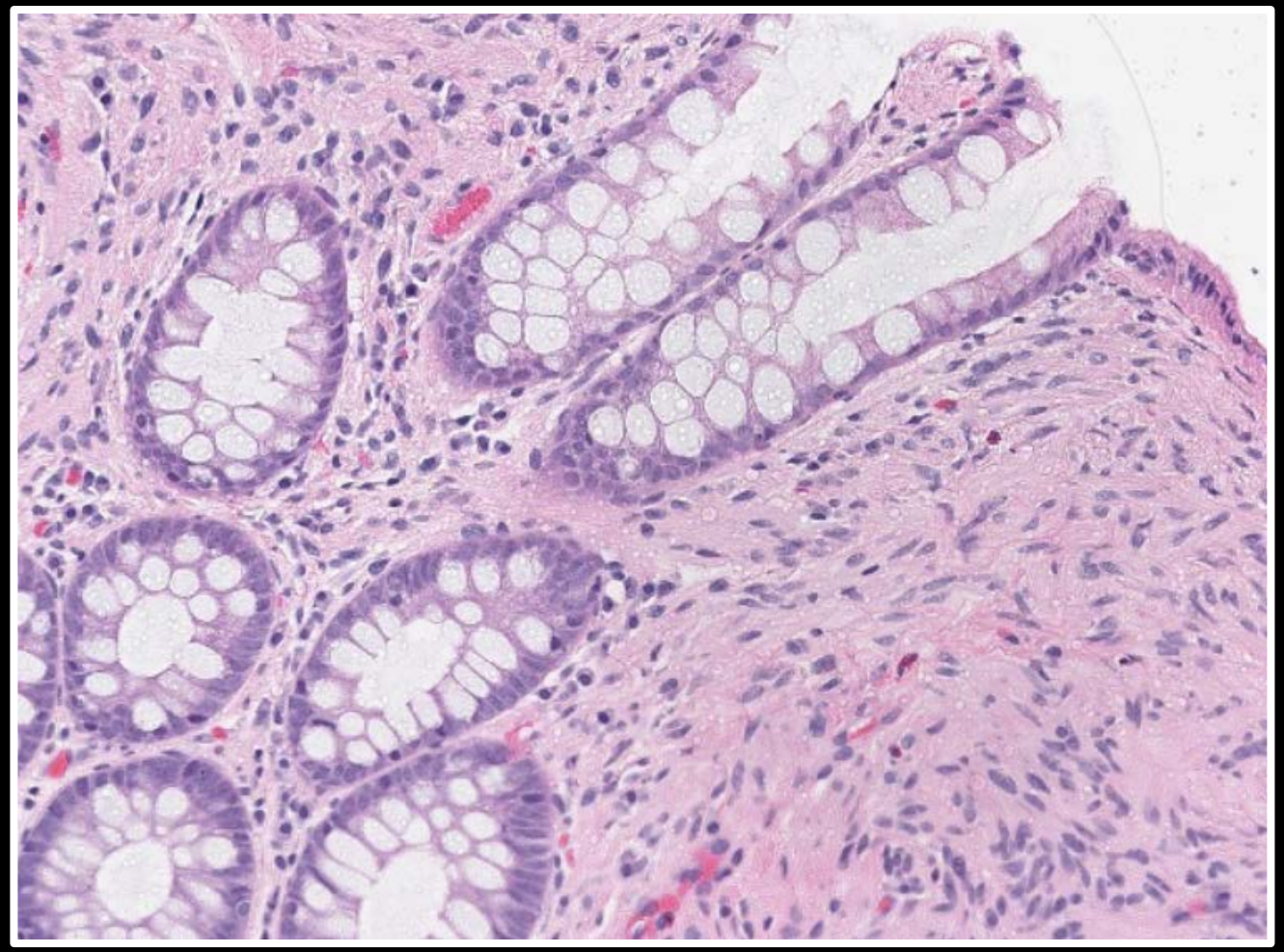
- **Only if ganglion cells absent on biopsy

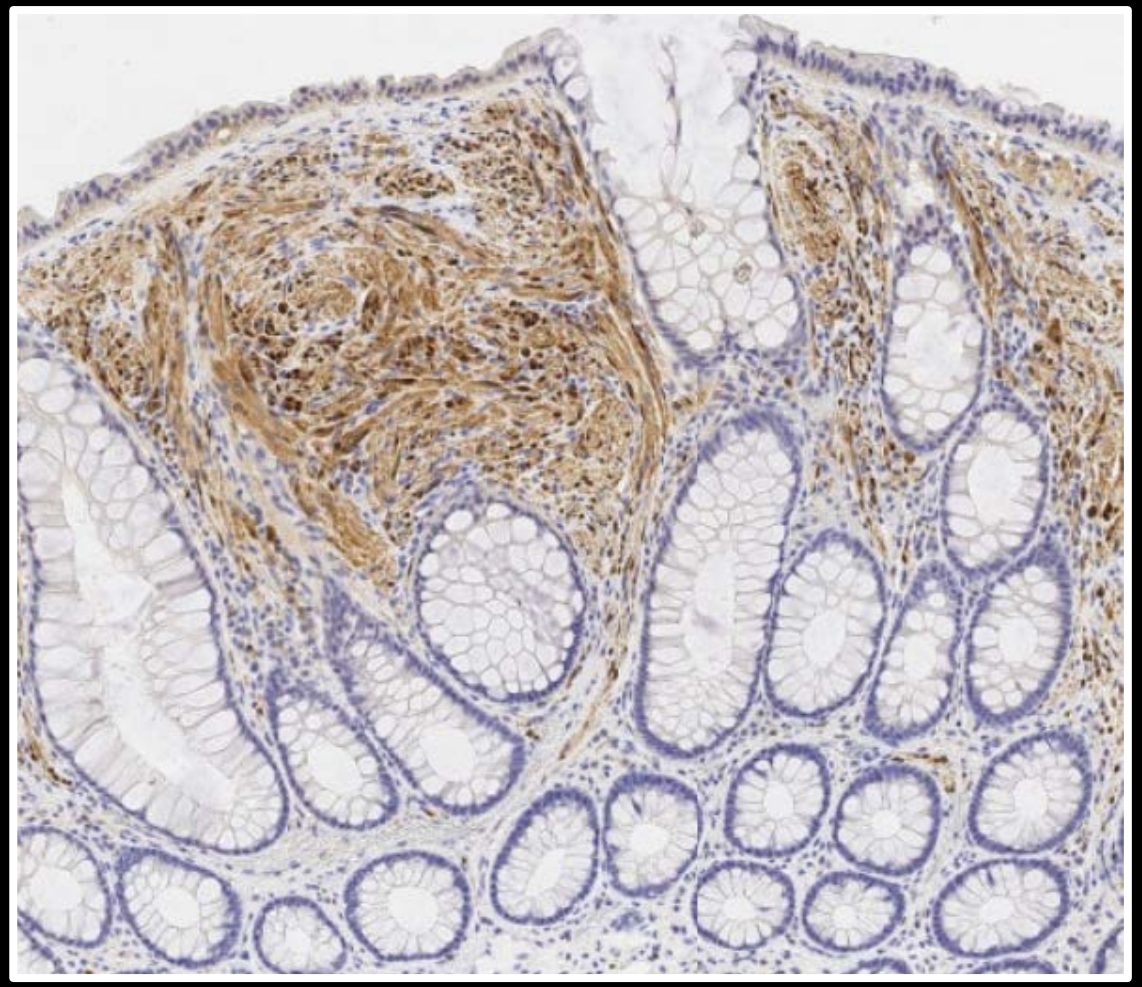
Mucosal Schwann Cell Hamartoma

- No associated syndromes
- Incidental
- Pan-colonic, especially rectosigmoid
- Polyp (0.1 – 0.6 cm)
- Involves mucosa
- Spindled schwann cells
- S100 positive
- No ganglion cells



Mucosal Schwann Cell Hamartoma

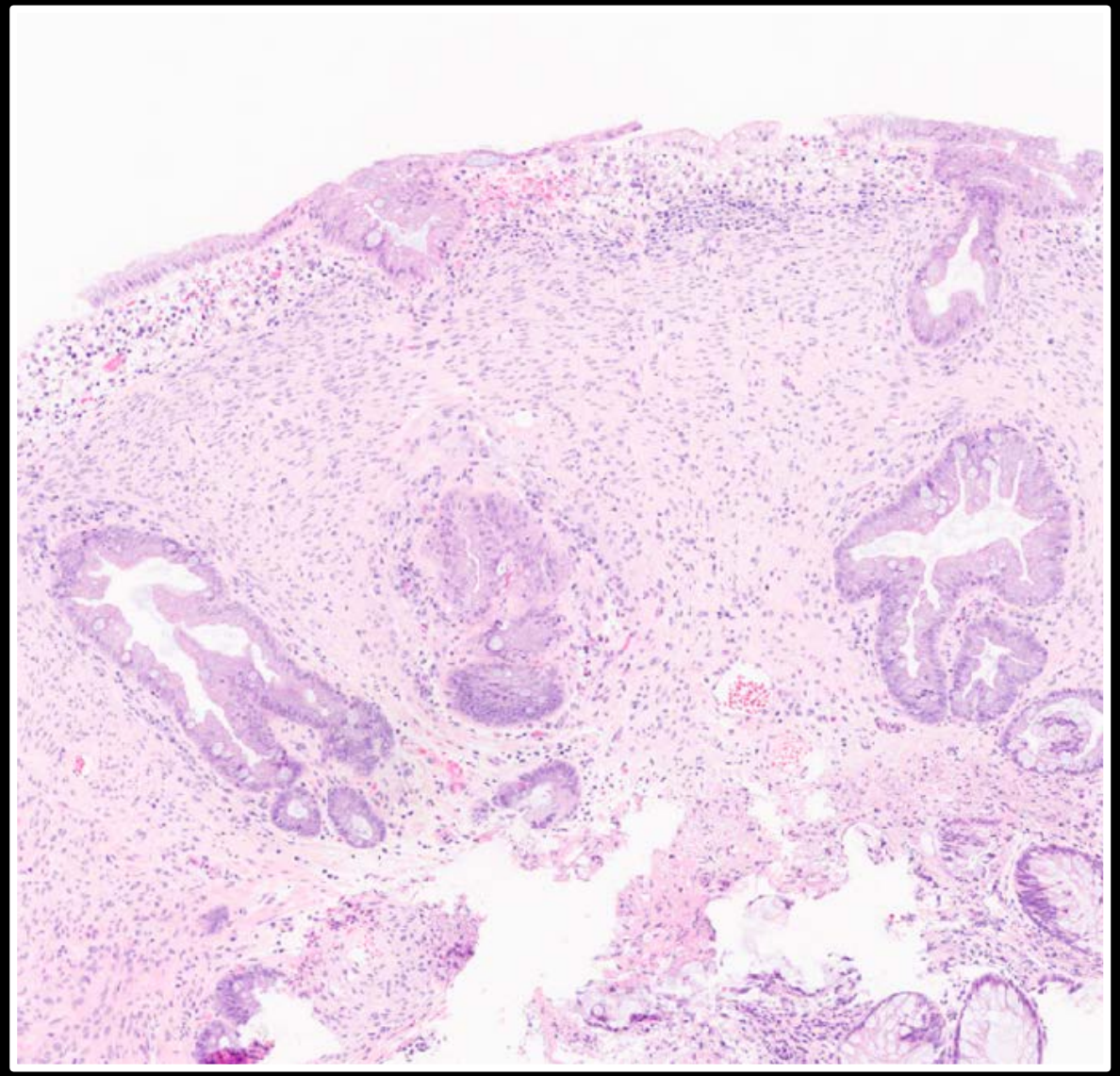


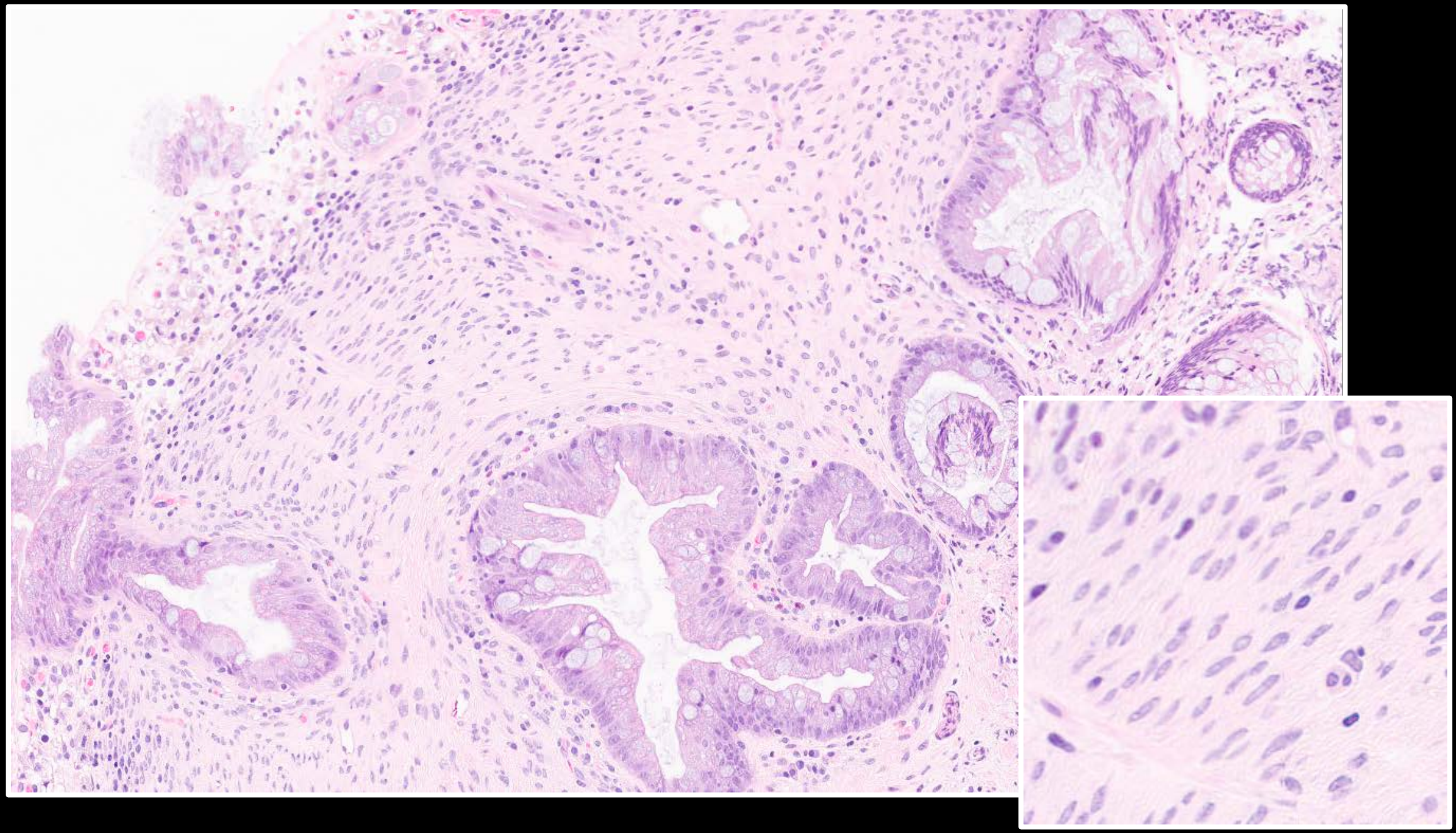


S100

Mucosal Perineurioma

- No associated syndromes
- Virtually all colon/rectum
- Aka “benign fibroblastic polyp”
- Mucosa +/- submucosa
- **Crypts entrapped, distorted, hyperplastic/serrated**
- ***Synchronous/metachronous polyps (TAs, HPs, SSAs)*



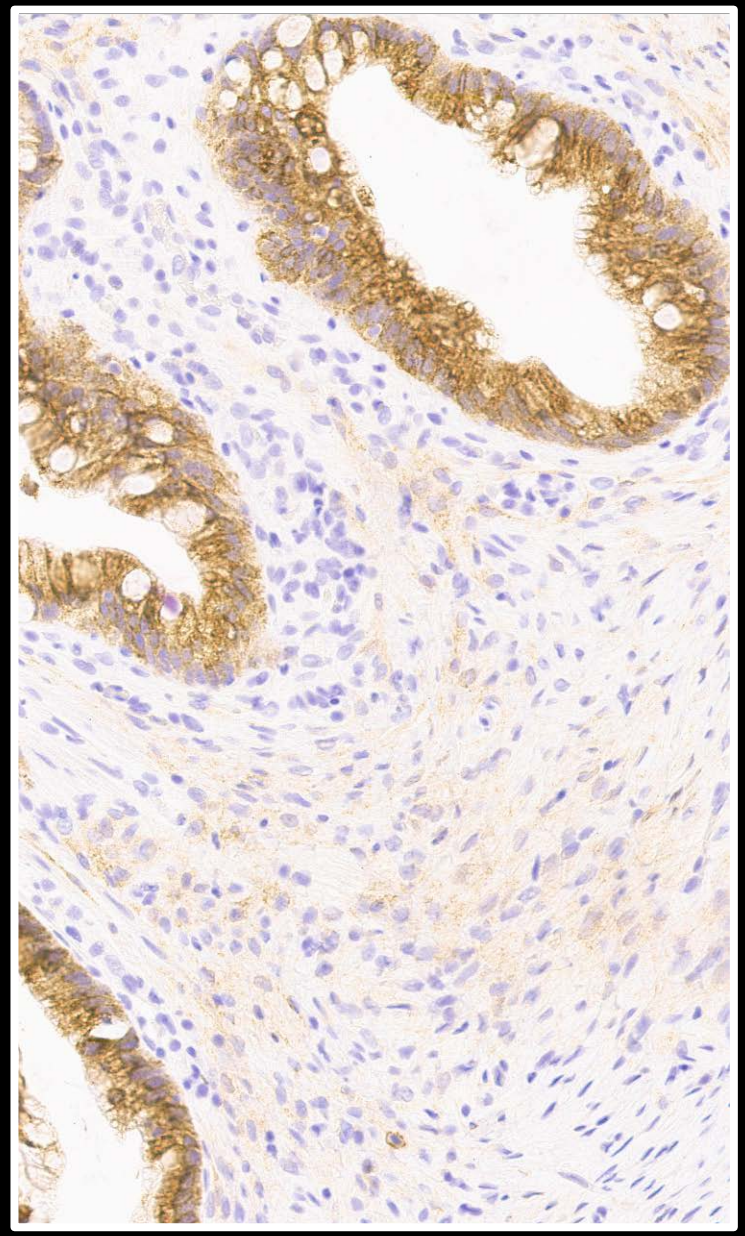


S100 Negative

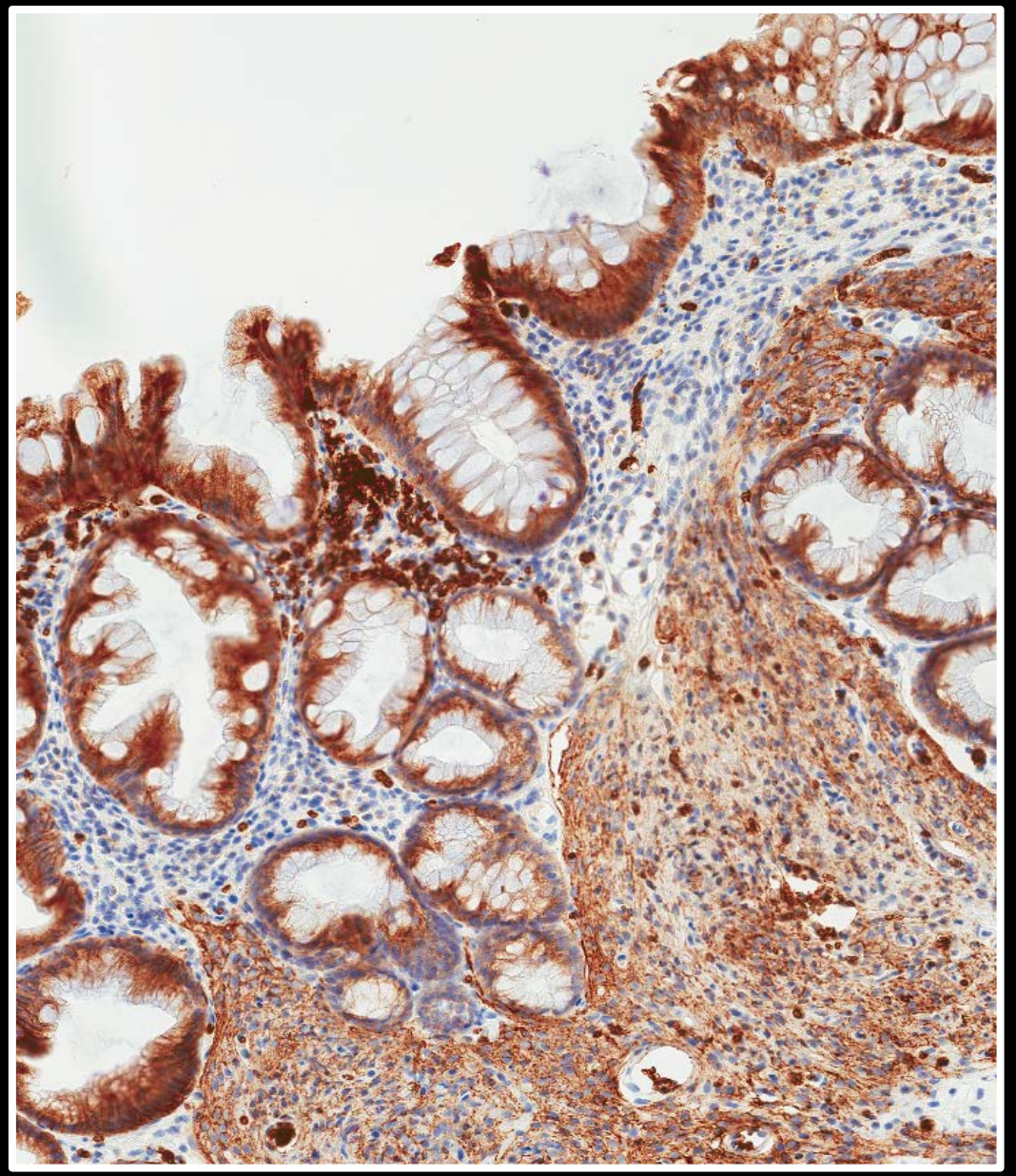
EMA weak patchy positive

GLUT-1/Claudin 1 positive

EMA



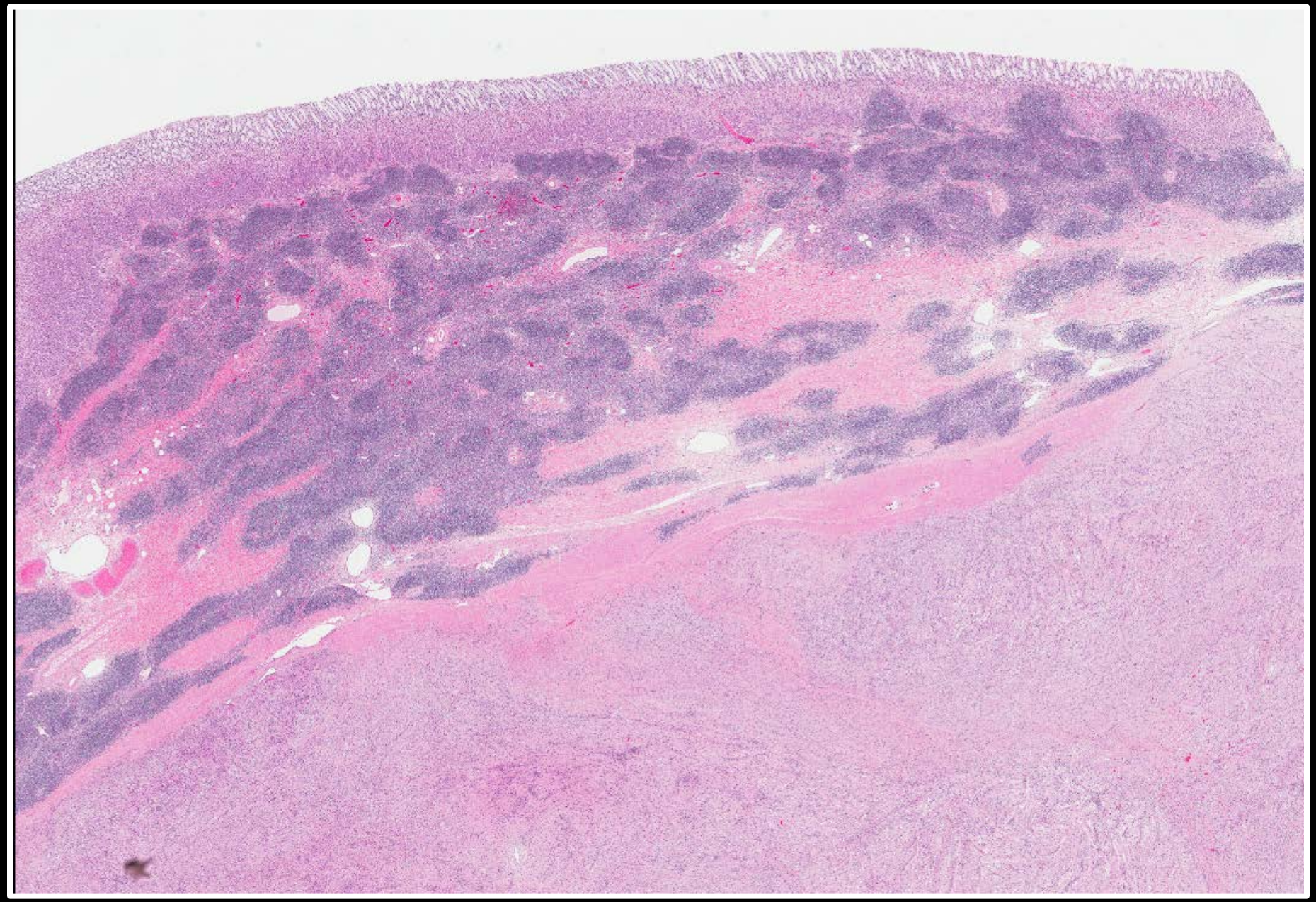
GLUT-1

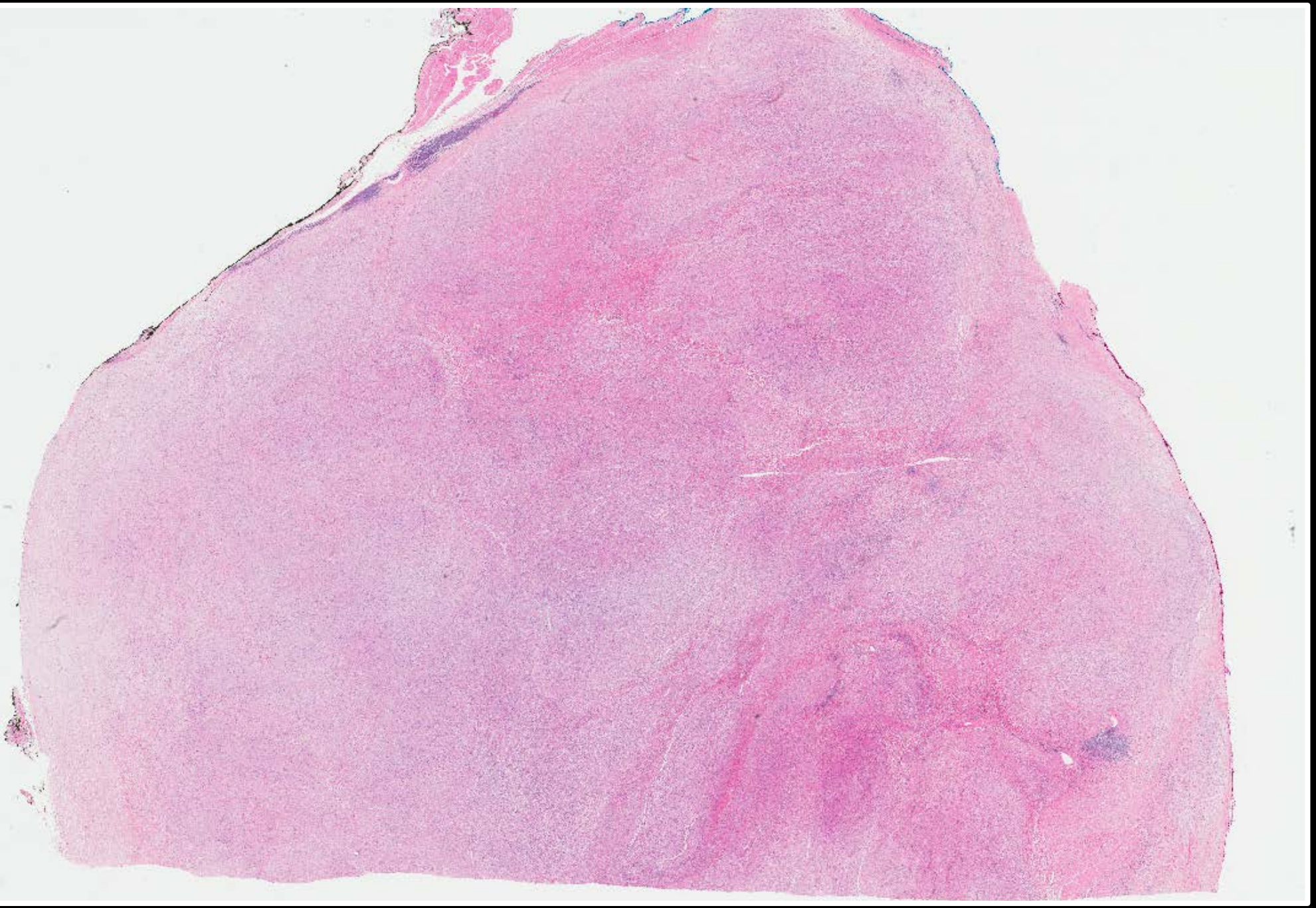


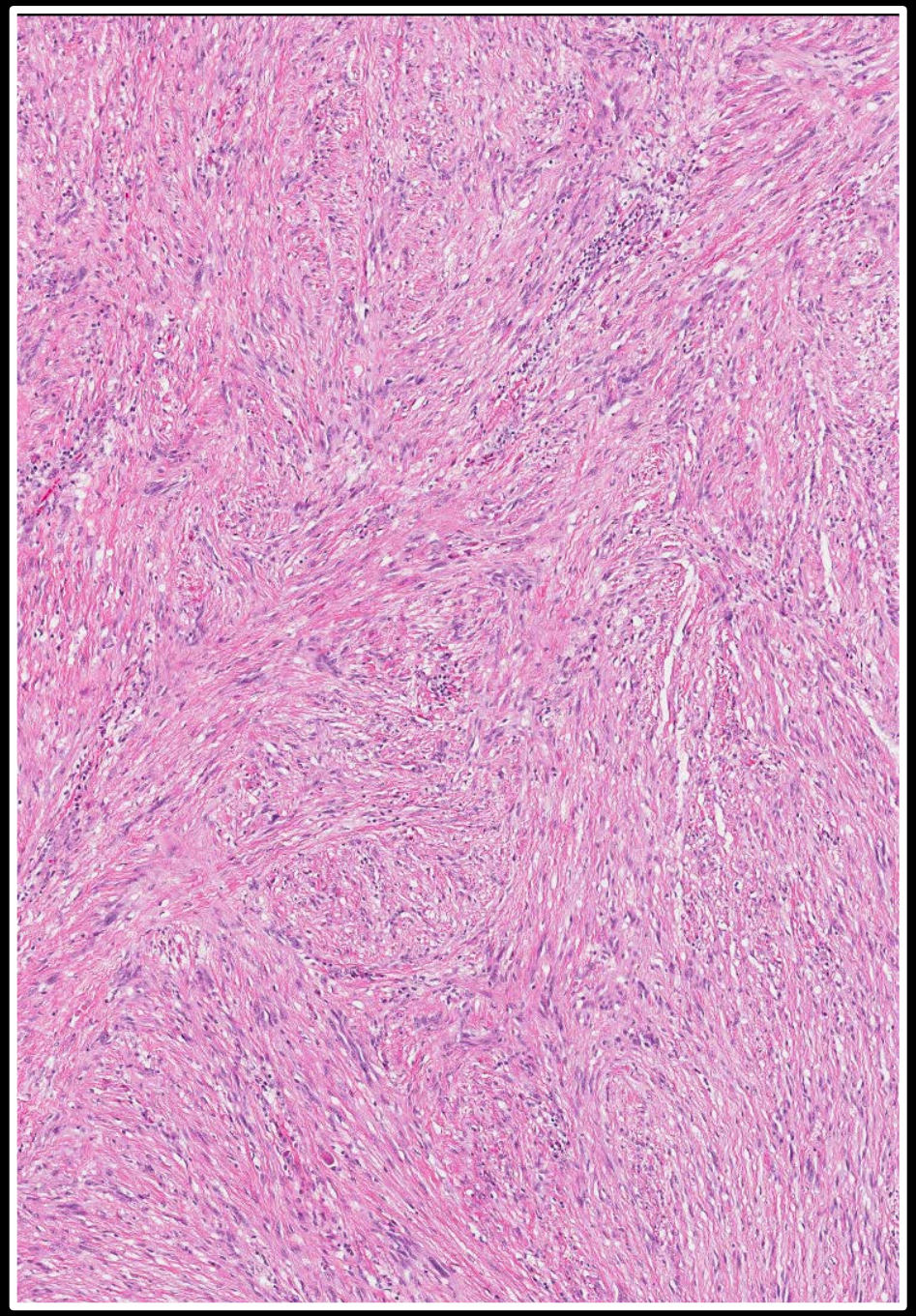
Schwannoma

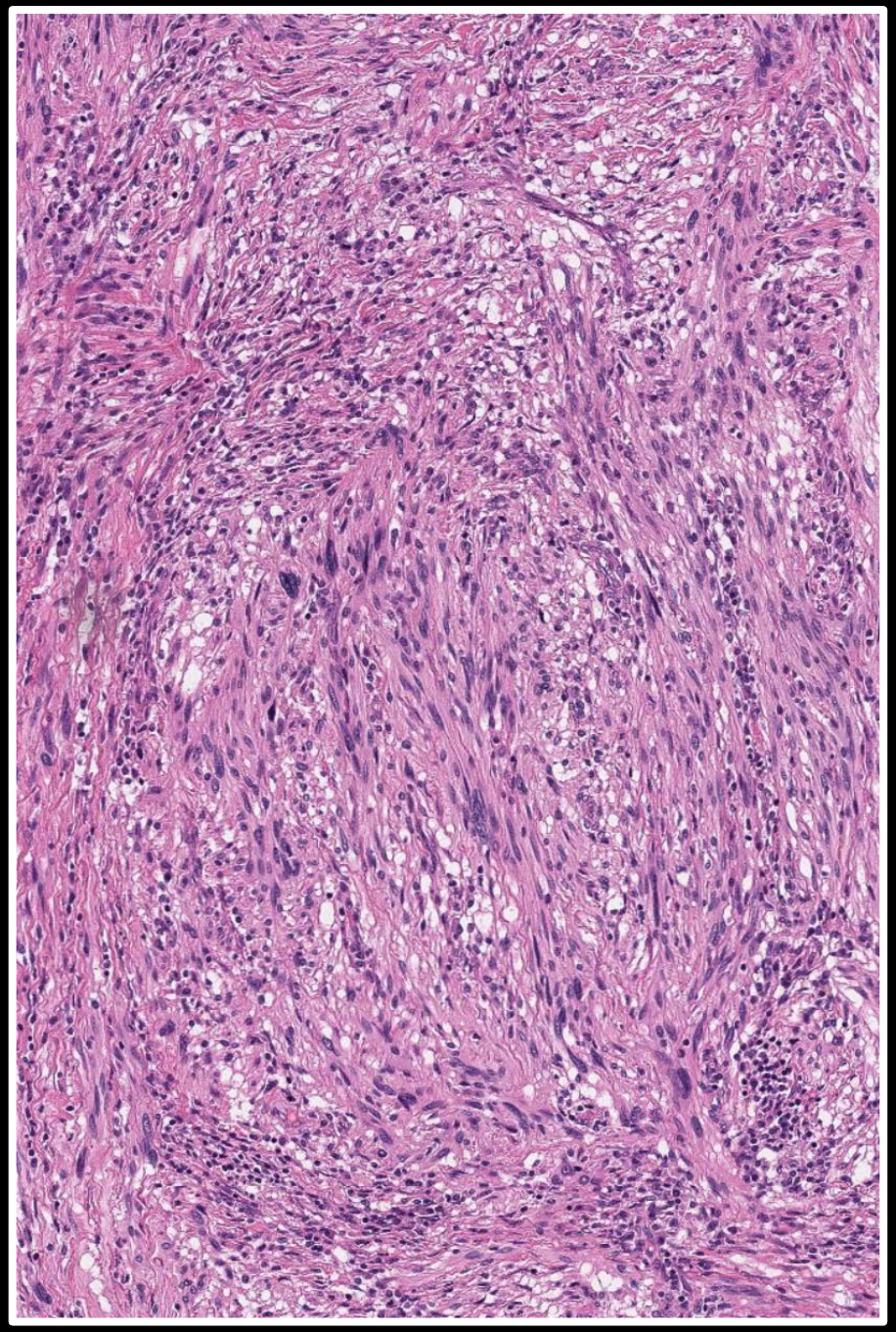
- Stomach
- Mural centered mass
- Do not have characteristic features of soft tissue schwannomas
  - More evenly cellular
  - Verocay bodies/hyalinized vessels absent or rare
- *Peripheral, peri-tumoral chronic inflammatory infiltrate*
- S100+
- Benign

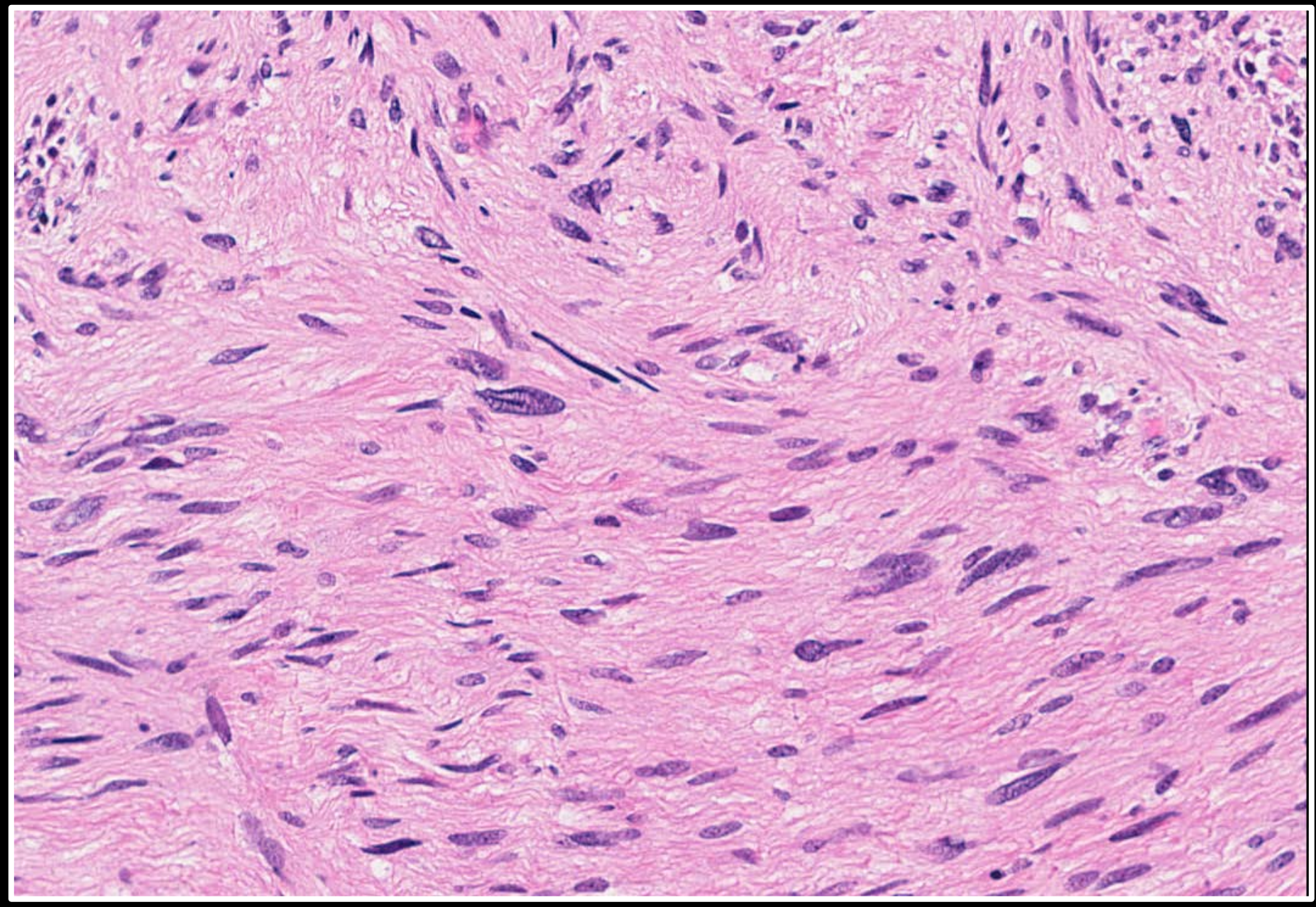
Schwannoma











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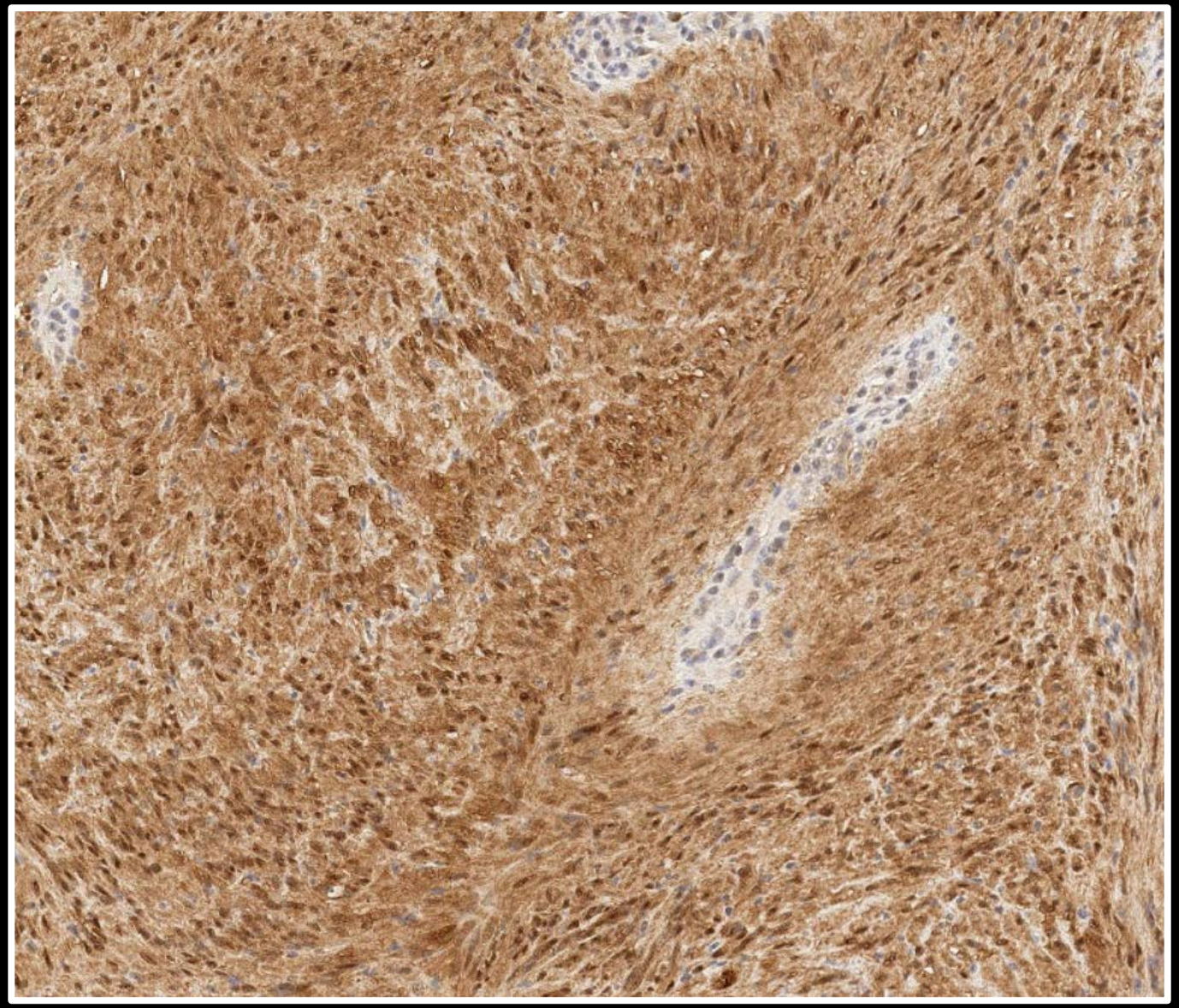
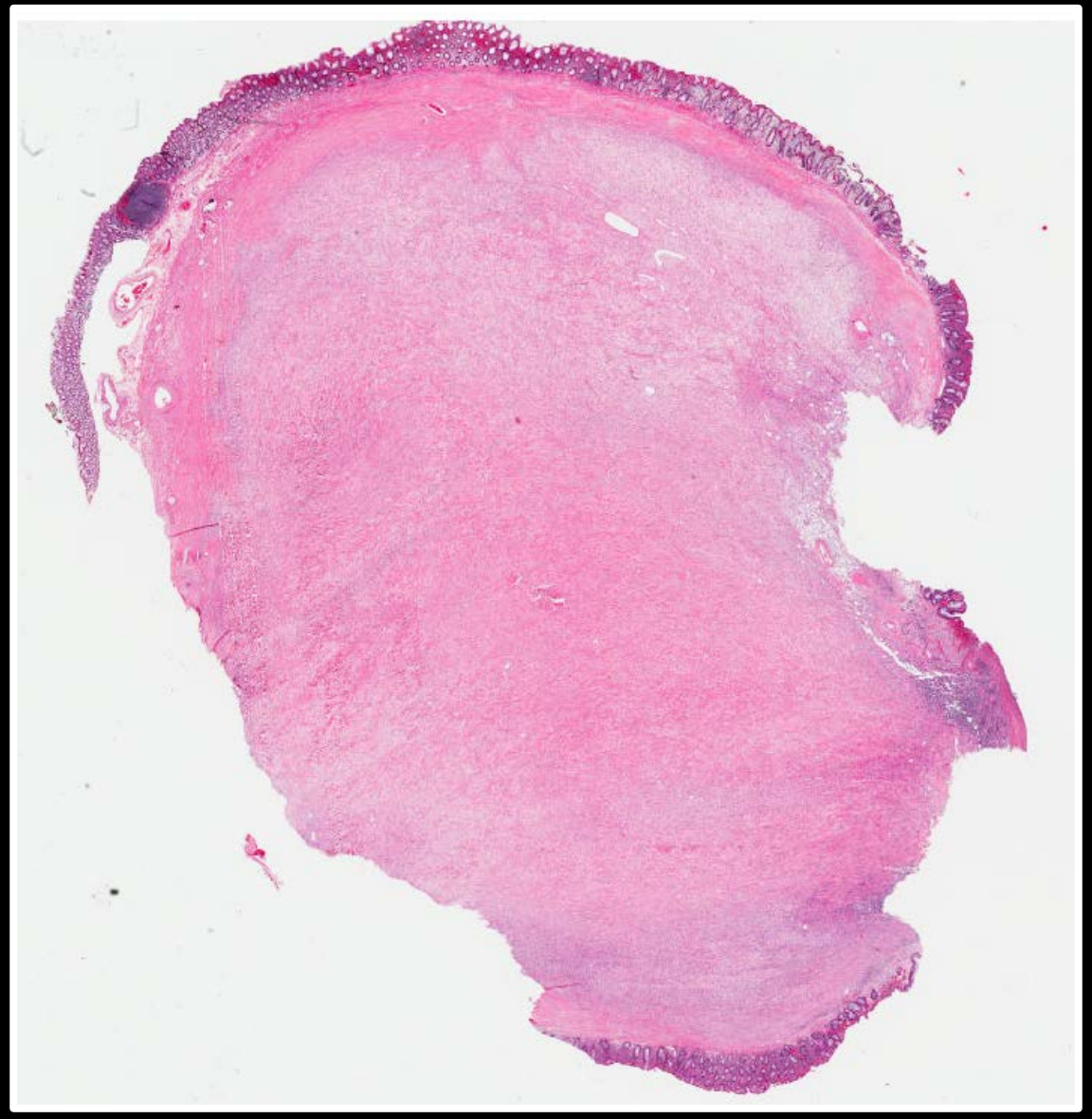
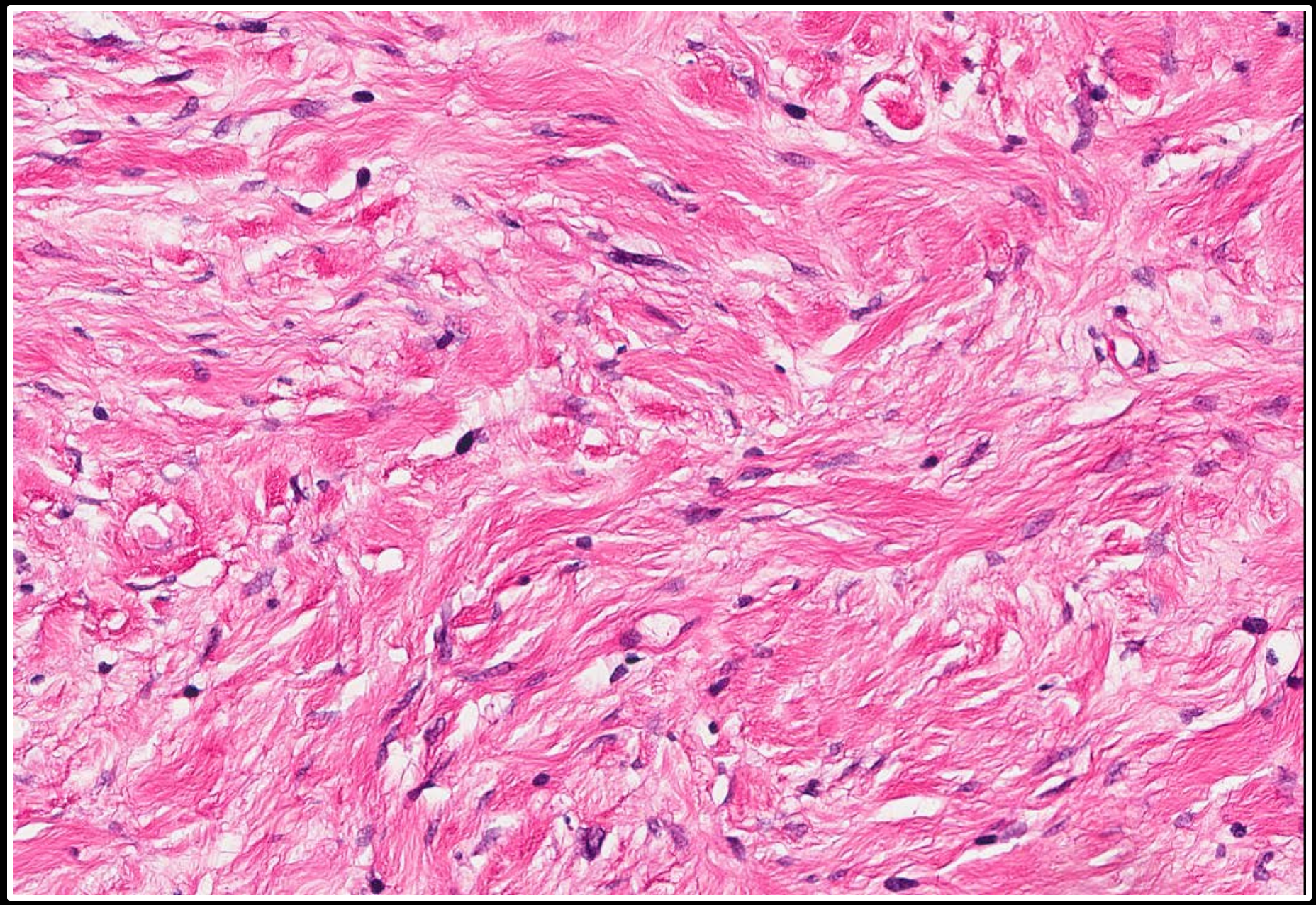


Neurofibroma

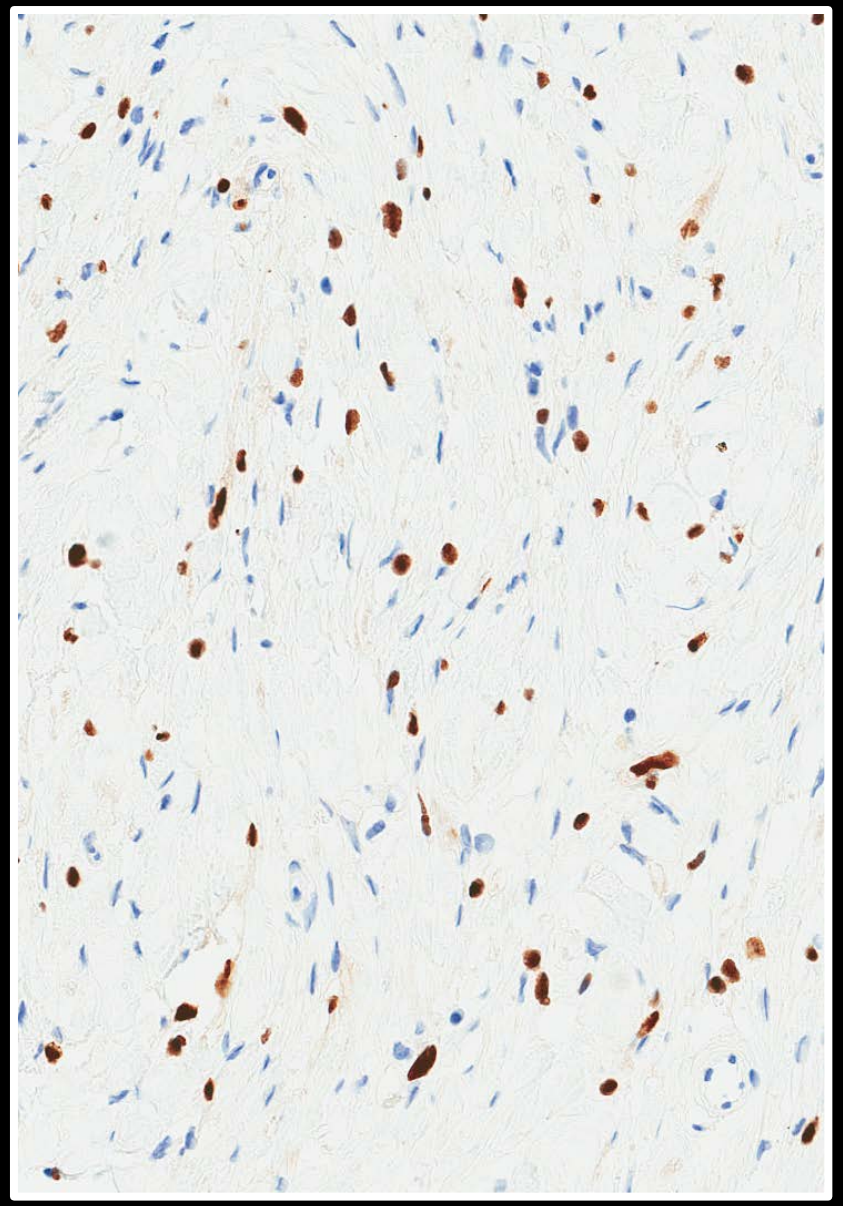
- Sporadic OR in setting of NF1
- **Rare in GI tract
- Bland spindled cells with variation in cell size
- Collagenous matrix
- Mitoses absent to extremely rare
- Subpopulation of cells S100/SOX-10+
- Subpopulation of cells CD34+

Neurofibroma

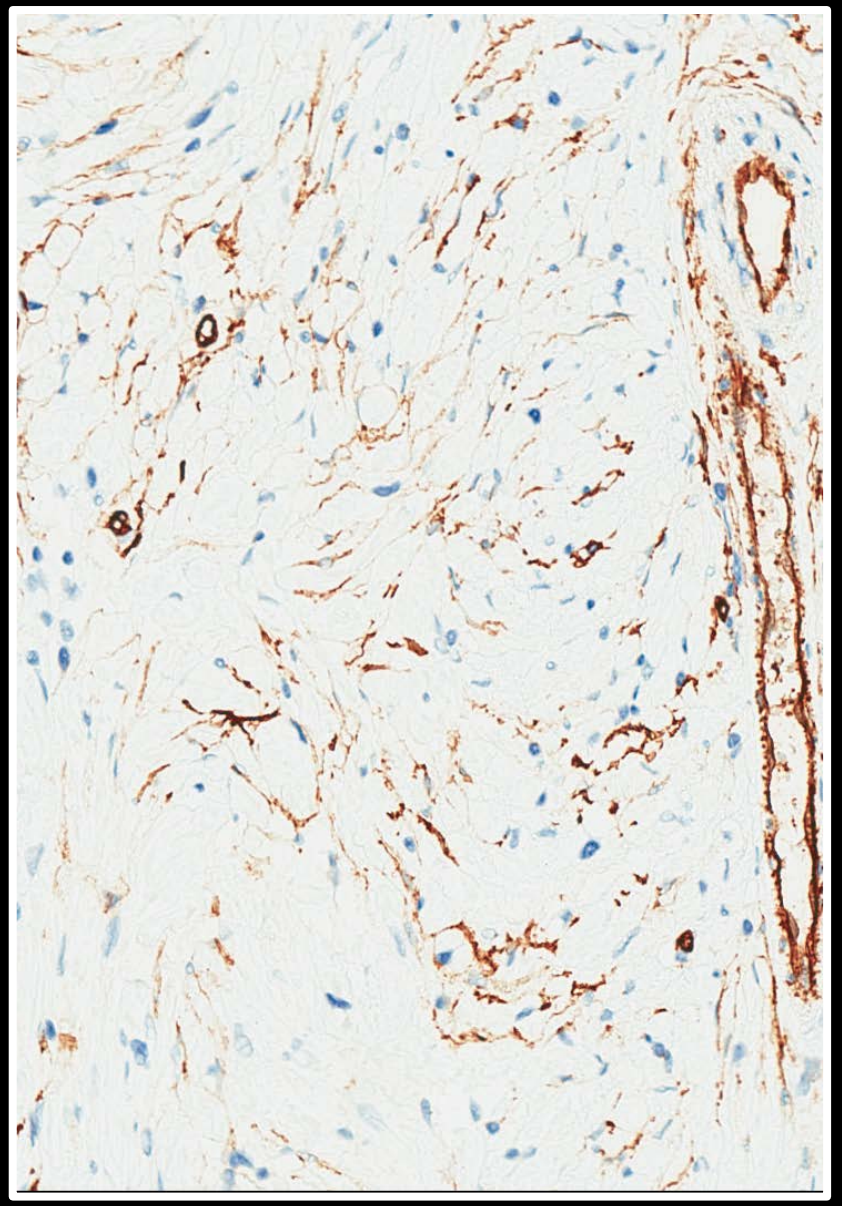




SOX-10



CD34



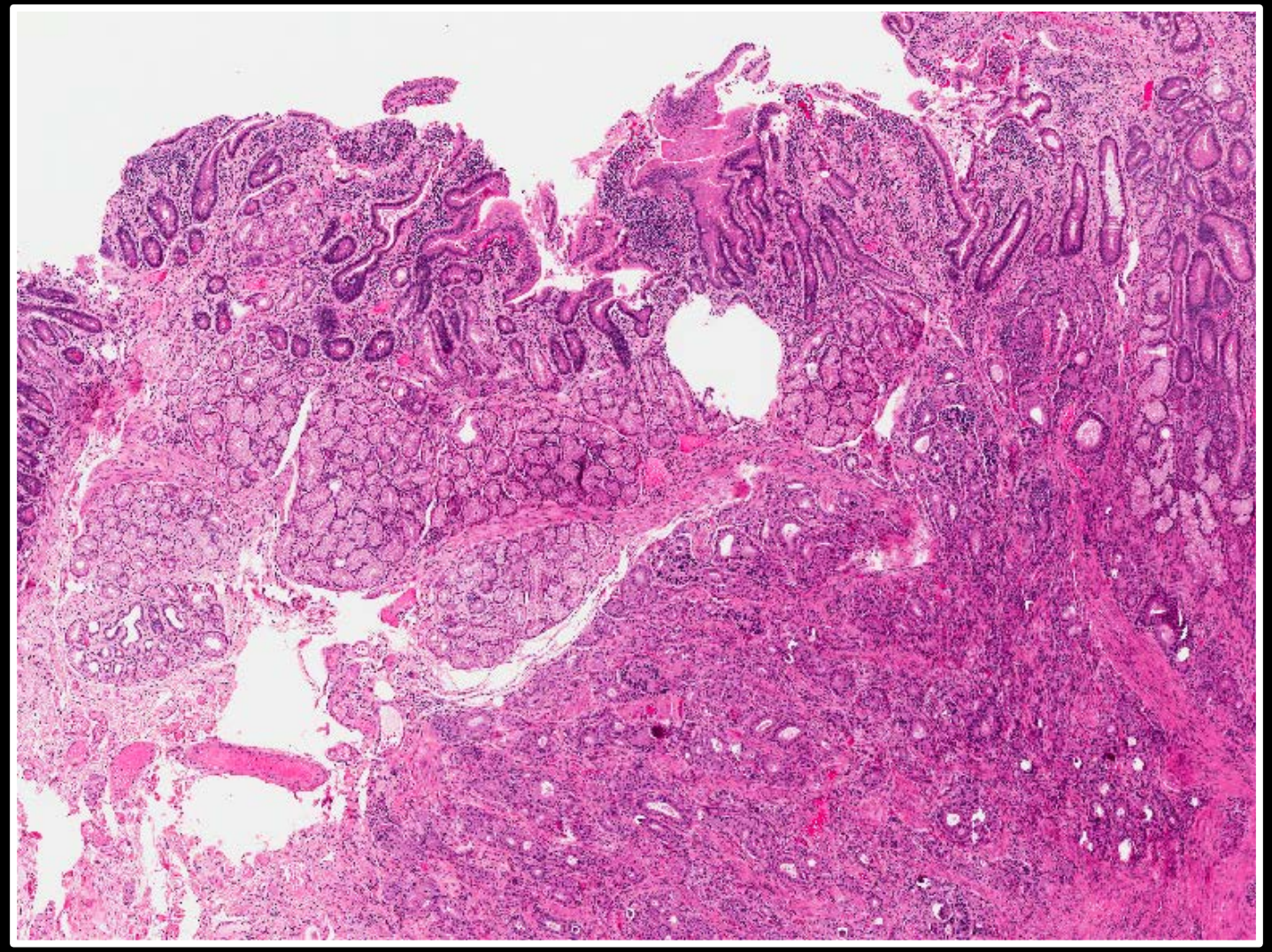
GI ganglioneuromatous proliferations

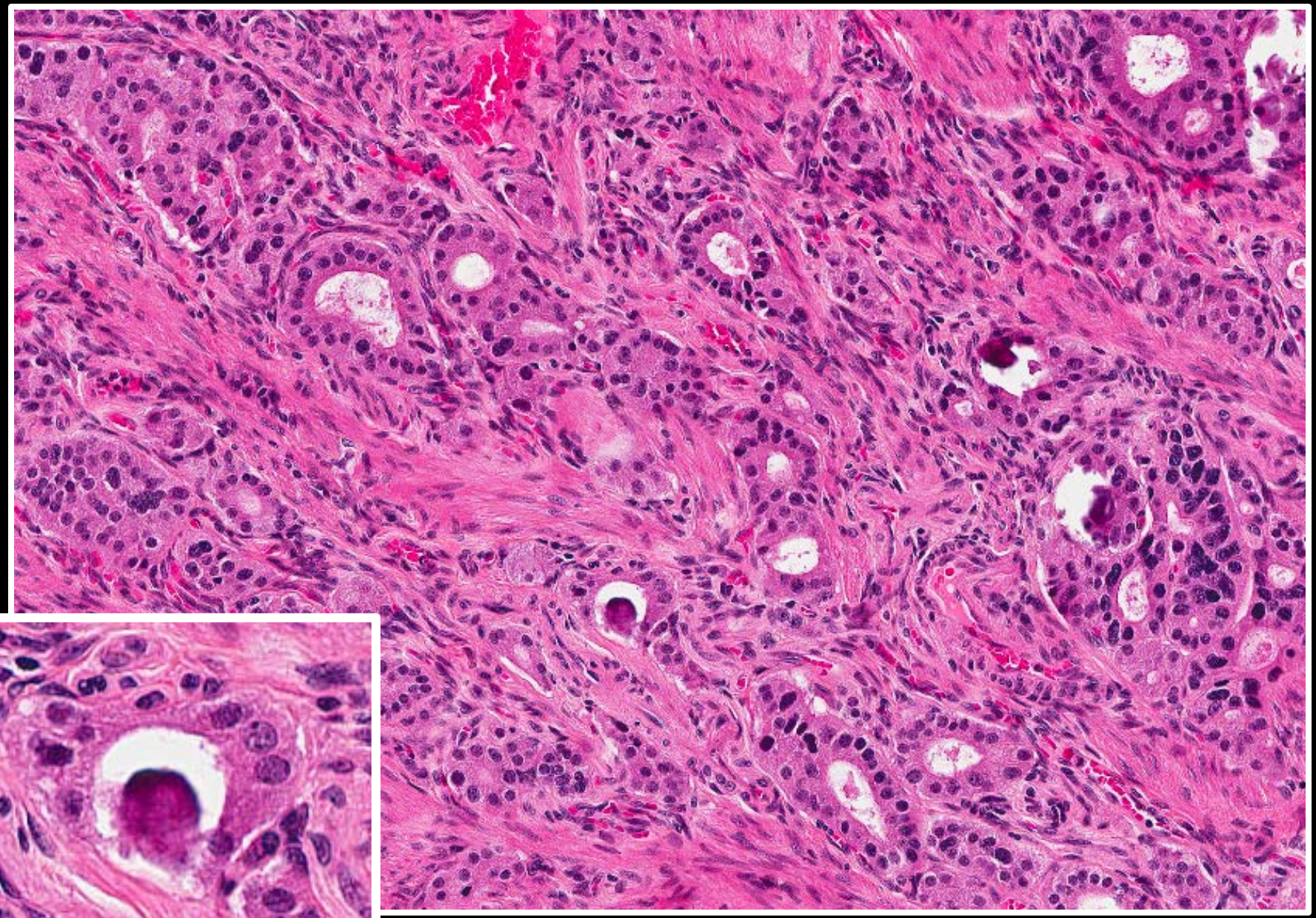
- Sporadic (solitary) polyps
- Ganglioneuromatous polyposis – Cowden's
  - Mixed polyposis
  - Increased cancer risk
- Diffuse ganglioneuromatosis – MEN2b, NF1
  - Benign but symptomatic : pseudoobstruction, megacolon

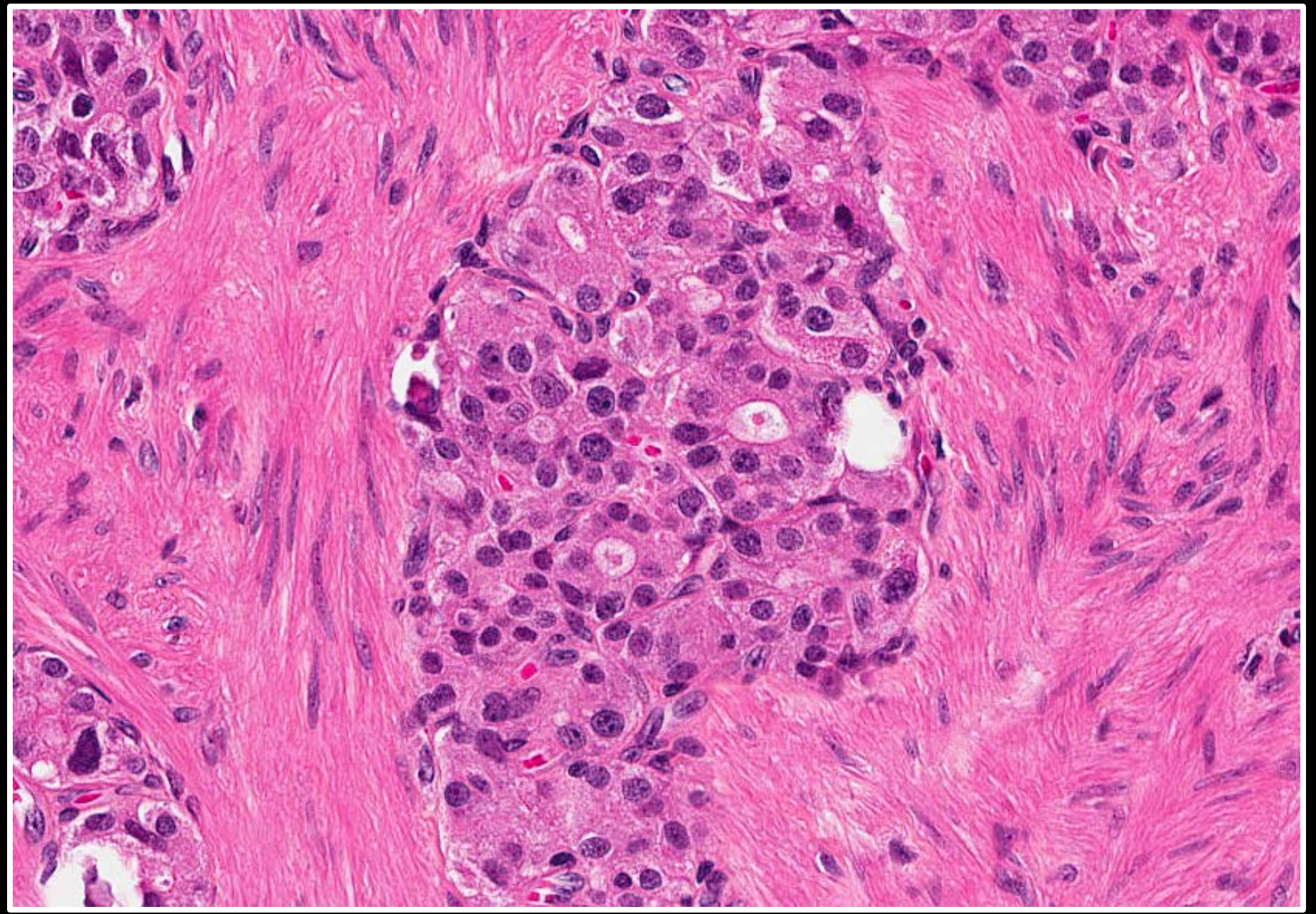
Case 2: 54 y.o. female, no PMHx

Presents with abdominal pain

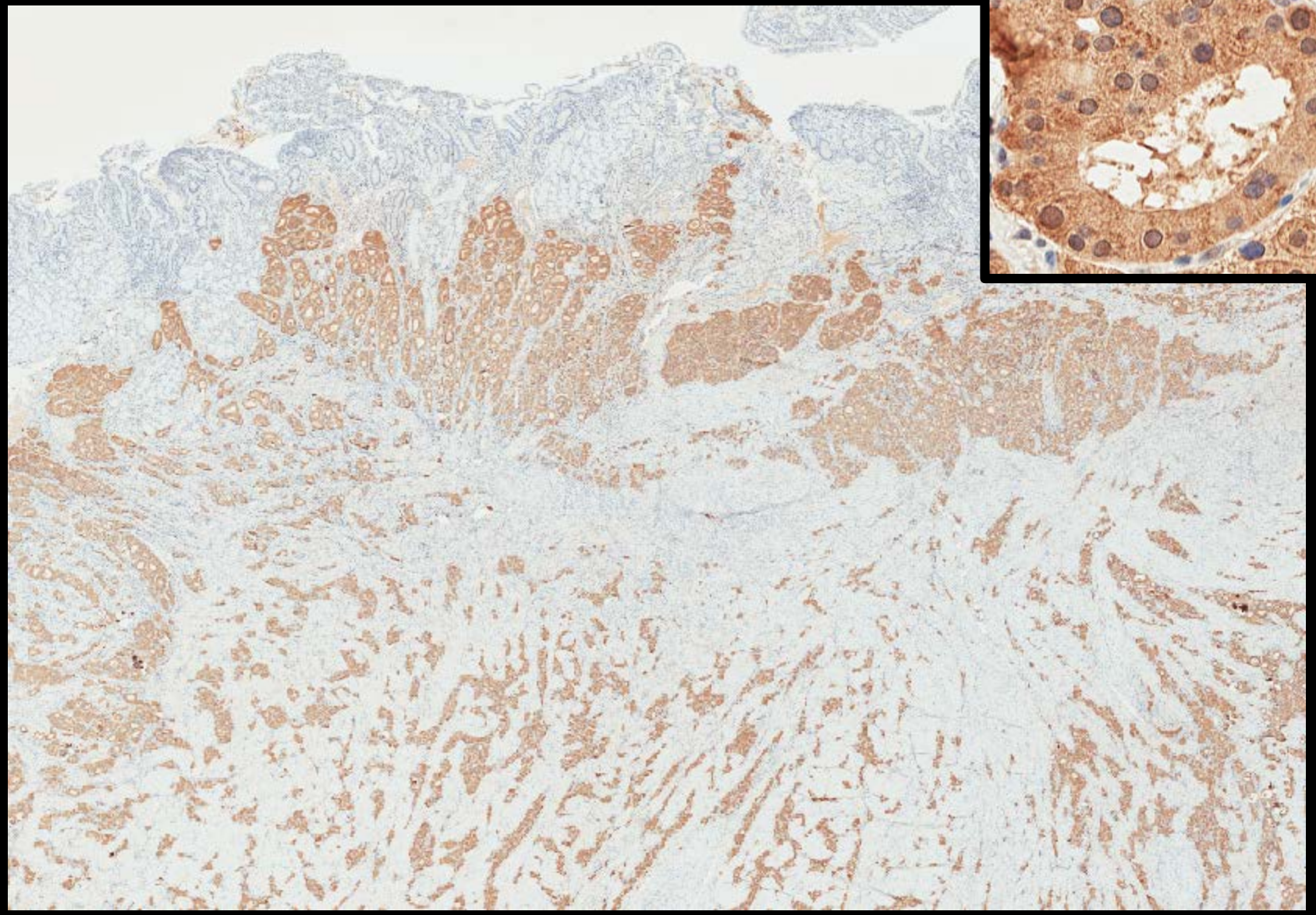
3.7 cm duodenal mass, undergoes Whipple procedure

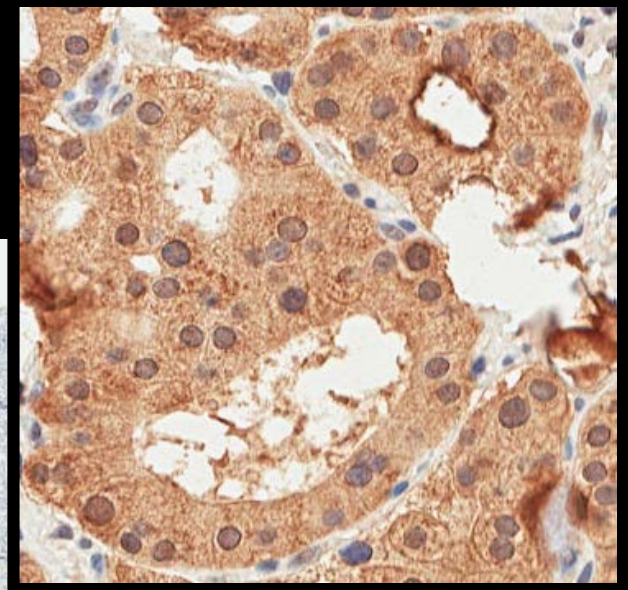




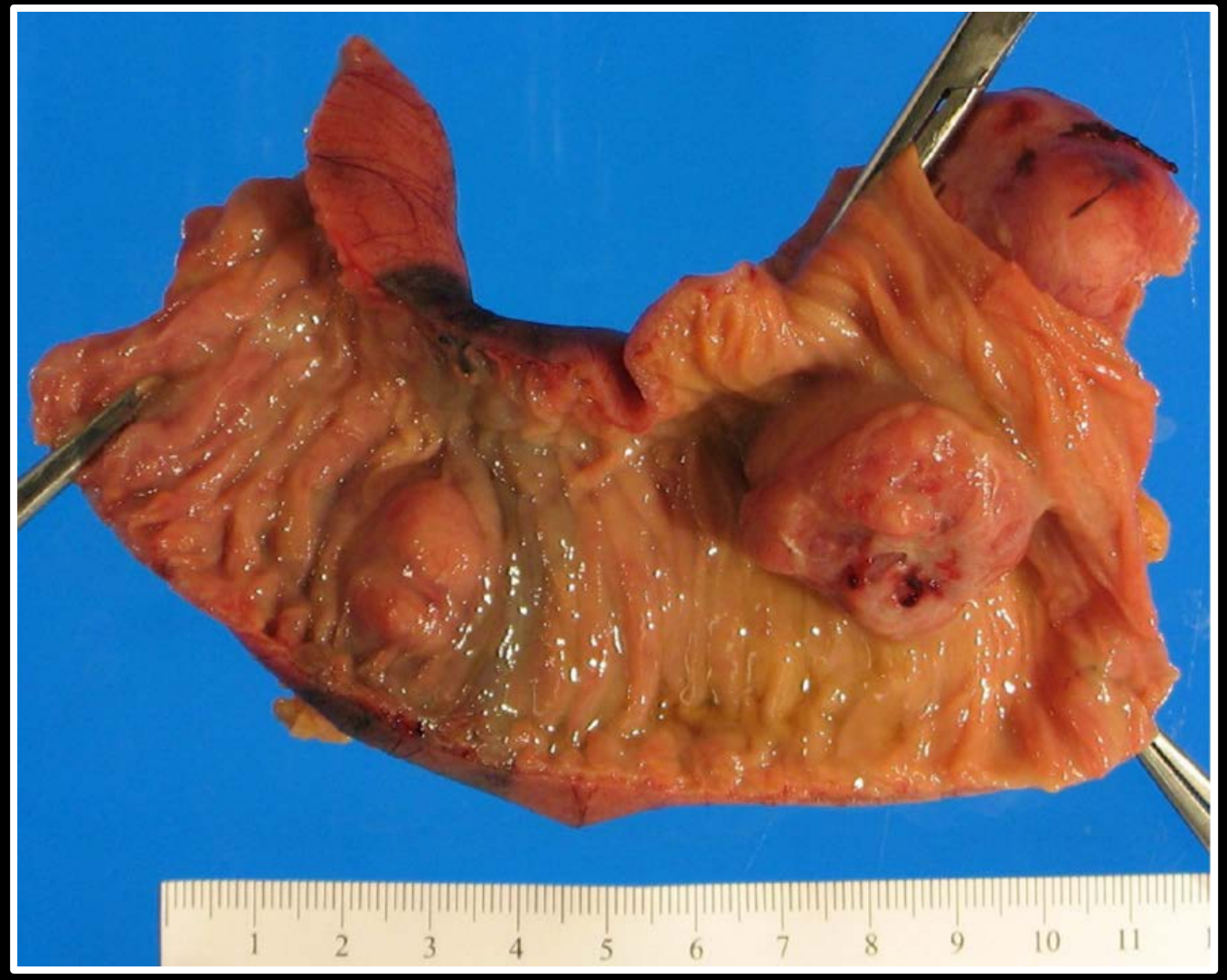


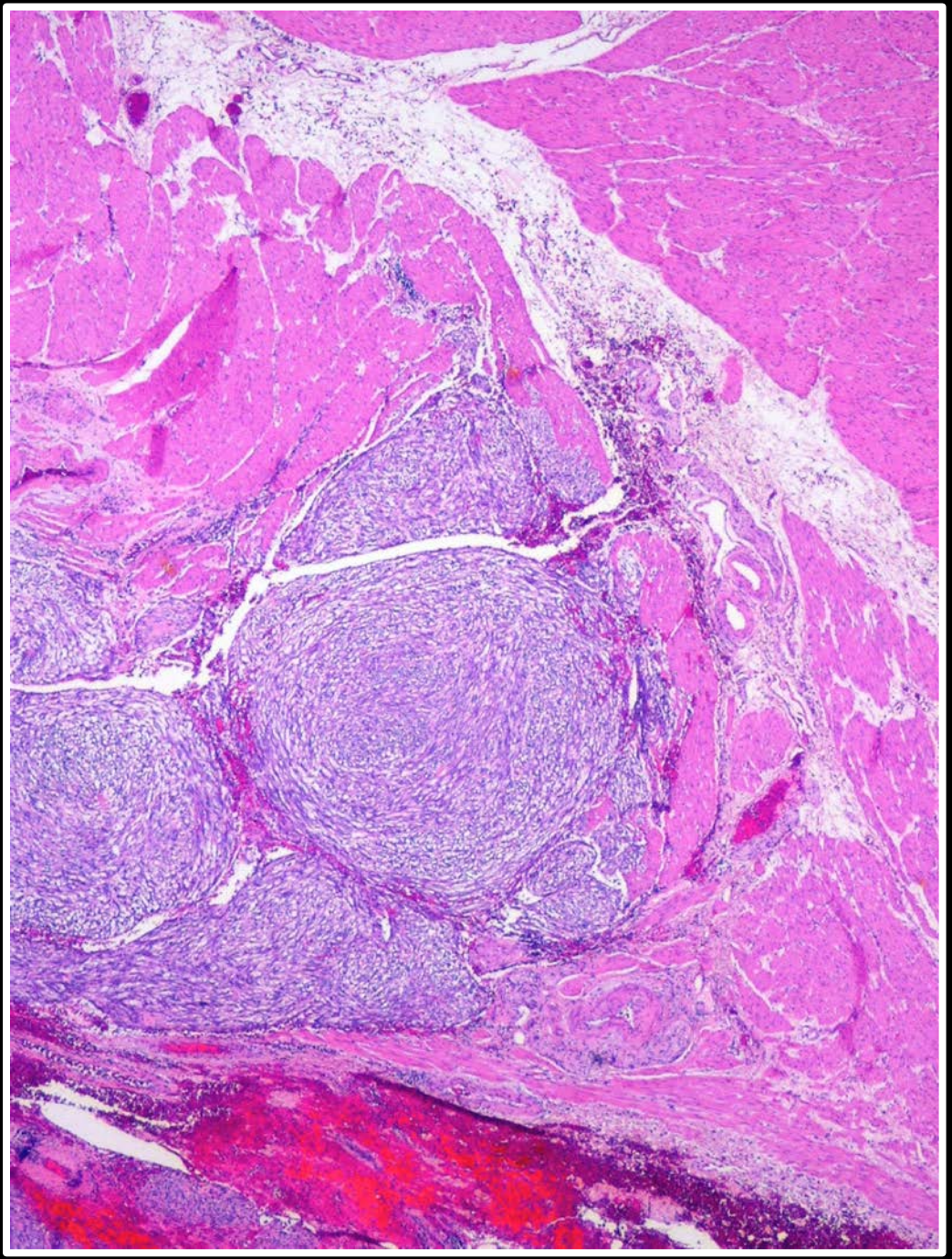
Somatostatin

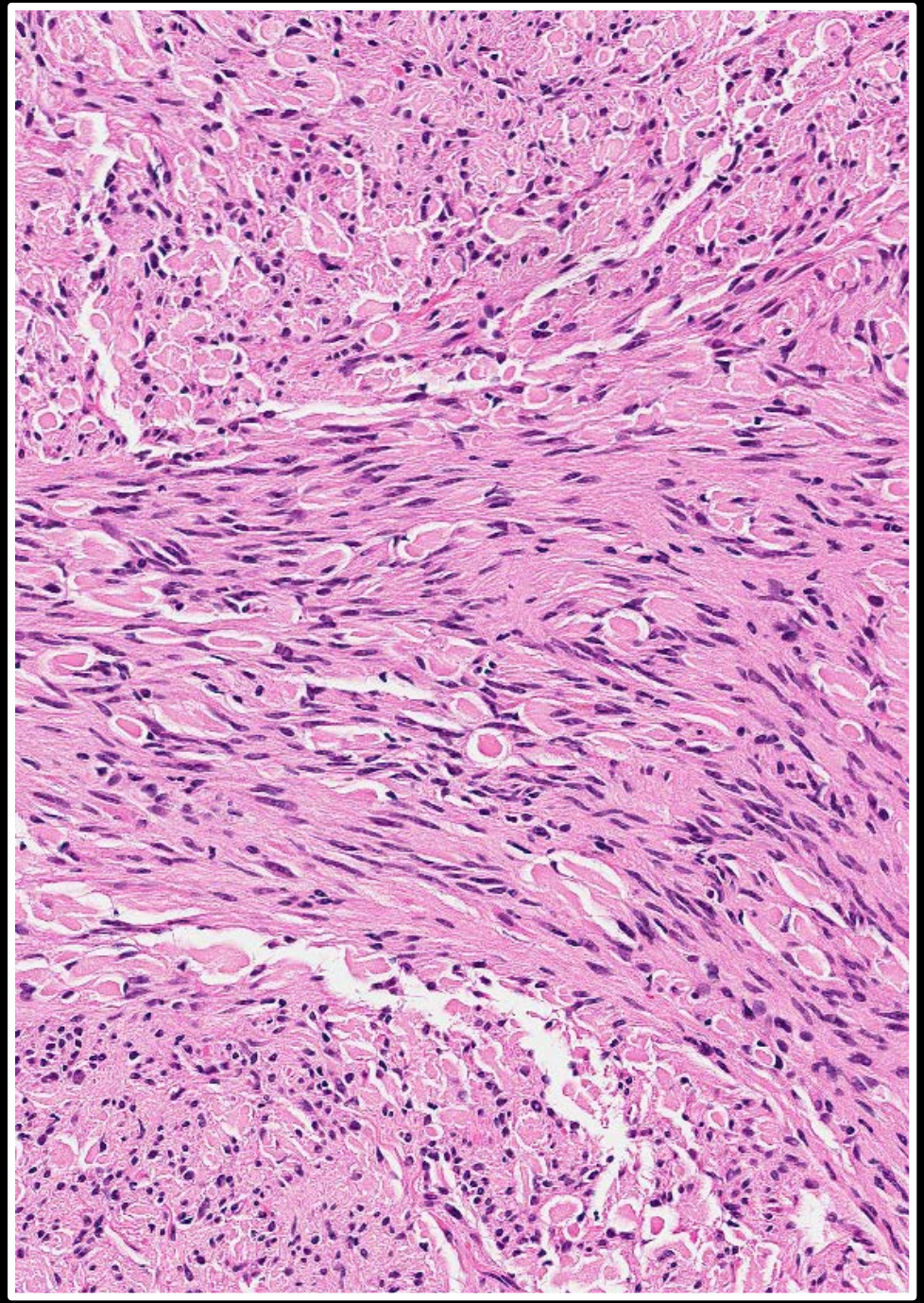


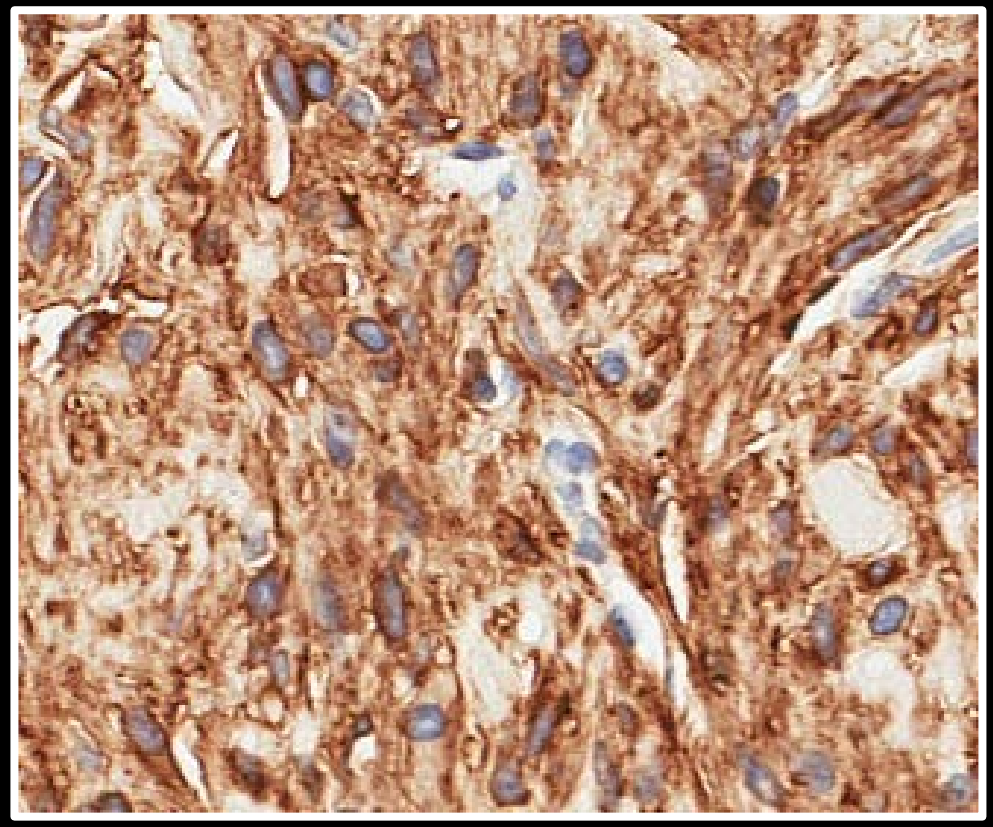


Additional gross findings









c-kit

Summary of findings

- Somatostatinoma (3.7 cm)
- Multiple GISTs, only very rare mitoses
- Coincidence, or syndromic?

Neurofibromatosis Type 1 (NF1)

- Autosomal dominant
- Incidence 1:3000 births
- NF-1: one of the highest new mutation rates
- 50% of patients have no family history
- No standard molecular test
  - Gene too large and no hot spots

NF1

- Variable expression
  - “segmental” form limited to dermatome
- Some experts believe GI tract involvement is a type of segmental NF1 presentation
- NF manifestations may be limited to GI tract or external features few/mild

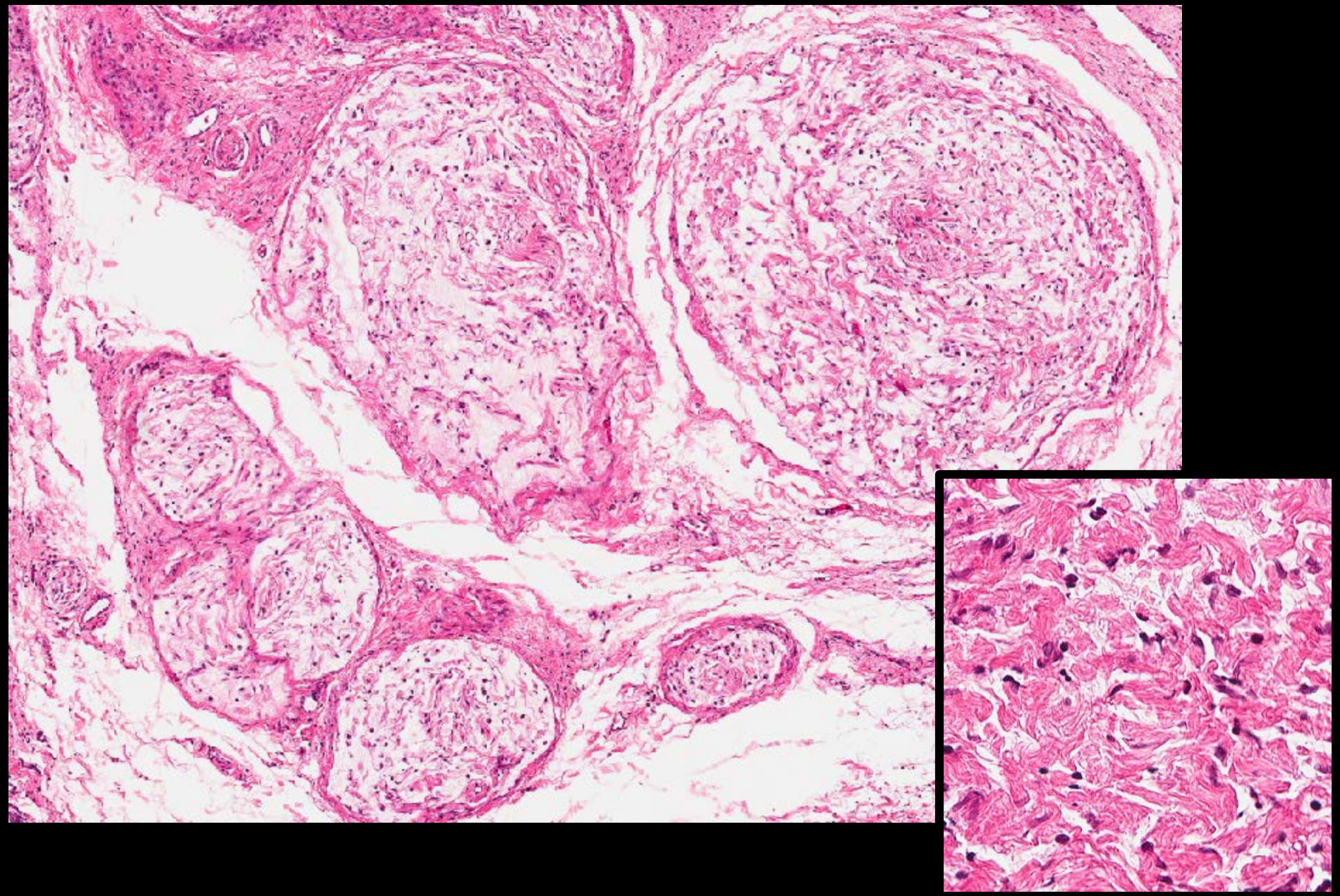
NIH Consensus Criteria for NF-1: 2 or more features required

- 6+ Café au lait spots
- 2+ cutaneous/subcutaneous neurofibromas OR a plexiform neurofibroma
- Axillary or inguinal freckling
- Optic nerve glioma
- 2+ Lisch nodule (iris hamartomas)
- 1 first degree relative with NF-1
- Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/- tibial pseudoarthrosis
- **No GI criteria

Neurofibromatosis Type 1 – GI features

- Uncommon (5-25% of NF1 patients), middle/older aged patients
- Clinically unrecognized?
  - Only 5% symptomatic
- Hyperplasia/hypertrophy of ganglion cells and neural processes
  - Distinct nodules or diffuse proliferation within myenteric plexus
- Multiple synchronous or metachronous tumors
  - **Multiple GISTs, typically small bowel
  - GI Neurofibromas
    - Often plexiform
    - Often full-thickness bowel involvement
    - Upper GI (small bowel, esophagus, stomach) more common
  - Diffuse ganglioneuromatosis
  - GI endocrine tumors (especially ampullary/periampullary tumors; somatostatinomas)

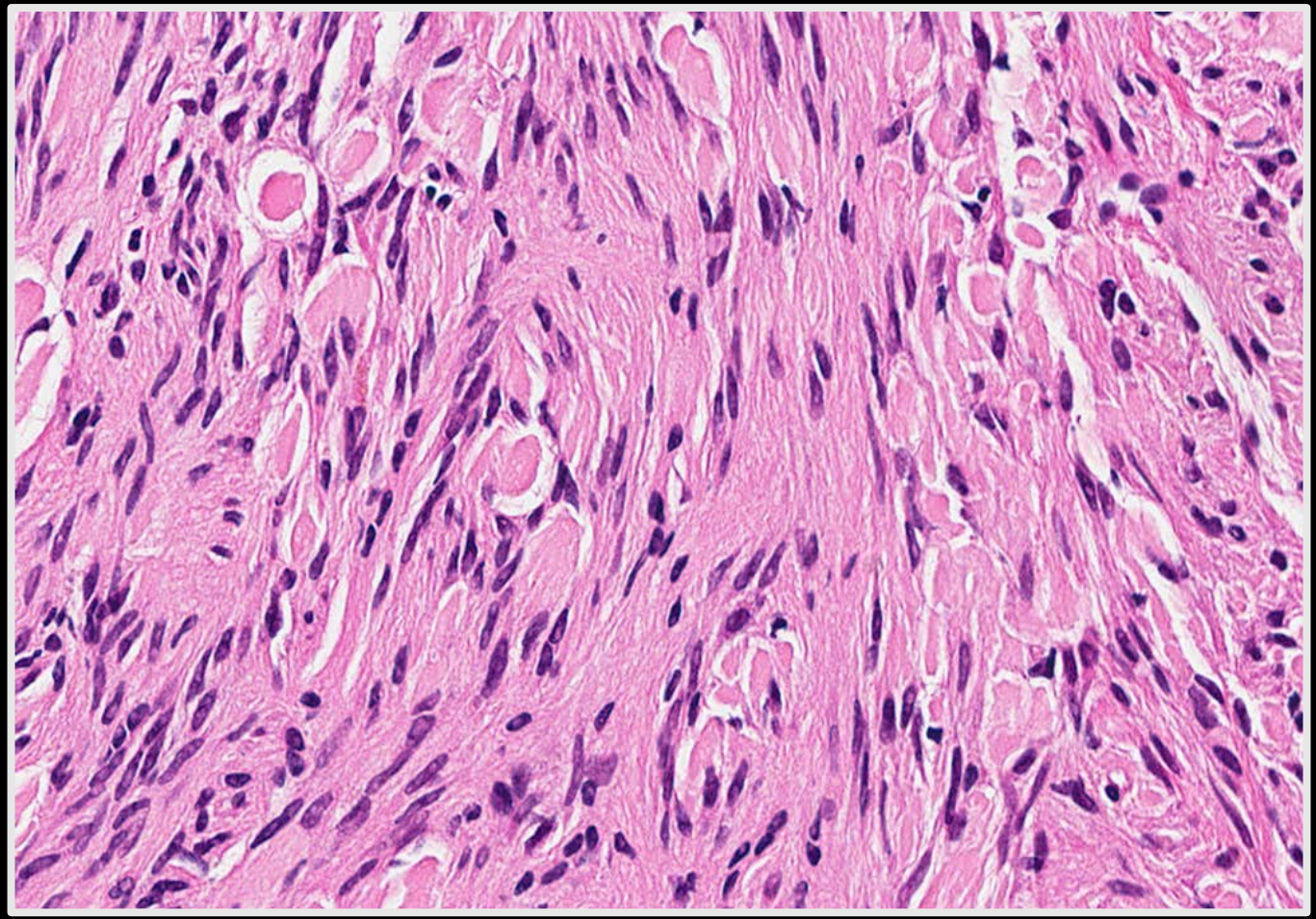
Plexiform neurofibroma



GISTs in NF1:

- Multiple, small (<2 cm)
- Small bowel
- Spindled (80-90%)
- ICC hyperplasia (30-40%)
- Skeinoid fibers characteristic
- Typically low to no mitoses
- Malignant GISTs (up to 20%)
- c-kit/DOG-1 IHC +
- *S100 diffusely/patchy +
- 10% mutations in KIT, PDGFRA
- Lack SDH mutations
- Poor response to imatinib

“Skeinoid” fibers in NF1 GISTs

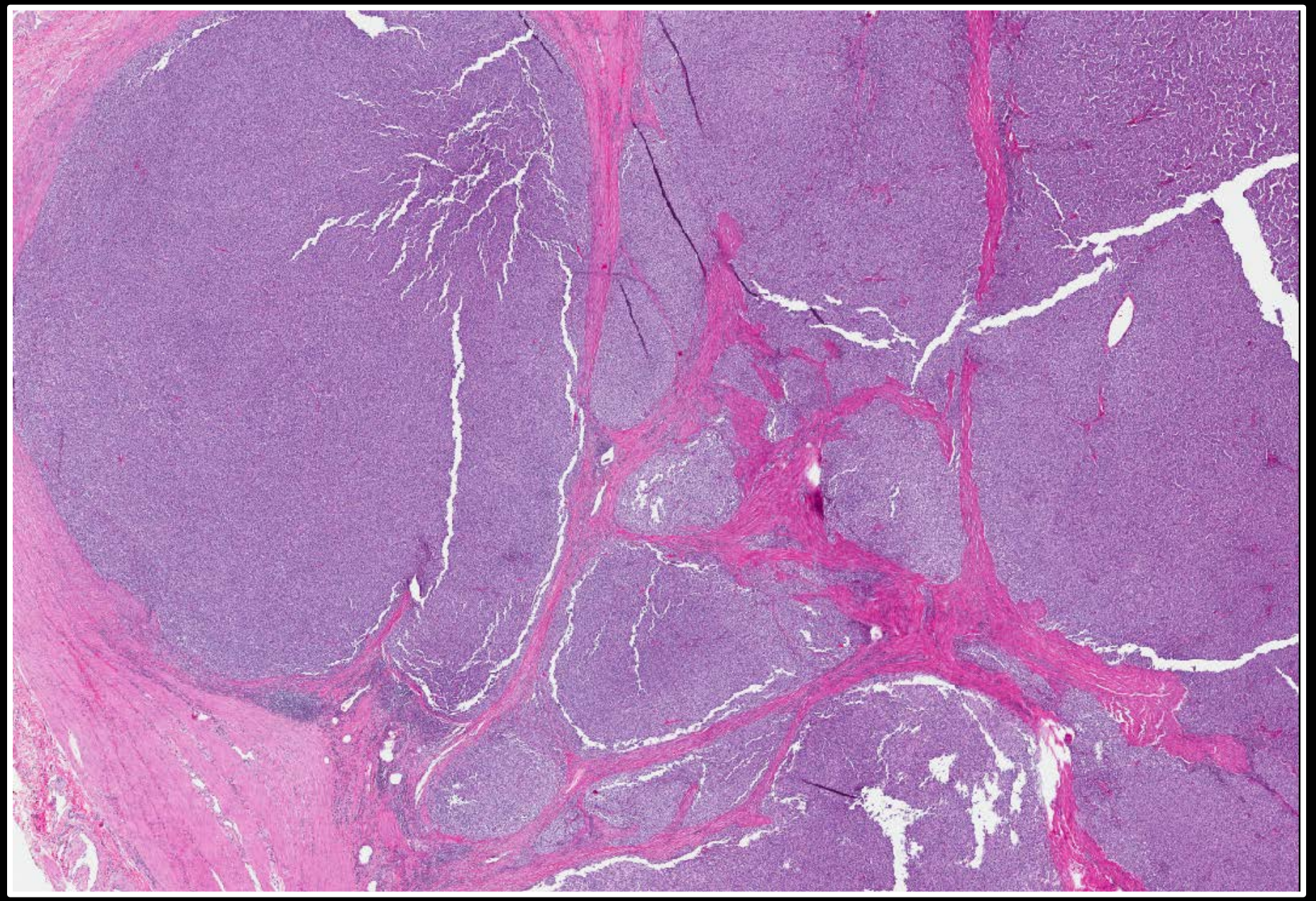


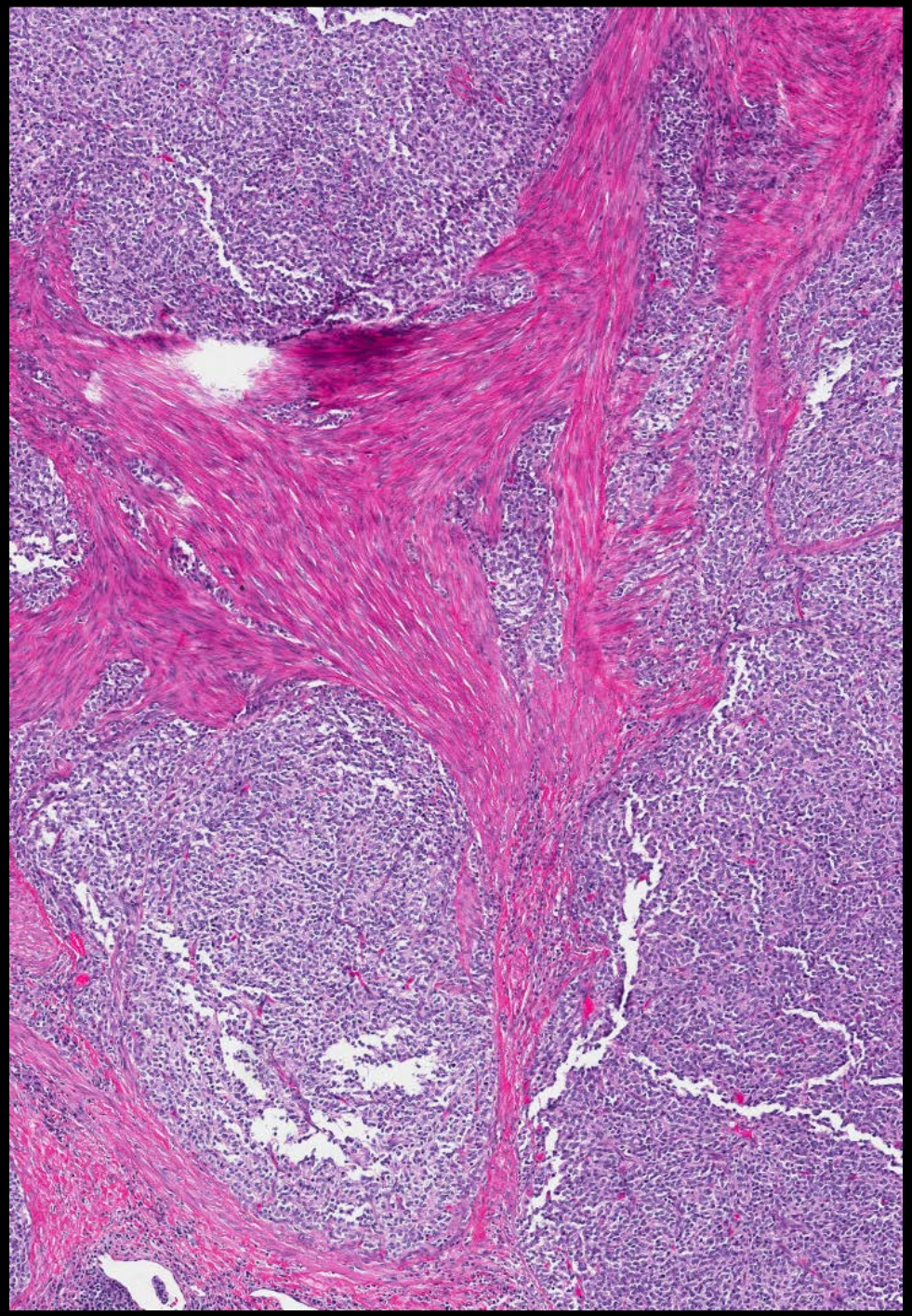
Summary: NF1 –mesenchymal GI tumors

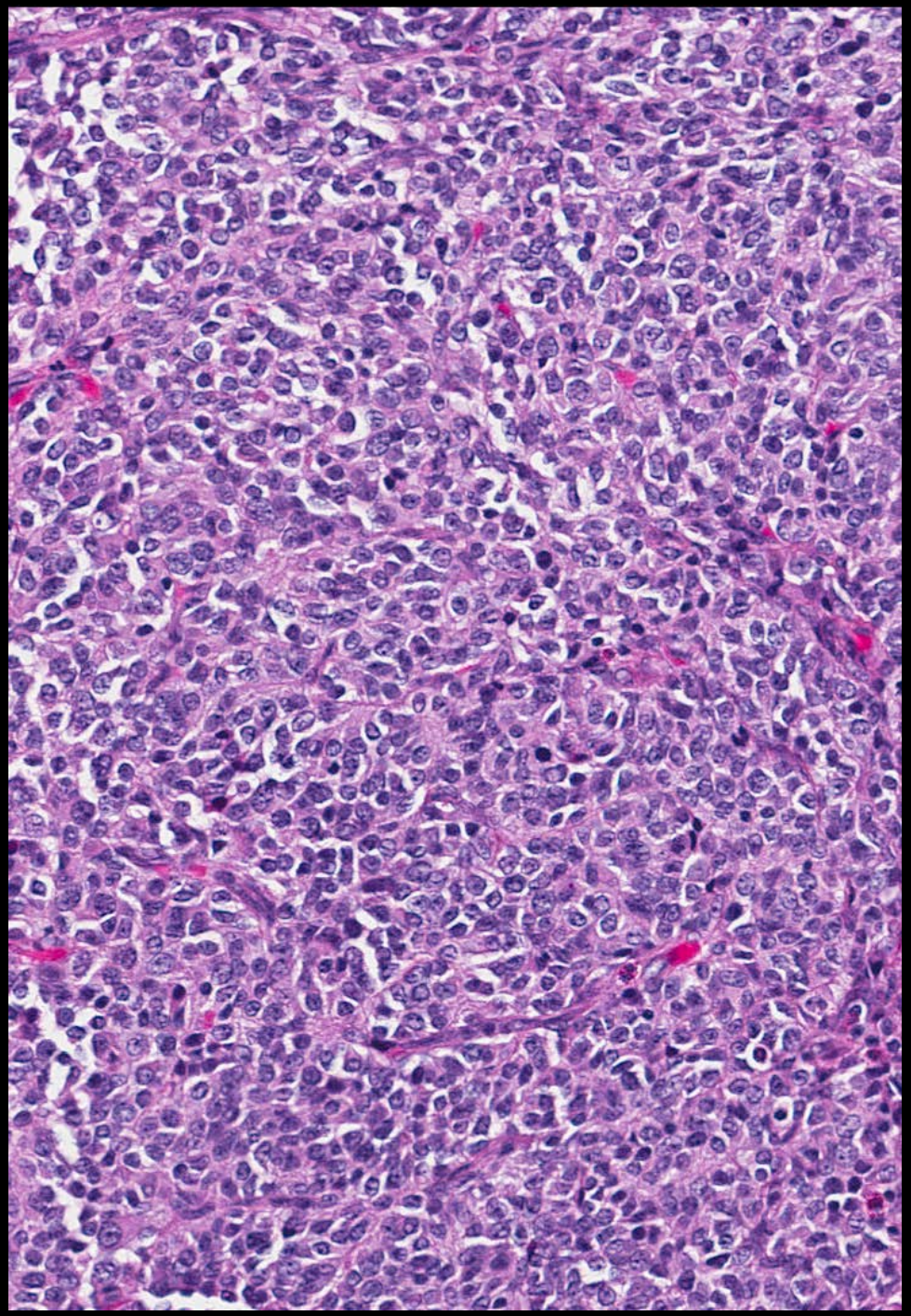
- Multiple small bowel GISTs (skeinoid fibers) most common tumor
- Ampullary/periampullary NETs, especially somatostatinomas
  - NETs at other GI sites less common
- Increased risk of malignant endocrine tumors
- GI presentations highly suspicious for NF1 are:
  - NET (especially ampullary/periampullary) + GIST
  - Neurofibroma + GIST
  - Ganglioneuroma + GIST
  - Plexiform neurofibroma of GI tract
  - Diffuse ganglioneuromatosis affecting the mucosa and submucosa

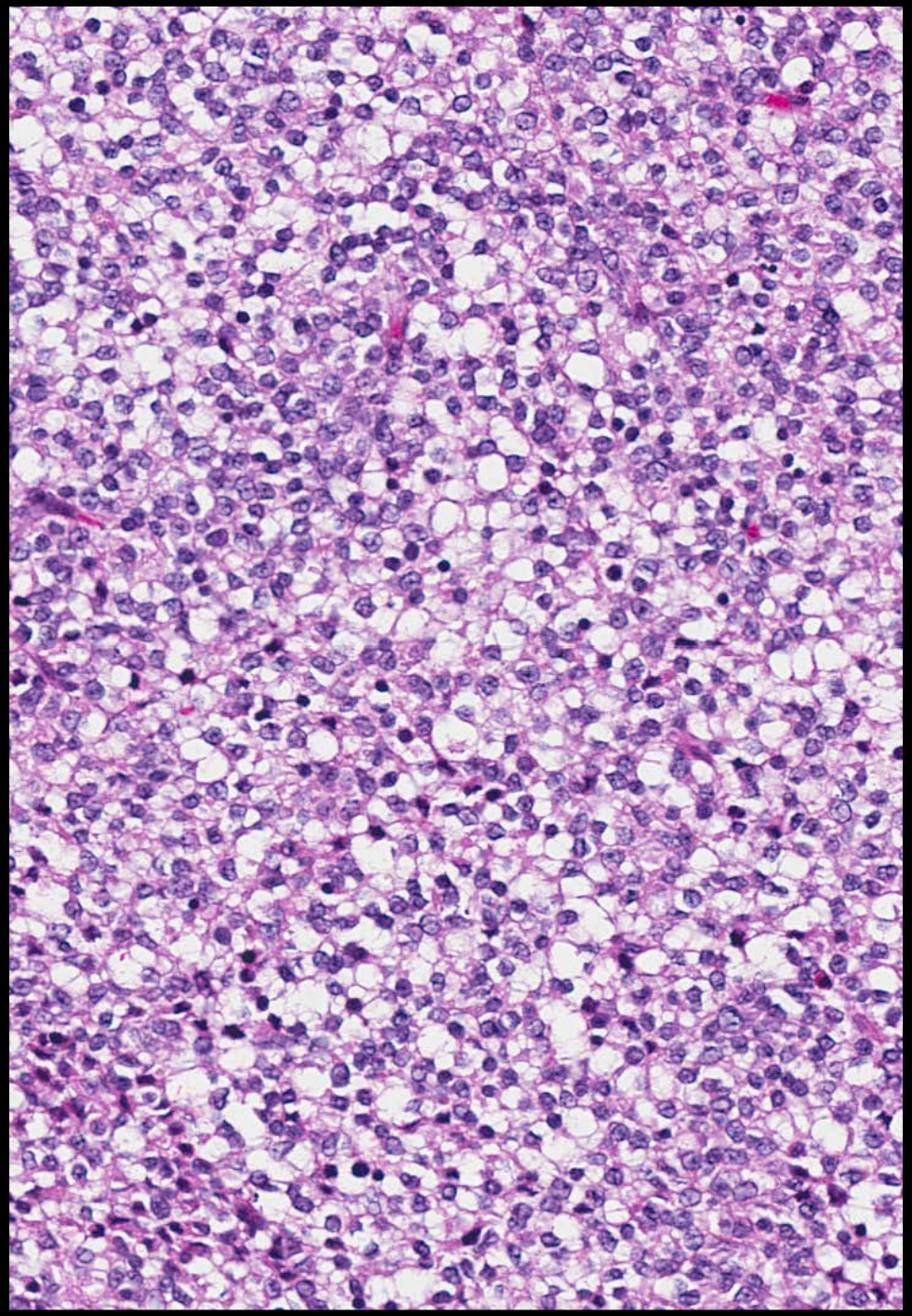
Case 3

- 22 y.o male presents for excision of 4.5 cm gastric tumor; imaging shows multiple gastric masses as well as enlarged peri-gastric lymph nodes and liver masses
- No personal medical history
- Patient’s father recently diagnosed with paraganglioma and there is a family history of “cancer”









All masses similar histology/IHC

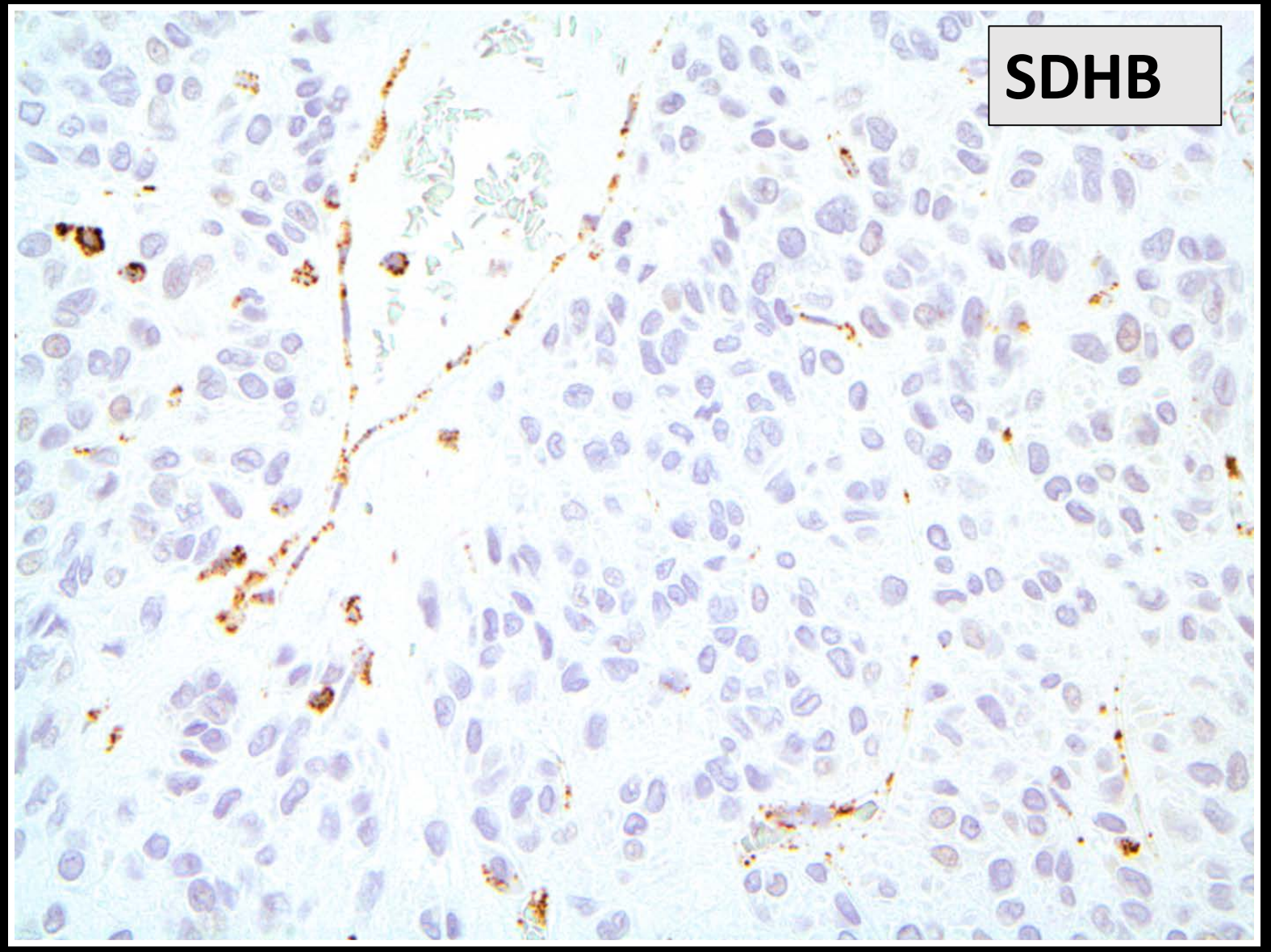
IHC: c-kit, DOG-1 +

Lymph nodes, peritoneum, liver involved

Mitoses >20/50 HPFs in several masses

Summary

- Multifocal epithelioid gastric GIST (c-kit, DOG-1 +)
- Metastases at presentation
- Young patient
- Is this anything other than a sporadic GIST?
- Is there any other information or ancillary testing you might want?


SDHB

Case: SDH-deficient GIST- Carney-Stratakis Dyad

- Multiple SDH deficient GISTs
- Father with paraganglioma
- Patient and father tested and both showed germline SDH mutation

Inherited GIST syndromes

- SDH intact
  - Germline KIT mutations
  - Germline PDGFRA mutations
  - Neurofibromatosis Type 1 (NF1 gene mutations)
- SDH loss
  - Carney-Stratakis Dyad
    - Germline Succinate Dehydrogenase (SDH) subunit B, C or D mutations
    - GIST + paraganglioma
    - 20% of SDH negative GISTs
  - SDHA germline mutations
    - 30% of SDH negative GISTs

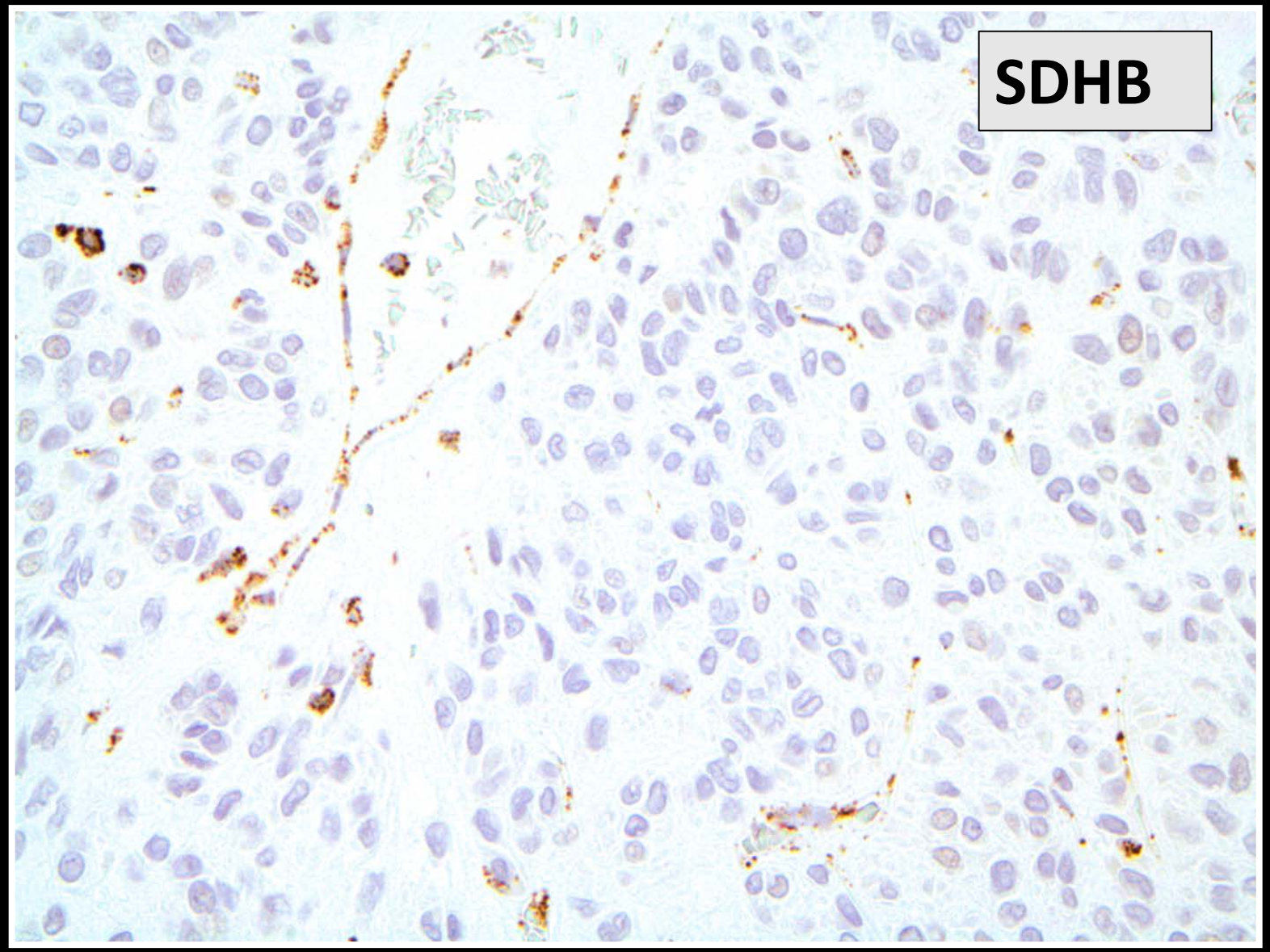
  - *50% of GISTs with loss of SDH seen in Carney Triad (not inherited*, syndromic, SDHC promoter hypermethylation*; GIST, paraganglioma, pulmonary chondroma)*

Succinate Dehydrogenase

- SDH: complex of proteins of the inner mitochondrial membrane, SDHA/B/C/D
  - Important for cellular respiration
- Germline SDH mutations in paragangliomas/pheochromocytomas, renal cell carcinoma, thyroid tumors, GISTs and pituitary adenomas
- Bi-allelic loss or promoter hypermethylation leads to destabilization of SDH complex and loss of SDHB by IHC.
- No matter which subunit (A/B/C/D) affected, SDHB IHC will be lost
  - SDHA loss (in addition to SDHB loss) identifies SDHA germline mutations
  - IHC for SDHC and SDHD not reliable currently

Accurate SDH IHC interpretation essential

- Loss of SDHB by IHC = germline SDH mutation or Carney Triad (SDHC promoter hypermethylation)
- Positive staining: granular, cytoplasmic (mitochondrial)
- Need internal positive control (endothelium, inflammatory cells)



SDH-deficient GISTs: Clinical features

- Gastric
- Female predominance
- Younger age
- Multifocal or metachronous dx
- LN, liver, peritoneal metastases common
- Prolonged survival
  - Survival not predicted by NCCN criteria (size, mitotic rate, location)
- Primary resistance to imatinib (Gleevac)
- Epithelioid or mixed epithelioid/spindled >>> pure spindled

Carney-Stratakis Dyad/CSS

- Dyad of GISTs and paragangliomas, first described 2002
- Average age of presentation: early 20s
- Males and females equally affected
- Germline loss of function mutations of SDHB/C/D
  - AD inheritance with incomplete penetrance
  - Variable phenotypic expression
  - Monozygotic twins, 1 w/GIST, other w/PG at same age

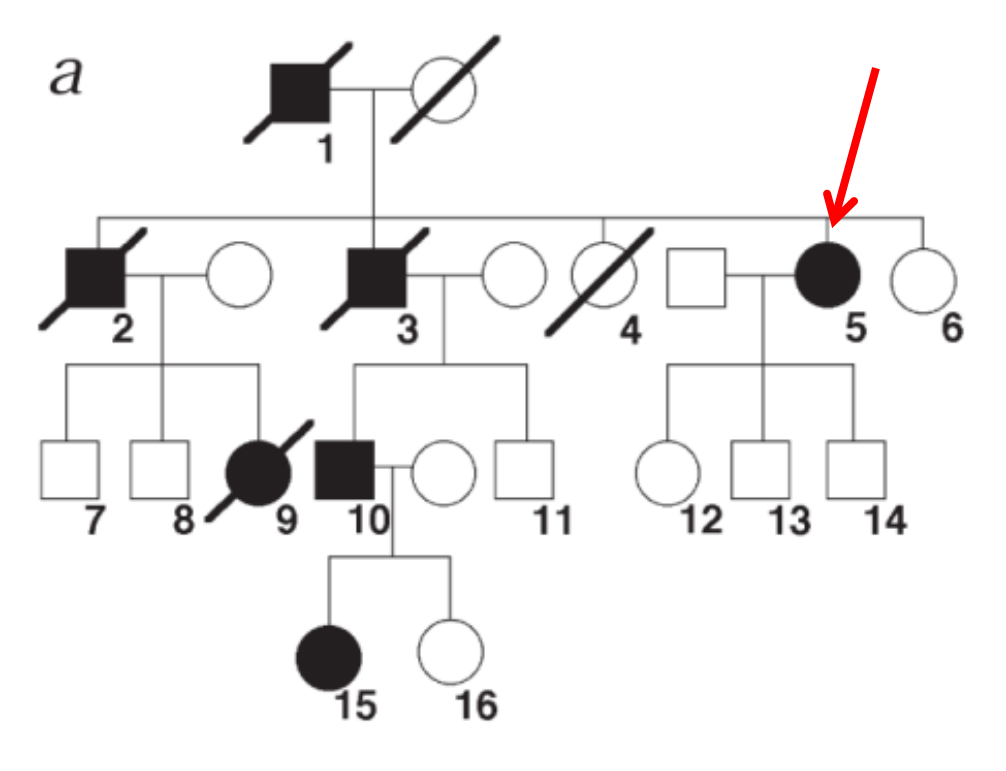
Carney Triad

- Triad SDH deficient GIST, Paragangliomas, pulmonary chondromas
  - Pheochromocytomas, adrenocortical adenomas (usually nonfunctional) also seen
  - Minority (~25%) of patients have all three tumors
- Average age at presentation: teenage years
- Marked female dominance
- SDHC promoter hypermethylation – not inherited
  - accounts for 50% of all SDH deficient GIST
  - *Recent report of rare SDHx mutations in Carney Triad

SDH intact familial GIST syndromes

Familial gastrointestinal stromal tumours with germline mutation of the *KIT* gene

Nishida T et al., Osaka University Medical School



Multiple benign GISTs: 5, 10

Multiple GISTs, benign and malignant: 9

Intestinal obstruction: 1, 2, 3

Confirmed CKIT Exon 11 mutation: 5, 9, 10, 15

KIT germline mutations

- More than 30 families described to date; mutations exons 8,9, 11, 13 and 17
- Autosomal dominant
- GISTs are spindle cell, arise throughout GI tract
- Diffuse ICC hyperplasia
- Response to imatinib

KIT germline – non GIST clinical features

Exons 11, 17: dysphagia
Exon 11: hyperpigmentation (perineal, circumoral, hands, knees) and urticaria pigmentosa
Non-tumor manifestations difficult to confirm

Hyperpigmentation or dysphagia

Robson et al, Clin. Canc. Res 2004; 10:1250-4

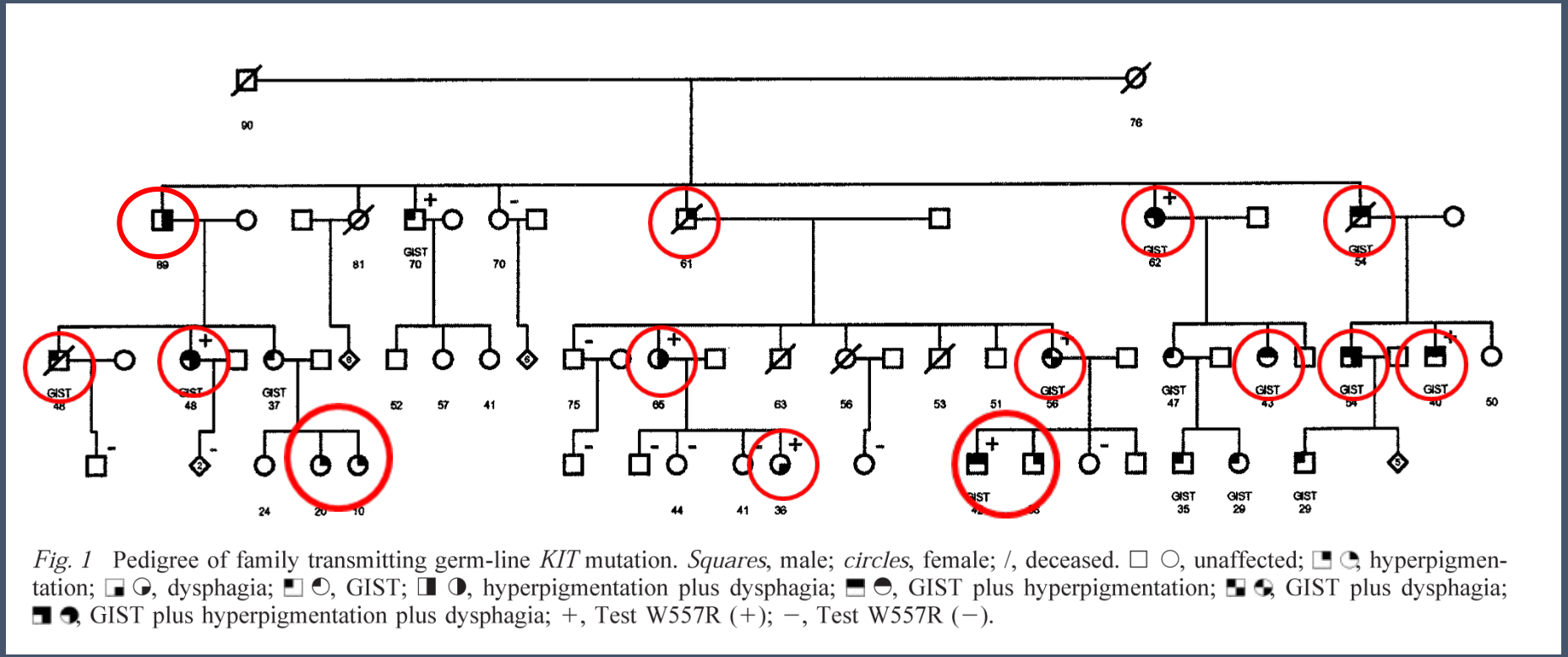
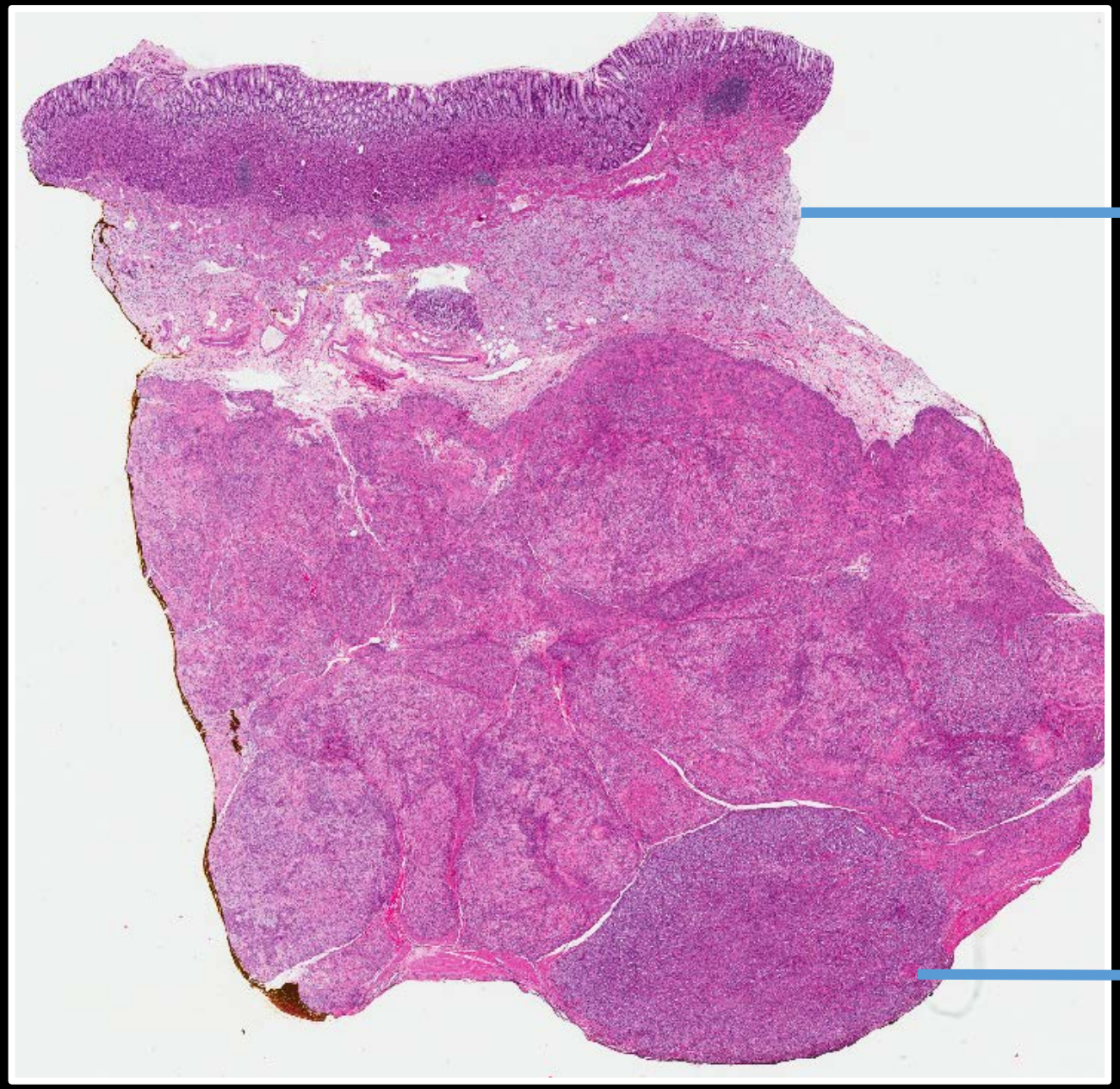


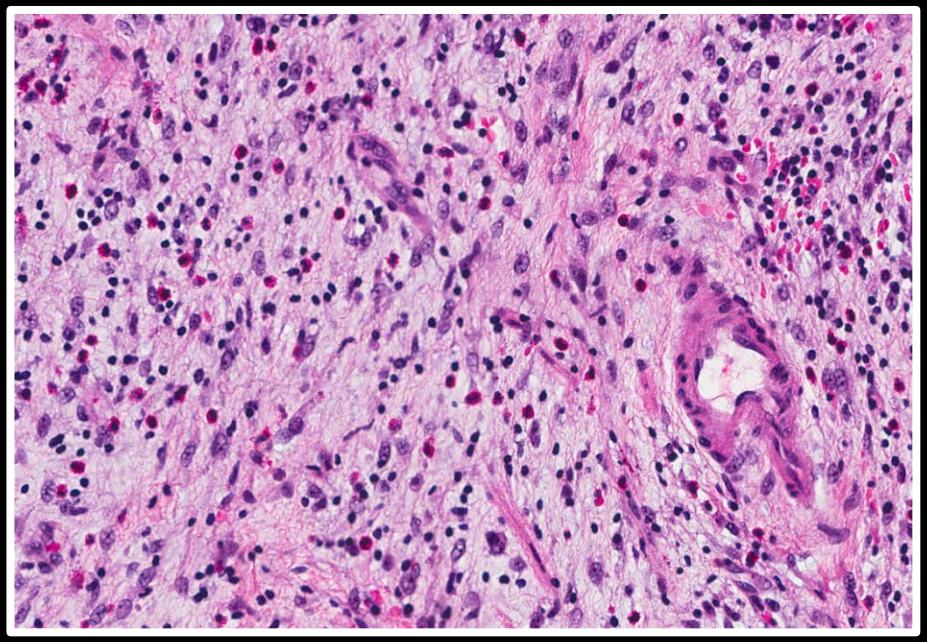
Fig. 1 Pedigree of family transmitting germ-line *KIT* mutation. *Squares*, male; *circles*, female; /, deceased. □ ○, unaffected; ◪ ◔, hyperpigmentation; ◪ ◔, dysphagia; ◧ ◴, GIST; ◨ ◑, hyperpigmentation plus dysphagia; ◓ ◓, GIST plus hyperpigmentation; ◩ ◕, GIST plus dysphagia; ◨ ◕, GIST plus hyperpigmentation plus dysphagia; +, Test W557R (+); −, Test W557R (−).

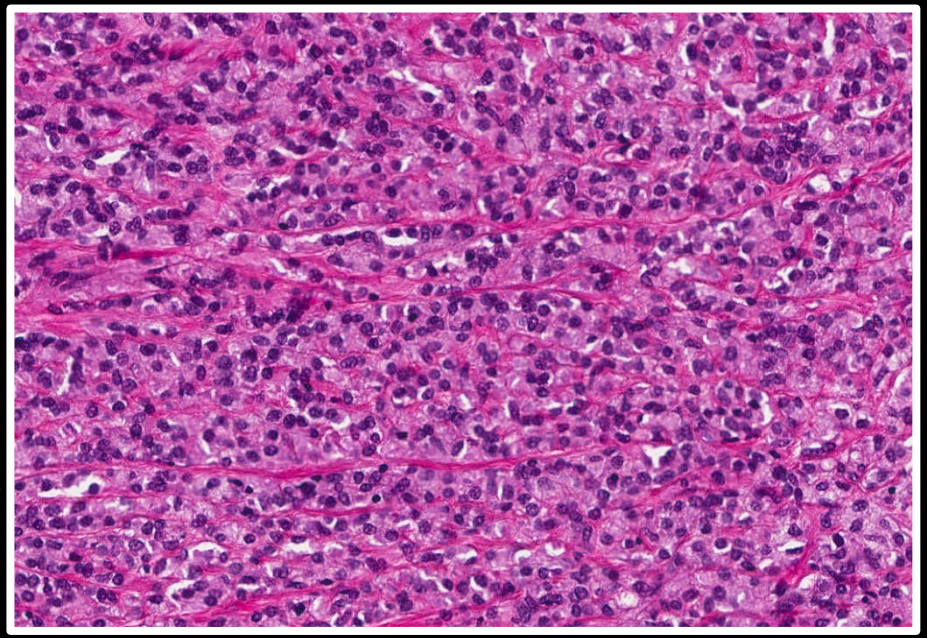
PDGFRA germline mutations

- 5 families described to date
- 5 separate germline mutations described in exons 12, 14 and 18
- Appears to be autosomal dominant with incomplete penetrance
- Clinical characteristics
  - Gastric GIST (single and multiple GISTs described) (4 reports)
  - Multiple small intestine or gastric “fibrous” tumors (4 reports)
  - Large hands (3 reports)
  - Multiple small intestine lipomas (2 reports)
  - Course facies (2 reports)
  - Premature loss of teeth requiring dentures (1 report)
- Clinical complications from fibrous polyps (intussusceptions)
- GISTs often epithelioid and predominantly gastric
- Lack diffuse ICC hyperplasia

23 y.o female, PDGFRA somatic mutant







Summary: Inherited/syndromic GISTs

- SDH intact (KIT, PDGFRA or NF1 mutations)
  - KIT/NF-1: pure spindled most common; PDGFRA epithelioid
  - KIT: through GI tract; PDGFRA: gastric; NF1: small bowel
  - KIT/NF1: background ICC hyperplasia
  - All: additional clinical features
- SDH loss (SDHx mutations or SDHC promoter hypermethylation)
  - Gastric multifocal tumors; epithelioid (pure or mixed) most common
  - Metastatic disease common; prolonged survival
- SDH intact vs. SDH-loss distinction clinically helpful
  - Rapid, inexpensive segregation to identify next management steps
  - SDH loss - genetic counselor to help distinguish inherited vs. non-inherited
  - SDH loss and NF1 with primary resistence to imatinib

Thank you!