VÅRMÖTE I PATOLOGI

NPM 2025

19–21 MAY

NORDIC PATHOLOGY MEETING

Distinguished Speaker

- Professor of Pathology
- World-renowned expert in GI and soft tissue pathology
- Pioneering work in diagnostic criteria and education
- Widely published author and speaker, mentor to many in the field
- **Why this matters:**
  Her insights shape how we understand, diagnose, and teach pathology across generations.

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Gastrointestinal Mesenchymal Lesions – Some Favorites

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Vice Chair, Academic Development

Disclosures

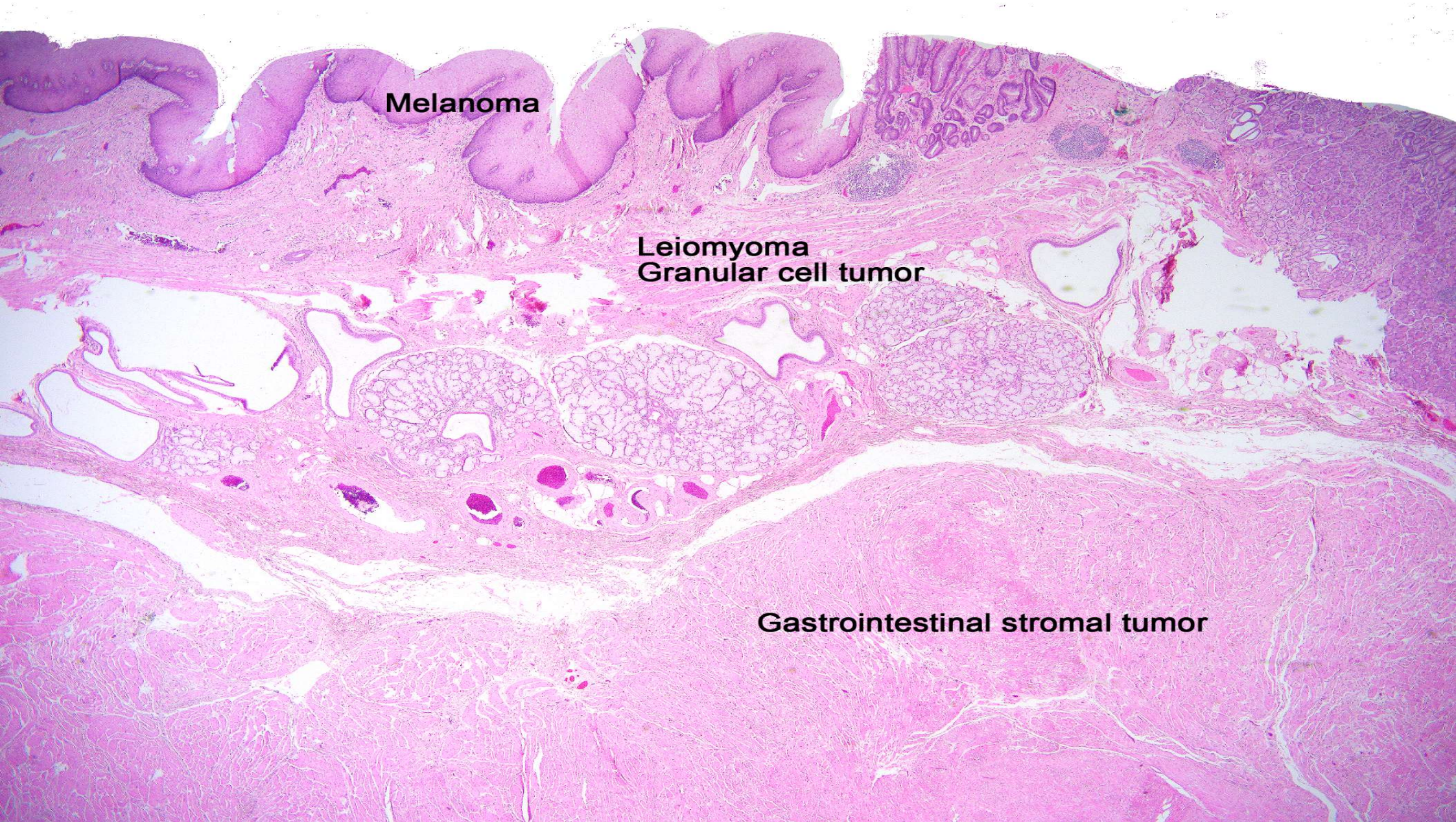
- Consultation for Olympus
- Consultant for Johnson and Johnson
- Consultant for Merck
- Received honorarium and travel expense money from ARUP Laboratories

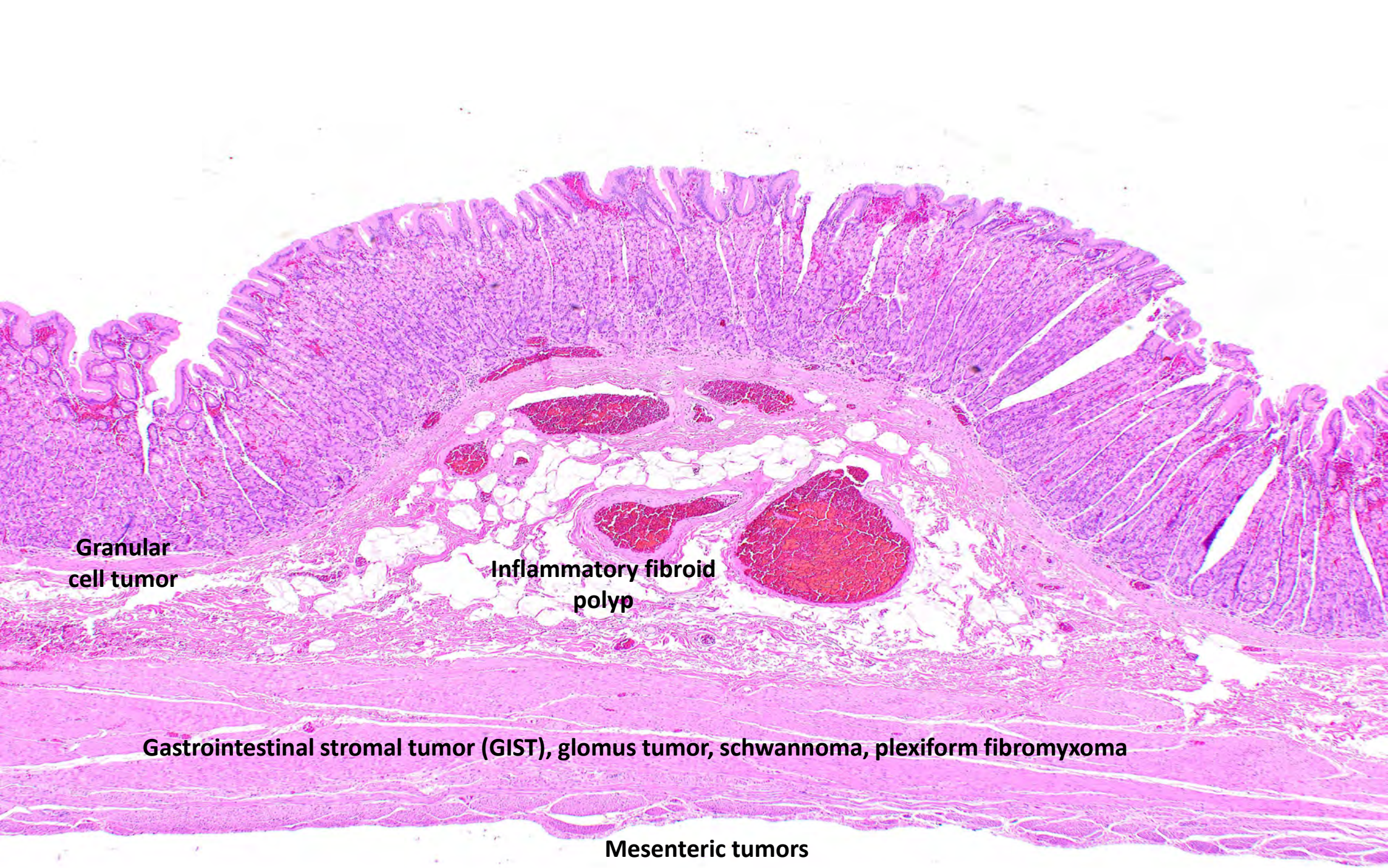
Objectives

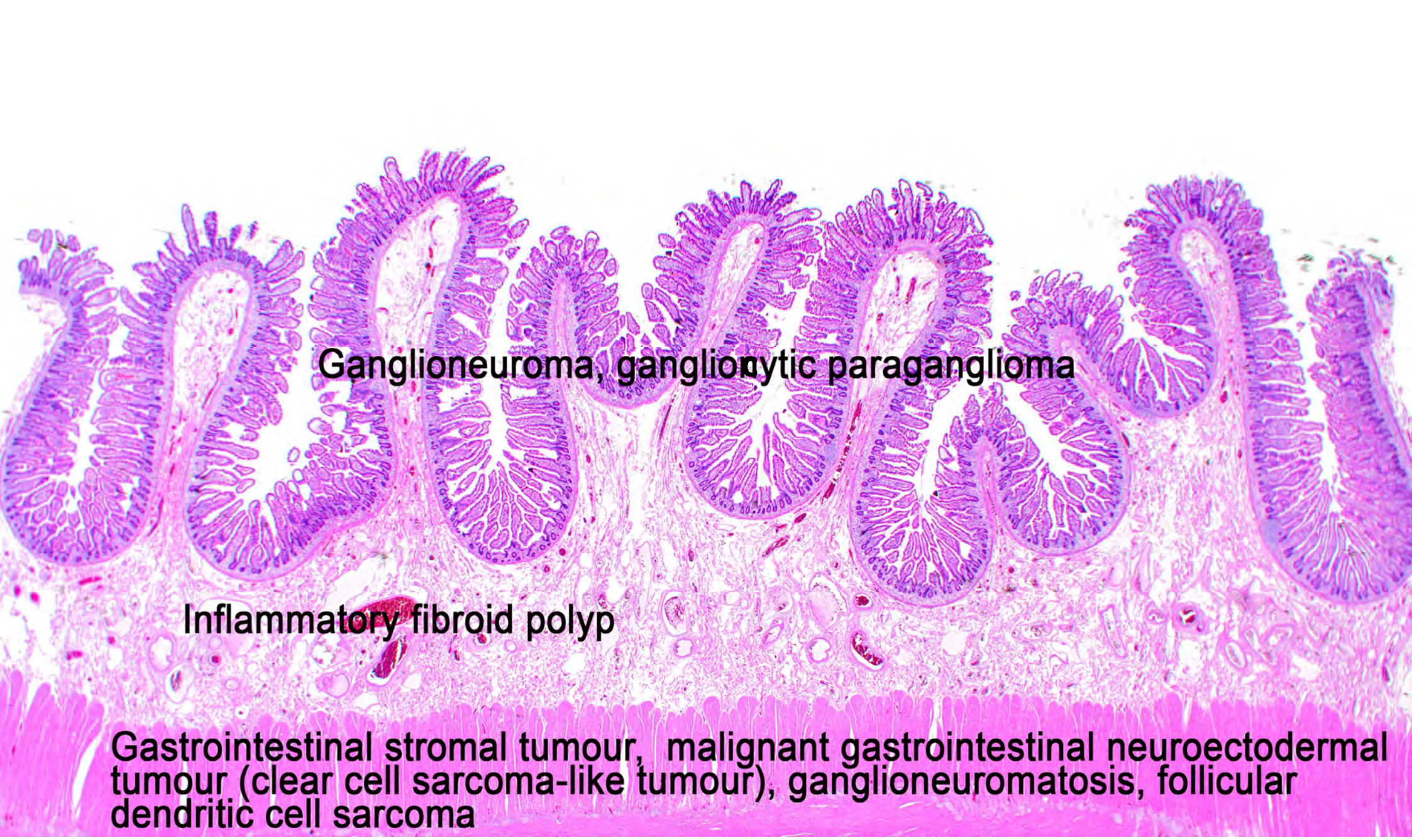
- To discuss the layers of the GI tract in which GI mesenchymal tumors tend to arise.
- To discuss several types of GI mesenchymal tumors, with emphasis on their location and depth in the GI tract.
- To comment on a few pitfalls that may be encountered

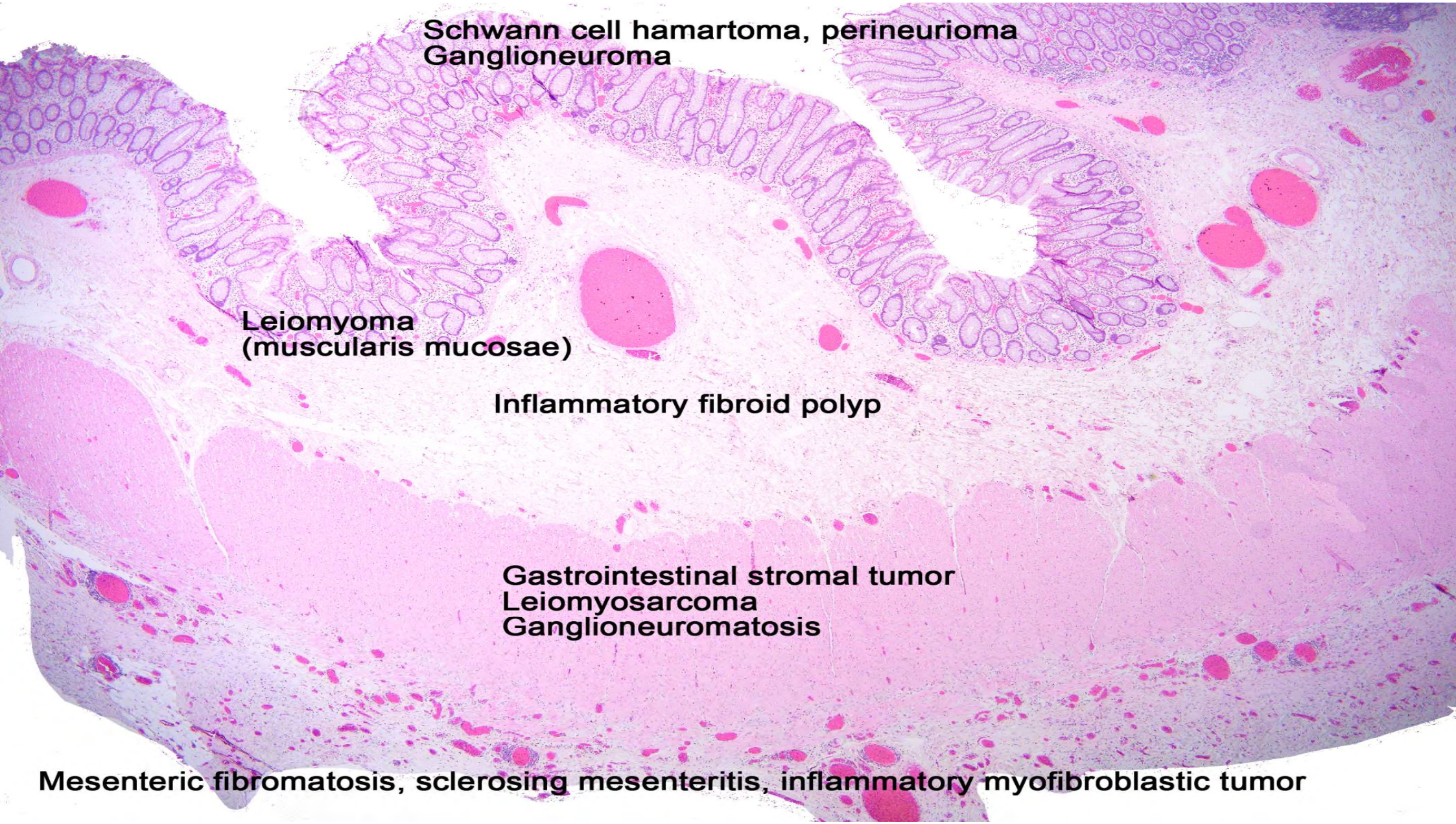
The Secret

- Diagnosing GIT mesenchymal tumors is really about knowing which tumors live in which layers
- For example, inflammatory fibroid polyp (with *PDGFRA* mutations) is in the submucosa whereas GIST (also with *PDGFRA* mutations) is in the muscularis propria


Melanoma
Leiomyoma
Granular cell tumor
Gastrointestinal stromal tumor


Granular
cell tumor
Inflammatory fibroid
polyp
Gastrointestinal stromal tumor (GIST), glomus tumor, schwannoma, plexiform fibromyxoma
Mesenteric tumors

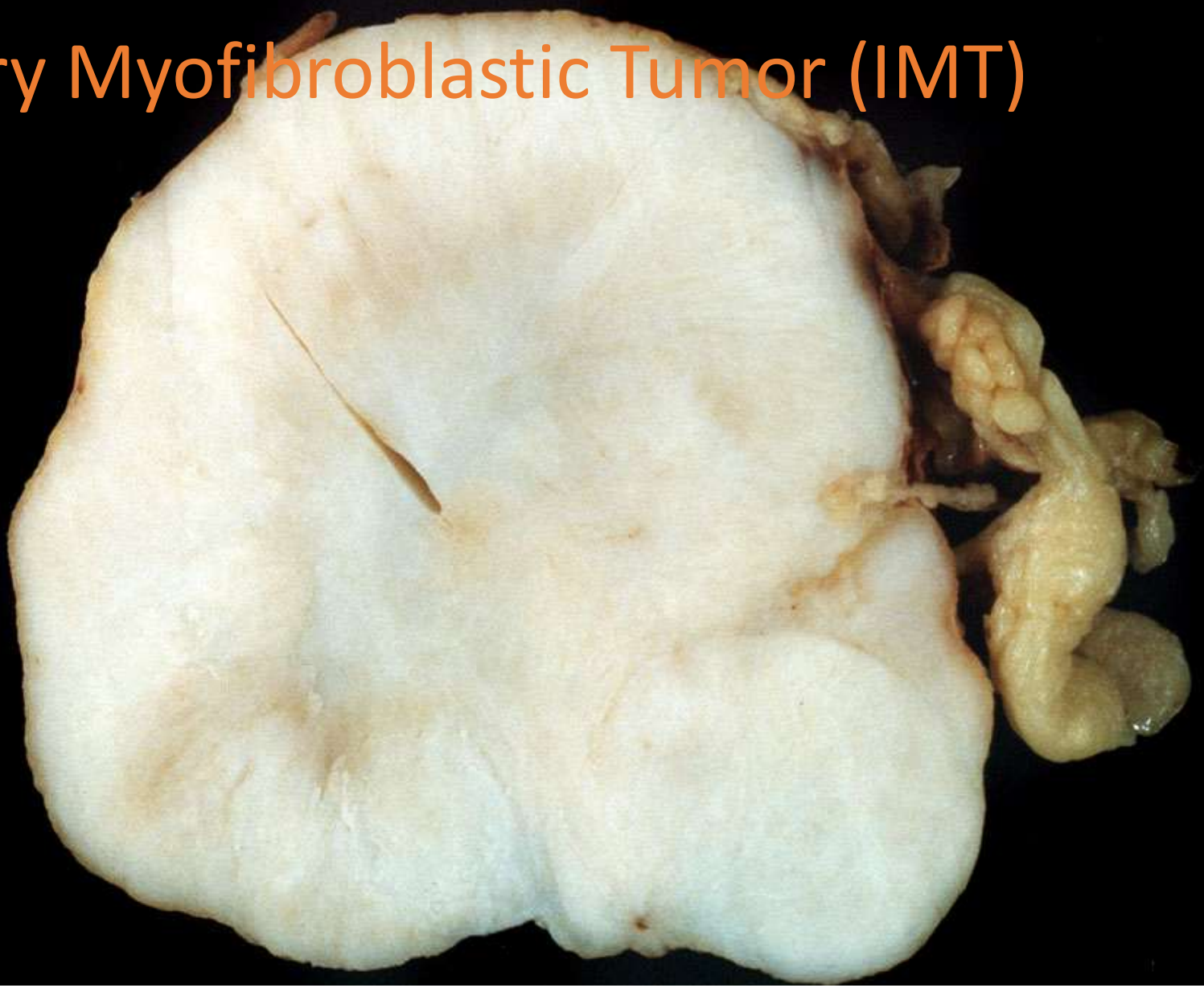

Ganglioneuroma, ganglionic paraganglioma
Inflammatory fibroid polyp
Gastrointestinal stromal tumour, malignant gastrointestinal neuroectodermal tumour (clear cell sarcoma-like tumour), ganglioneuromatosis, follicular dendritic cell sarcoma

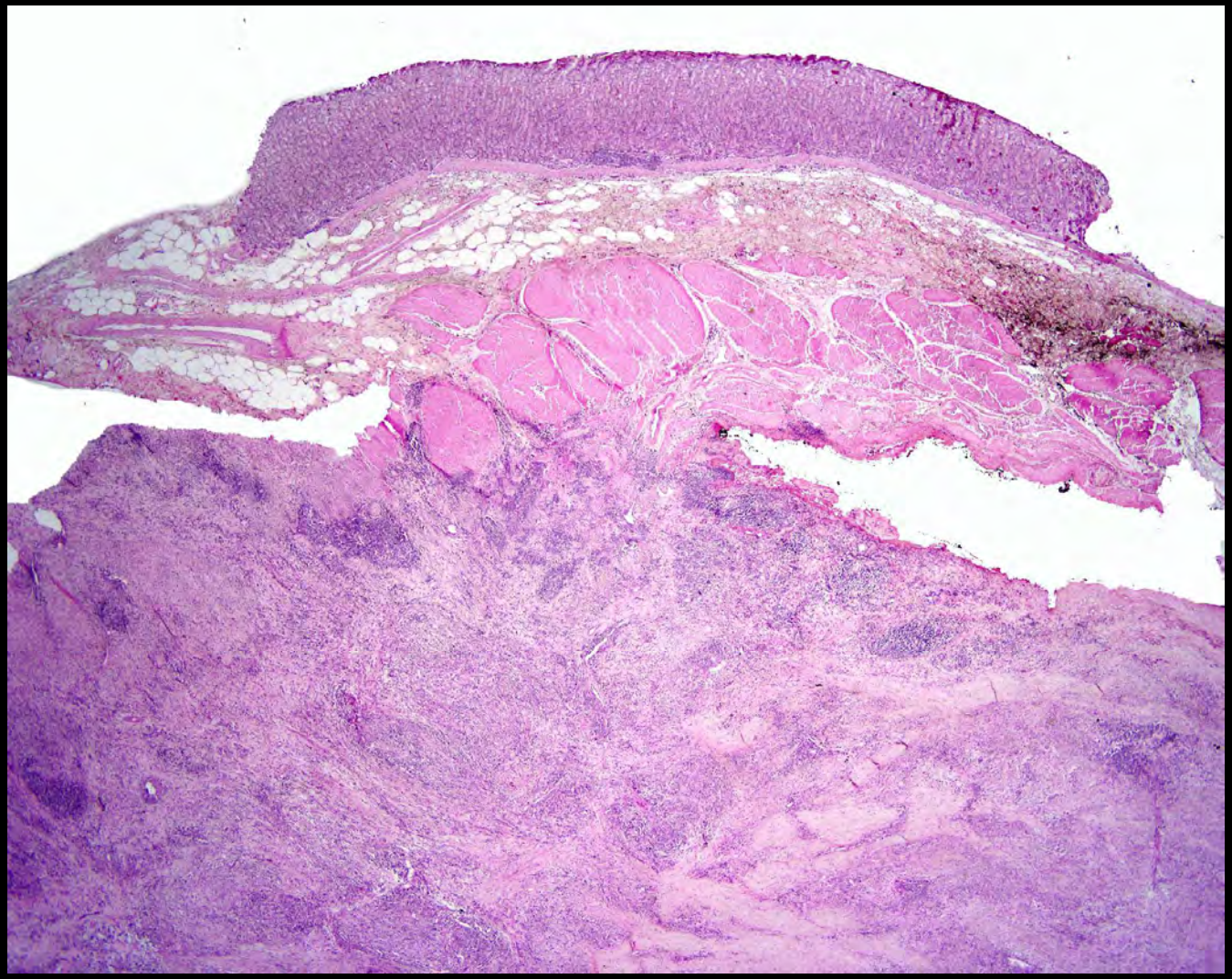

Schwann cell hamartoma, perineurioma
Ganglioneuroma
Leiomyoma
(muscularis mucosae)
Inflammatory fibroid polyp
Gastrointestinal stromal tumor
Leiomyosarcoma
Ganglioneuromatosis
Mesenteric fibromatosis, sclerosing mesenteritis, inflammatory myofibroblastic tumor

Mesentery – Working Into the Mucosa

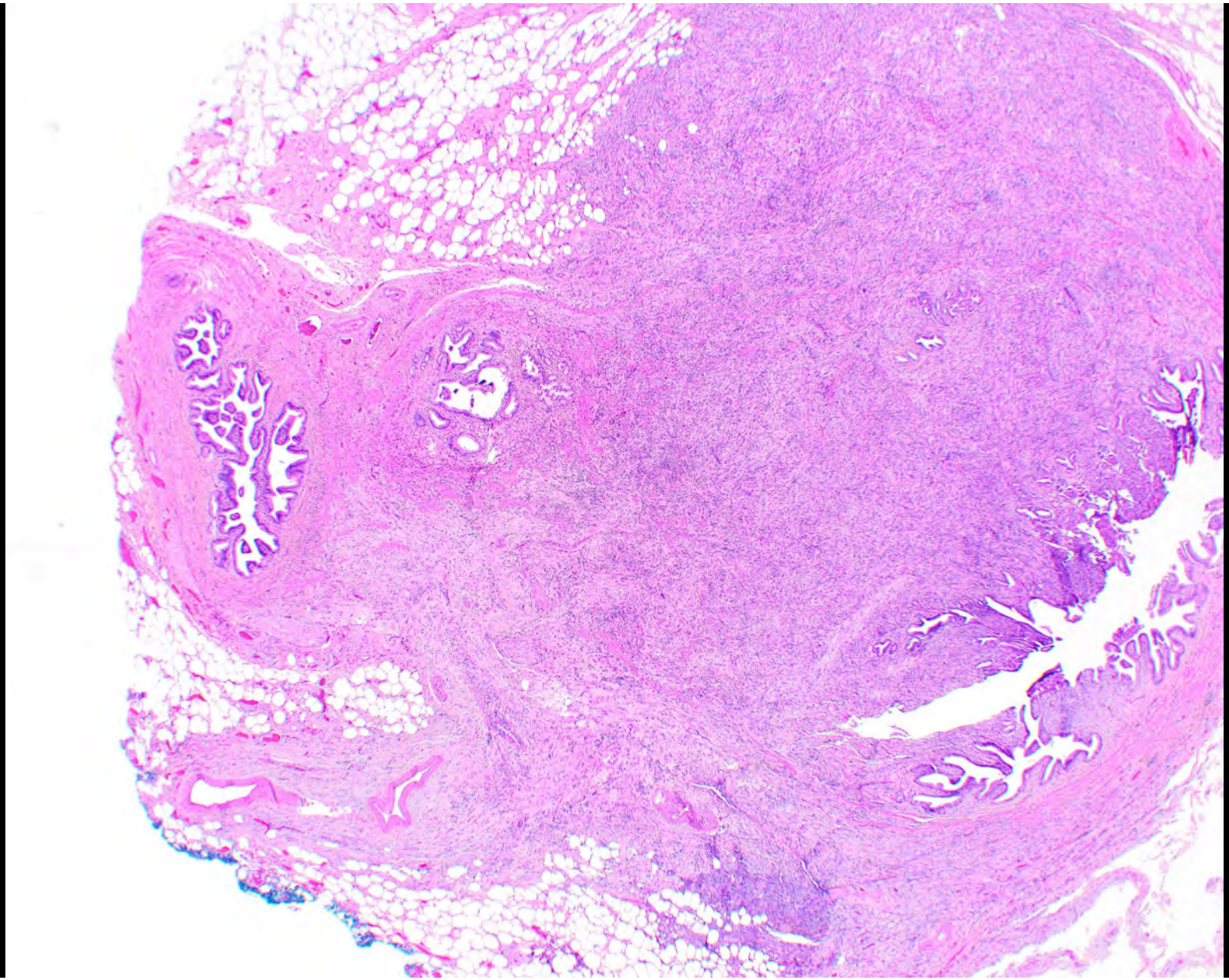
Inflammatory Myofibroblastic Tumor (IMT)

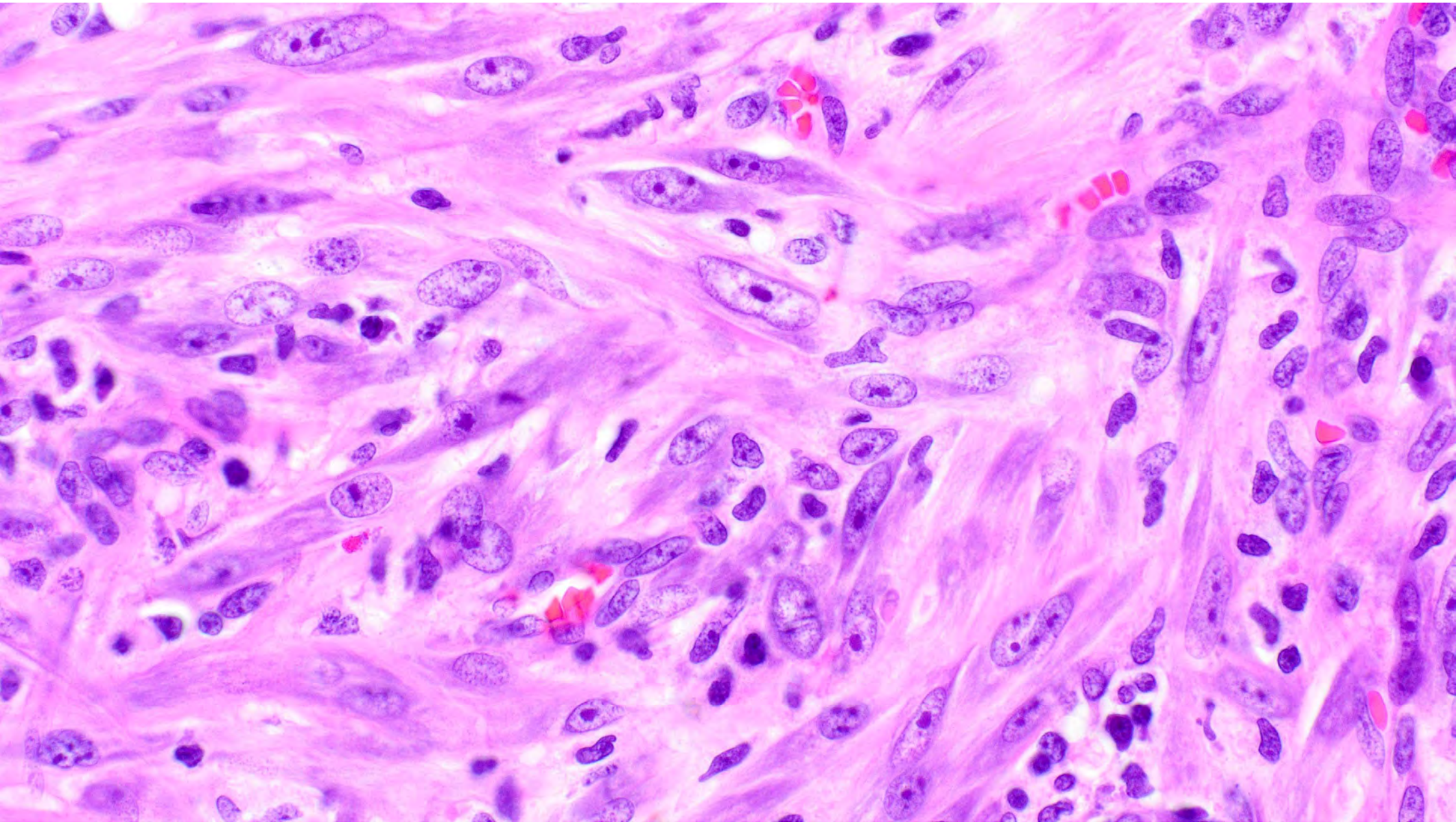
- Pulmonary lesions called “inflammatory pseudotumor” have been recognized for many years and regarded as part of a spectrum of lesions called “plasma cell granulomas”
- Subsequently, similar tumors were described in the abdomen and other soft tissue sites.





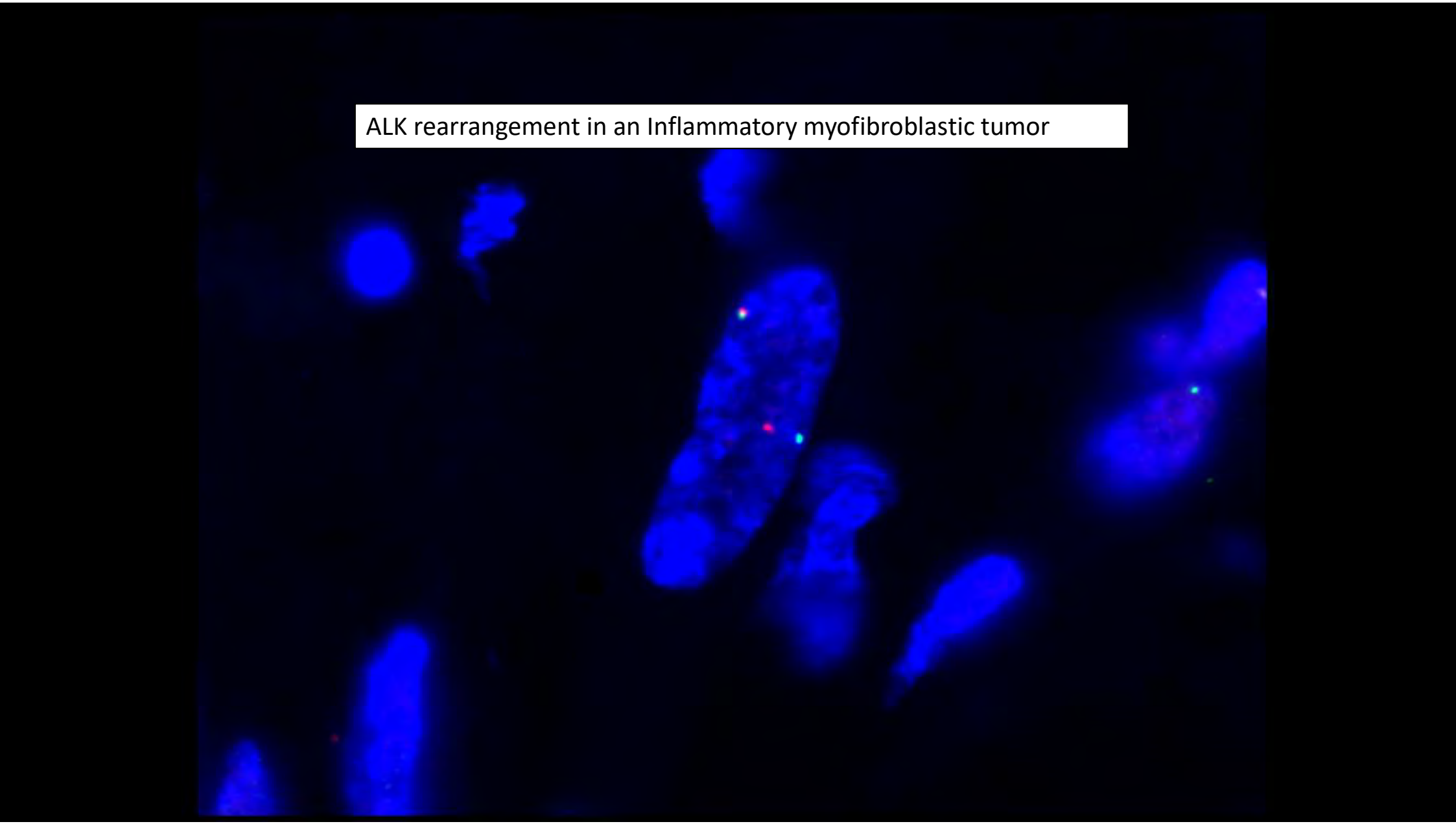
Inflammatory Myofibroblastic Tumor-Extrapulmonary

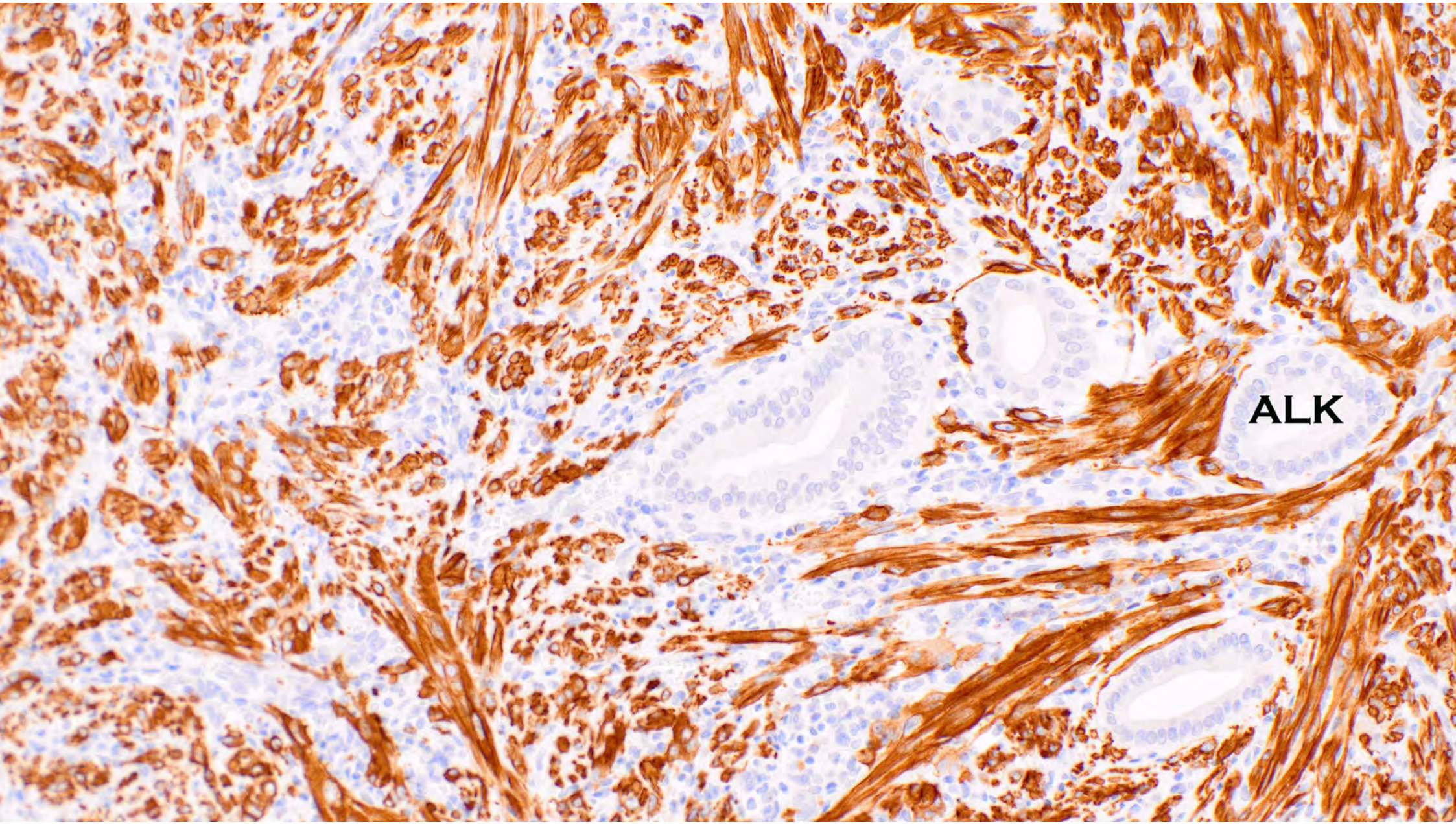




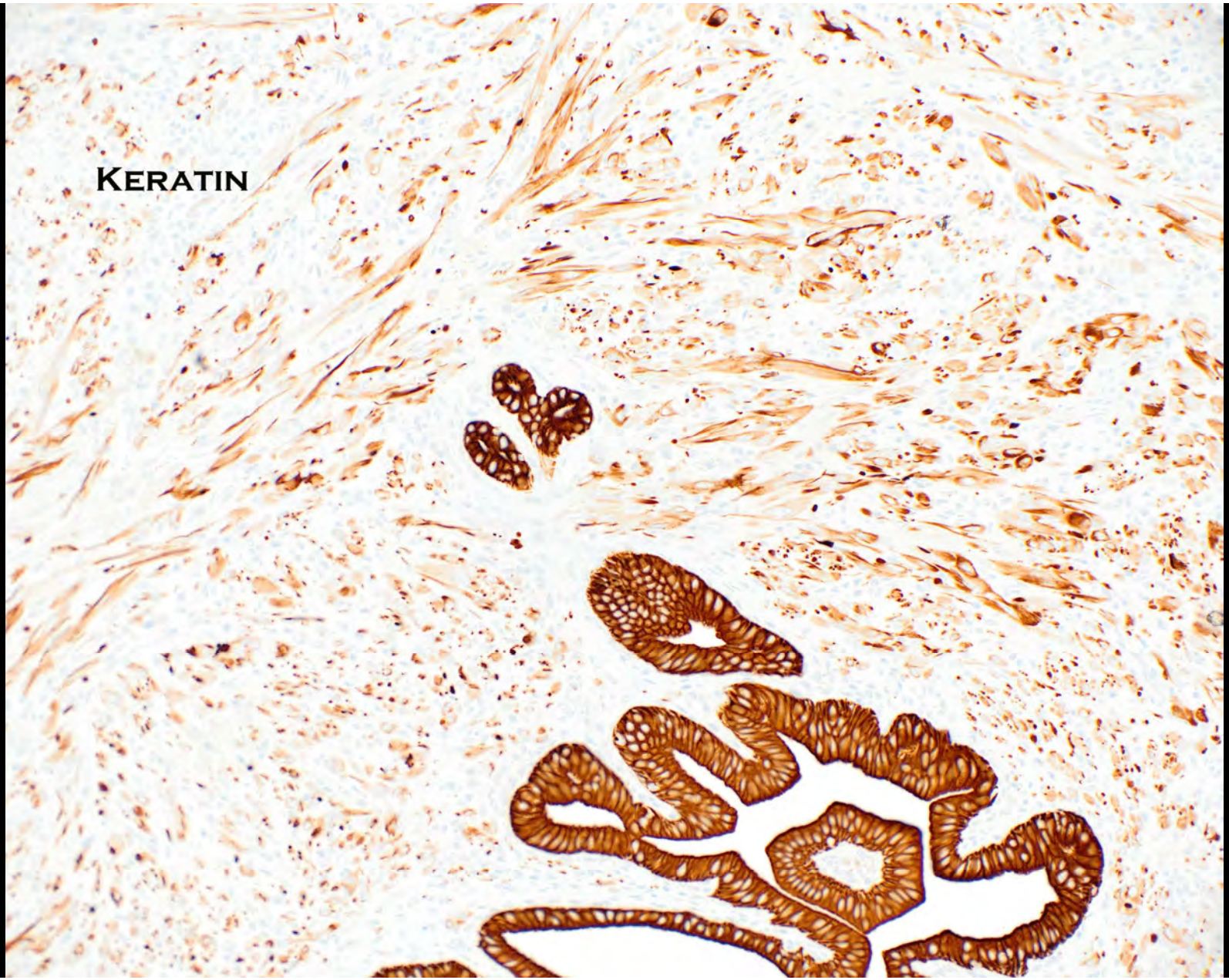
IMT; Important Discovery

- **Griffin et al [1999] reported 3 IMT with rearrangements at 2p23 involving *ALK* gene**
- **Subsequently, *ALK* shown to be rearranged in a subset of IMTs from many sites**
- **Identified partners including *CLTC* , *RANBP2*, *TPM3* , *TPM4* , *CARS* *ATIC*, and**


ALK rearrangement in an Inflammatory myofibroblastic tumor


ALK

IMT – Pitfall alert



Targeted Therapy

- Crizotinib (PF-02341066, Pfizer) - orally bioavailable, ATP-competitive, small-molecule inhibitor of the receptor tyrosine kinases (RTKs) c-Met (also known as hepatocyte growth factor receptor) and anaplastic lymphoma kinase (ALK)
- Used in lung cancer (about 5% of lung cancers have *ALK* rearrangements) and now IMT!!!
- Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, Ladanyi M, Capelletti M, Rodig SJ, Ramaiya N, Kwak EL, Clark JW, Wilner KD, Christensen JG, Jänne PA, Maki RG, Demetri GD, Shapiro GI. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010 Oct 28;363(18):1727-33.
- Ceritinib, Alectinib are newer agents

More Targets for IMT

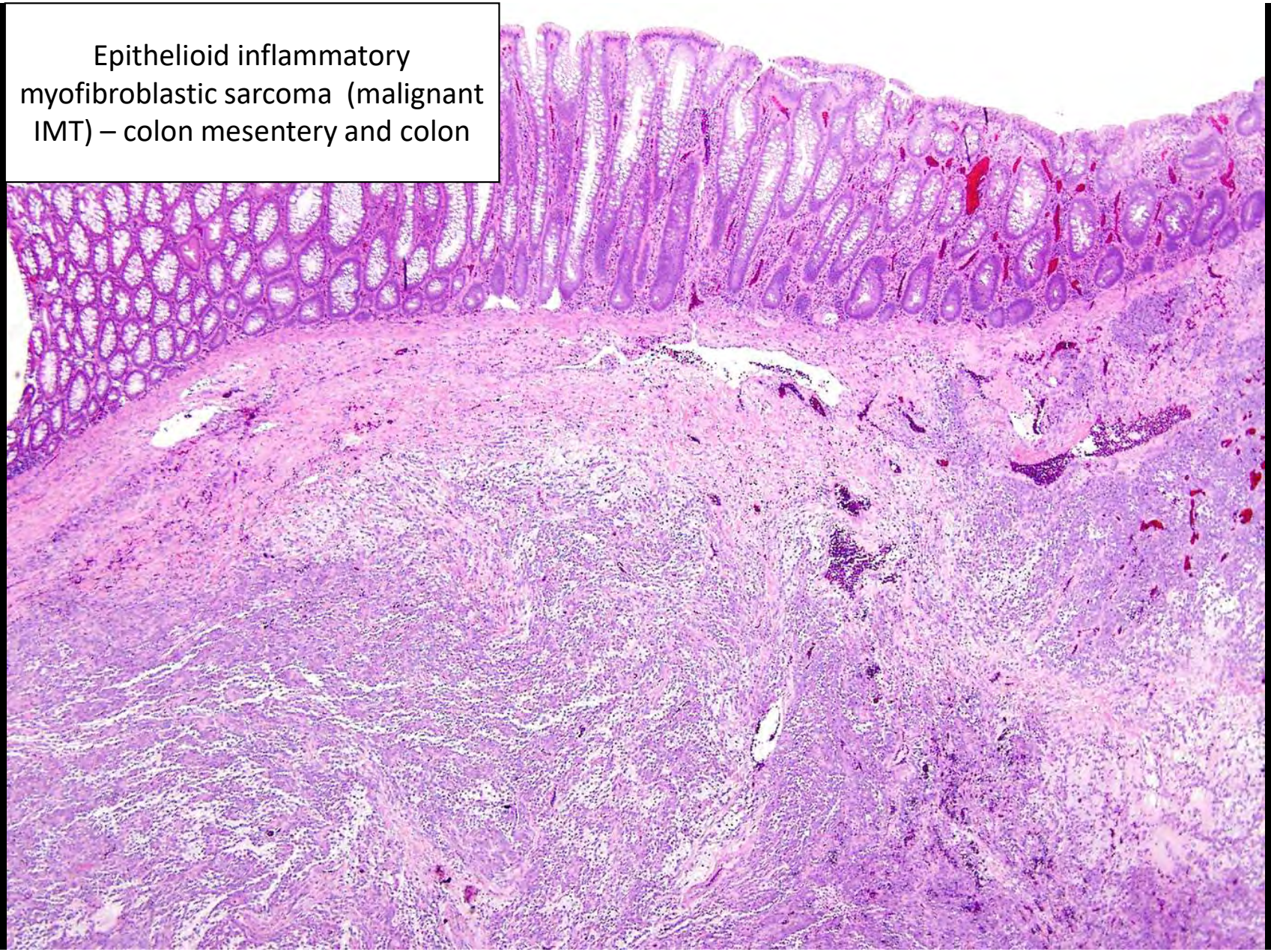
- There are *ROS1* rearrangements as well as *ALK* ones.
- *ROS1* more likely in children (also targetable with the same compounds as *ALK*)
- *ETV6::NTRK3* in some ALK negative IMTs – also targetable

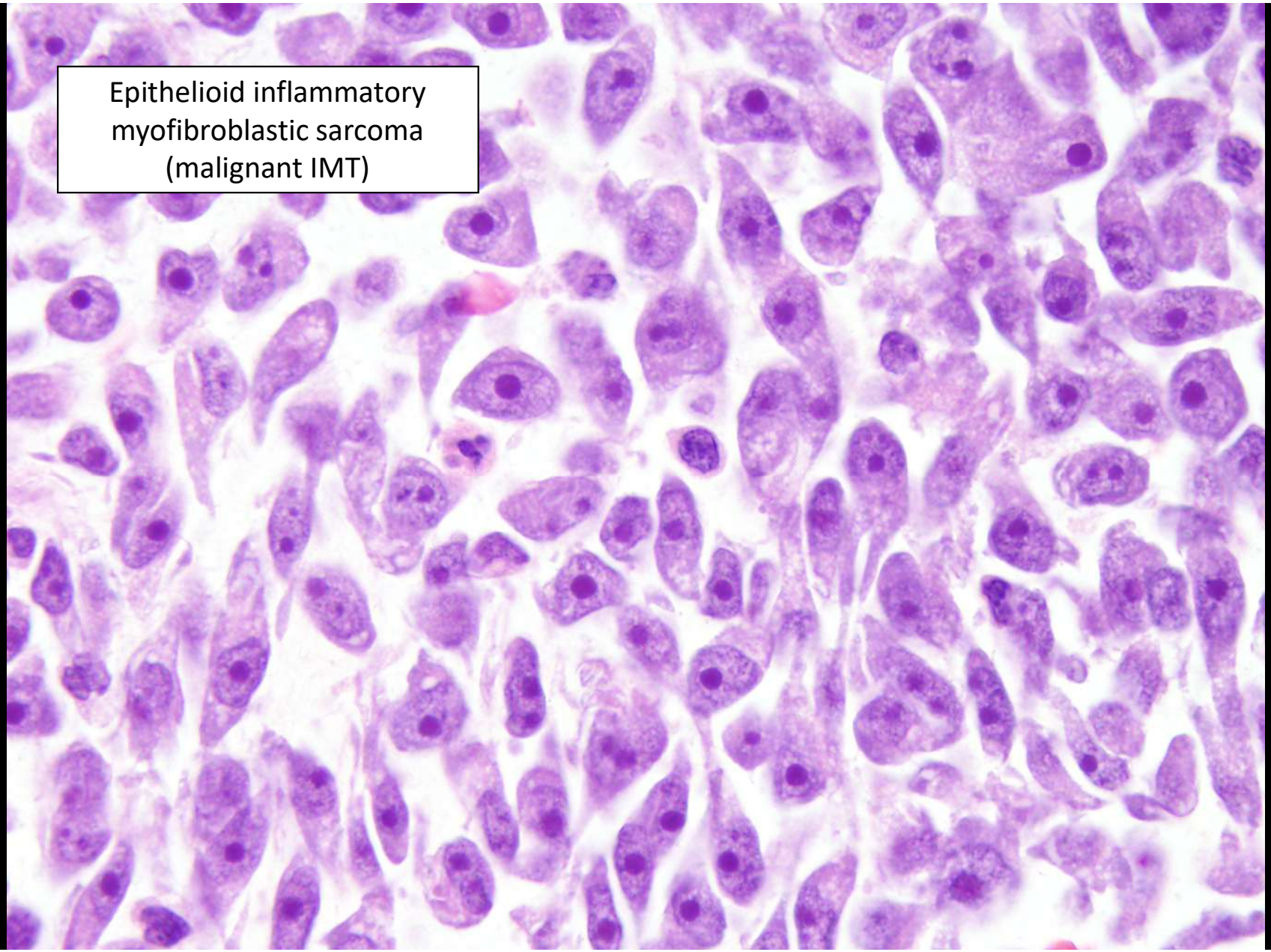
High grade form of IMT

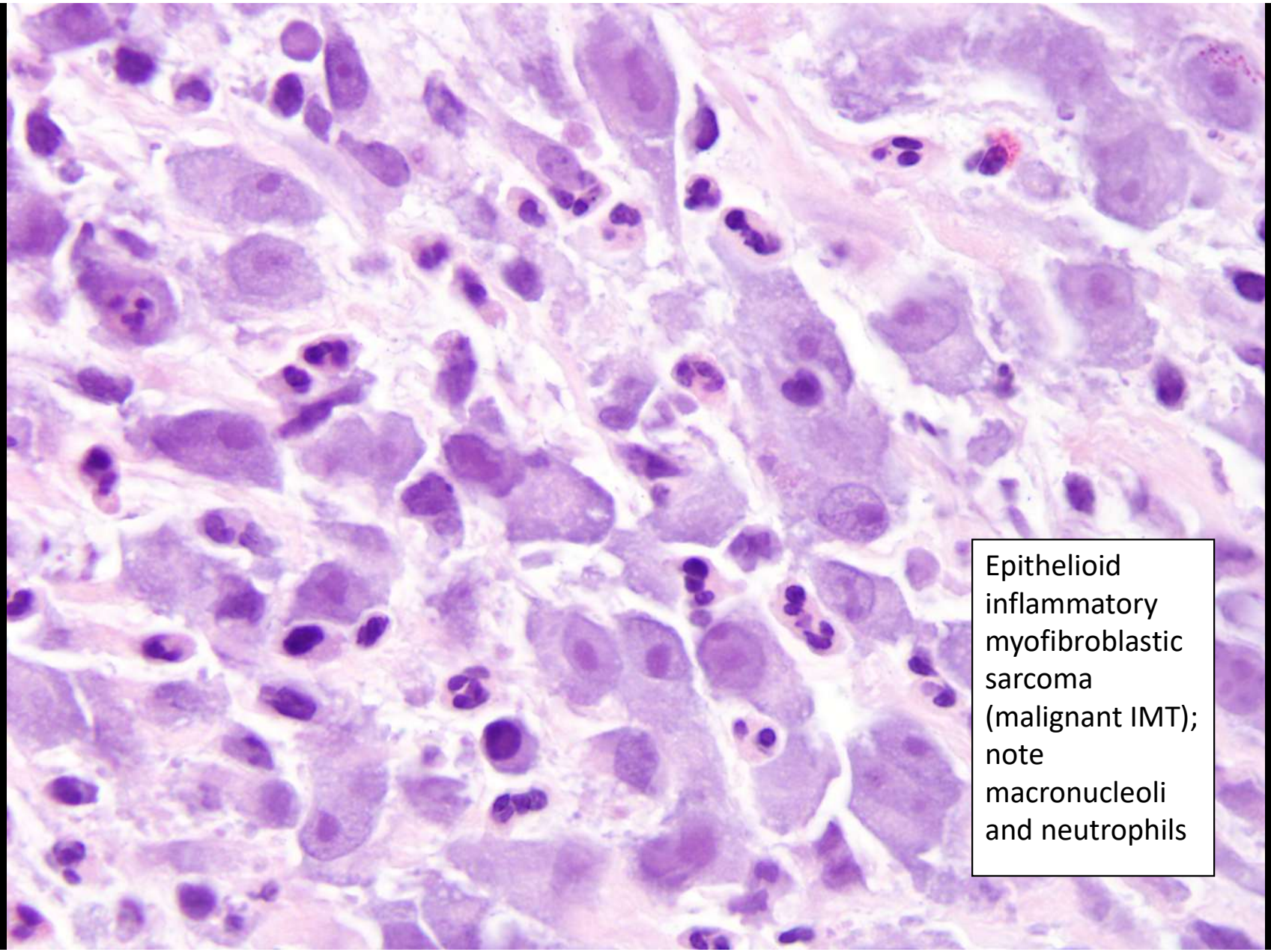
- Termed epithelioid inflammatory myofibroblastic sarcoma
- Appears similar to epithelioid leiomyosarcoma (and probably some old “epithelioid leiomyosarcomas” are these)
- Can have an unusual ALK pattern on immunolabeling
- Some response to targeted therapy then the tumor loses responsiveness

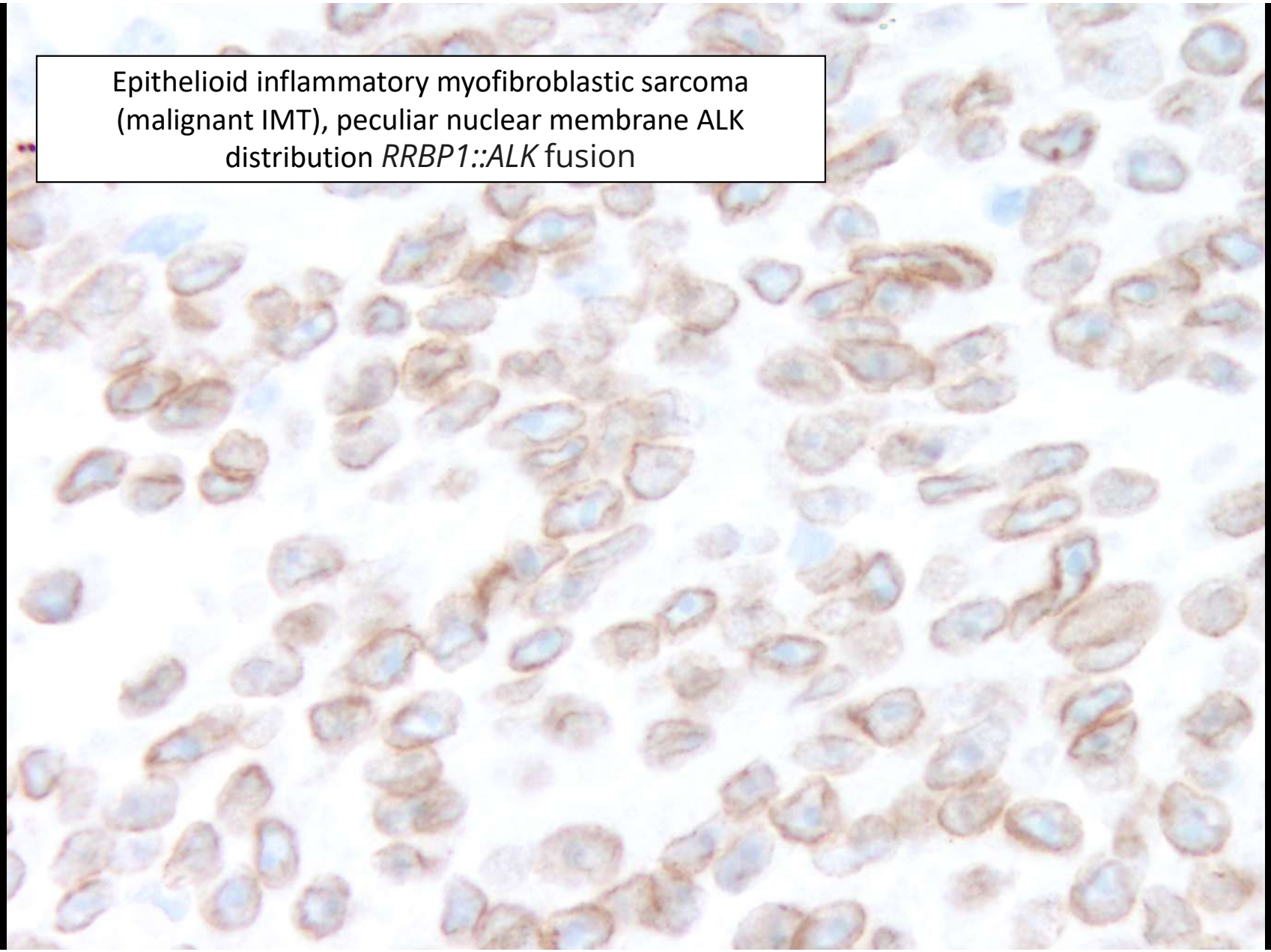
- Mariño-Enríquez A, Wang WL, Roy A, Lopez-Terrada D, Lazar AJ, Fletcher CD, Coffin CM, Hornick JL. Epithelioid inflammatory myofibroblastic sarcoma: An aggressive intra-abdominal variant of inflammatory myofibroblastic tumor with nuclear membrane or perinuclear ALK. Am J Surg Pathol. 2011 Jan;35(1):135-44.

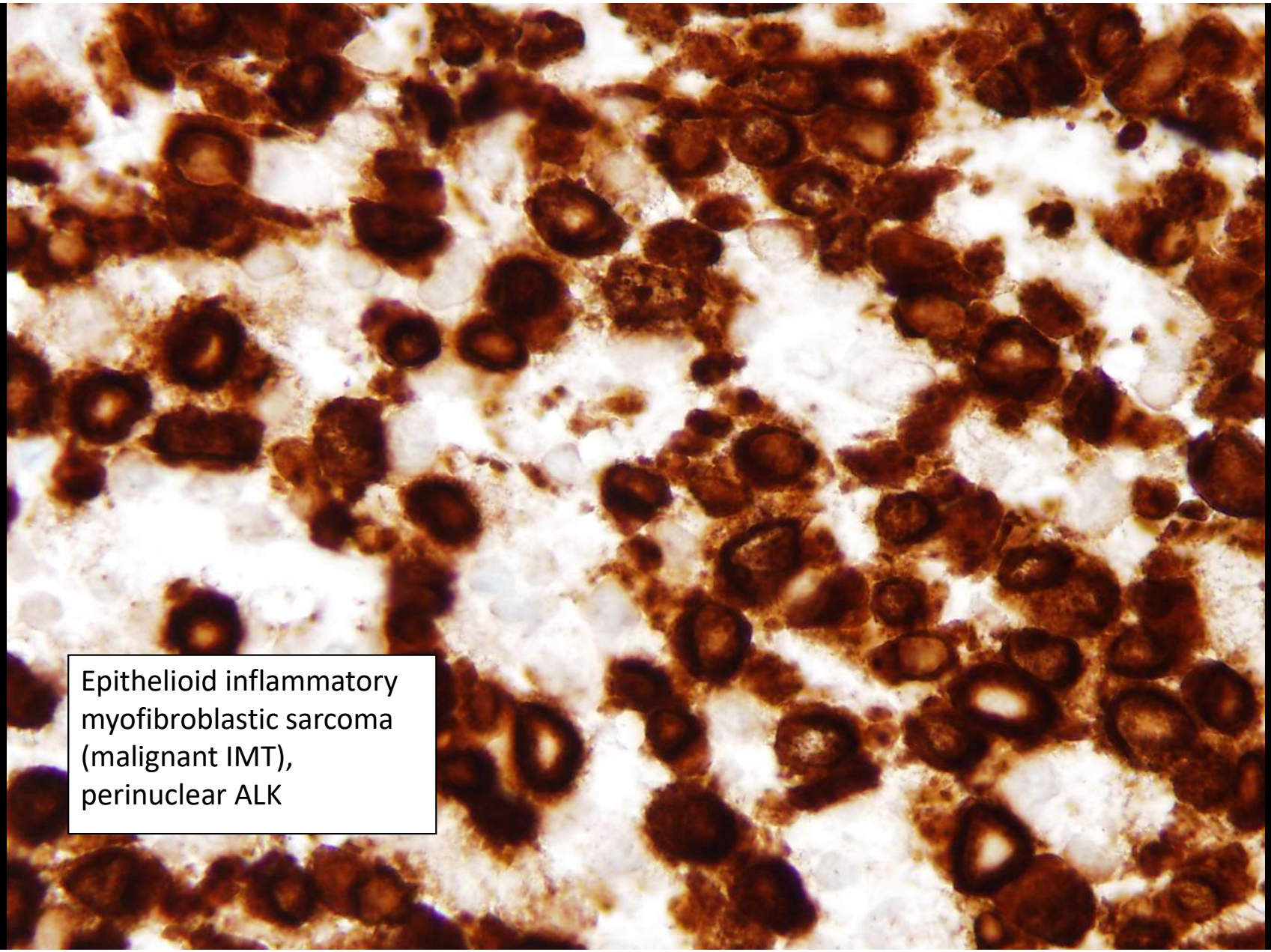
Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT) – colon mesentery and colon




Epithelioid inflammatory
myofibroblastic sarcoma
(malignant IMT)


Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT); note macronucleoli and neutrophils

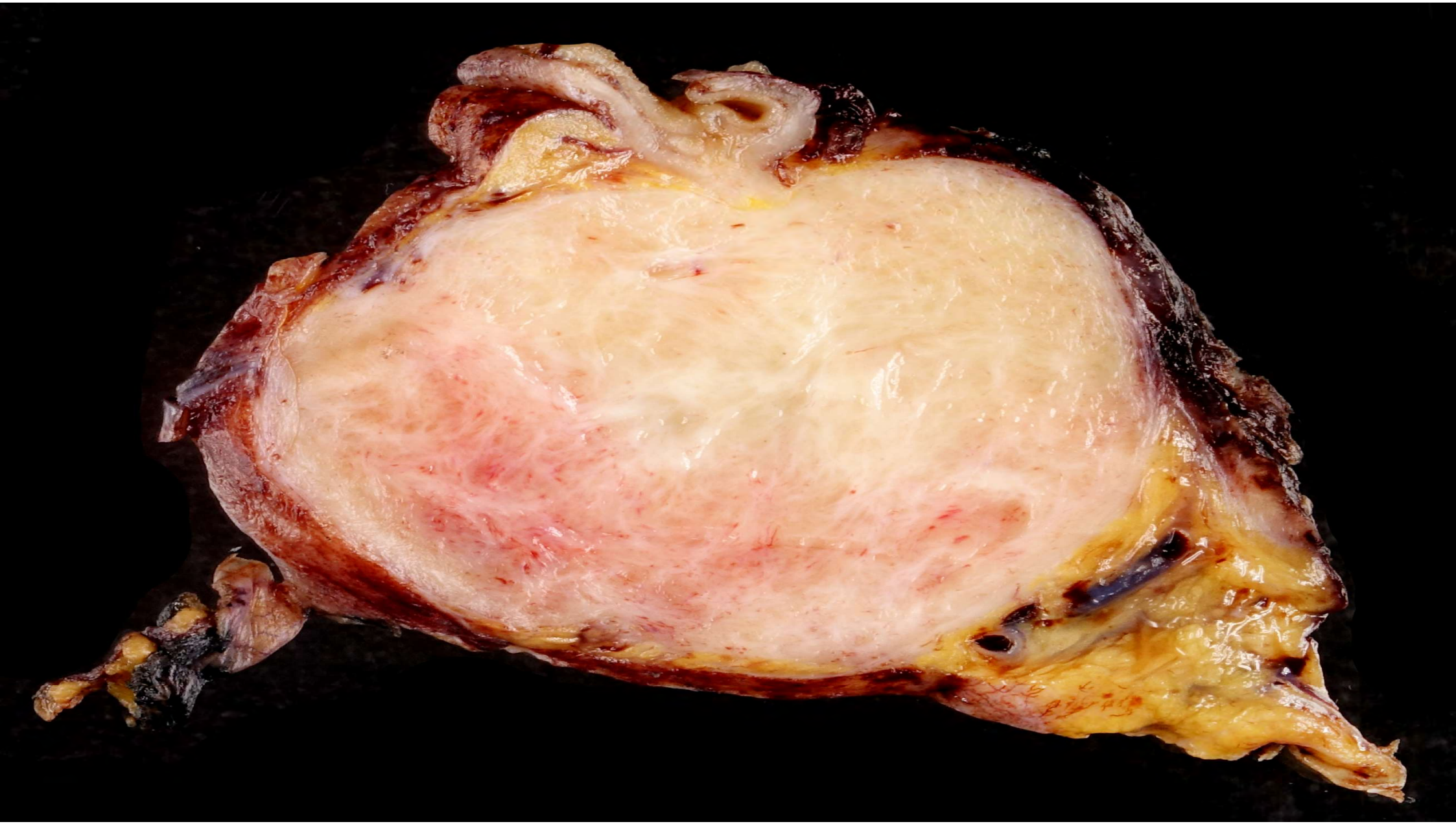

Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT), peculiar nuclear membrane ALK distribution *RRBP1::ALK* fusion


Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT), perinuclear ALK

So let’s all get ready to target these lesions!

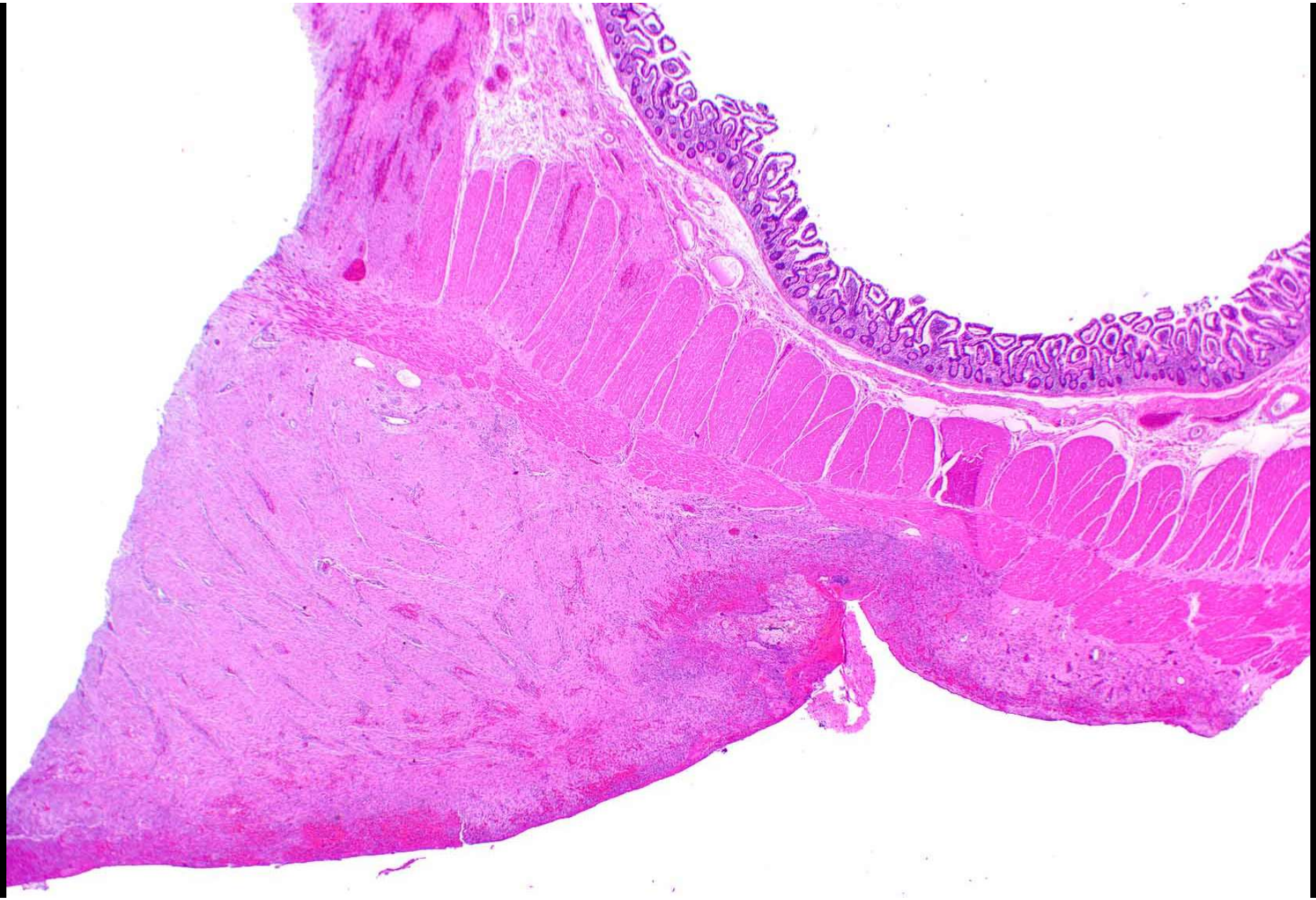
Mesenteric Fibromatoses - Clinical

- 2-4 individuals per million per year.
- In children, equal gender incidence, mostly extra-abdominal.
- Puberty – age 40 usually in females [estrogen driven] and in abdominal wall.
- Older adults – mostly extra-abdominal – equal gender incidence.

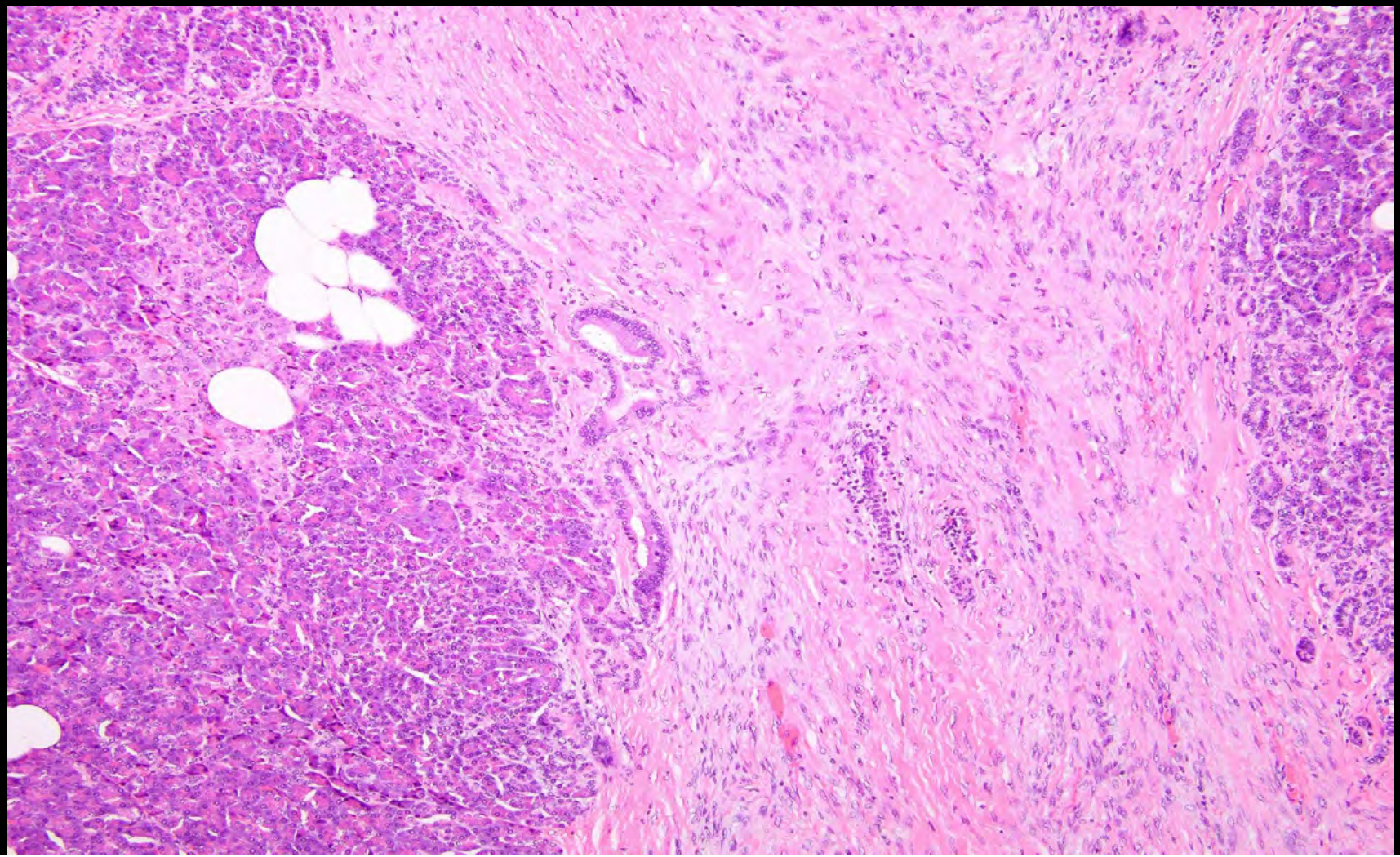


Features of Fibromatoses

- Sweeping Fascicles of Fibroblasts/myofibroblasts
- Infiltrative Growth Pattern
- Characteristic Vascular Pattern

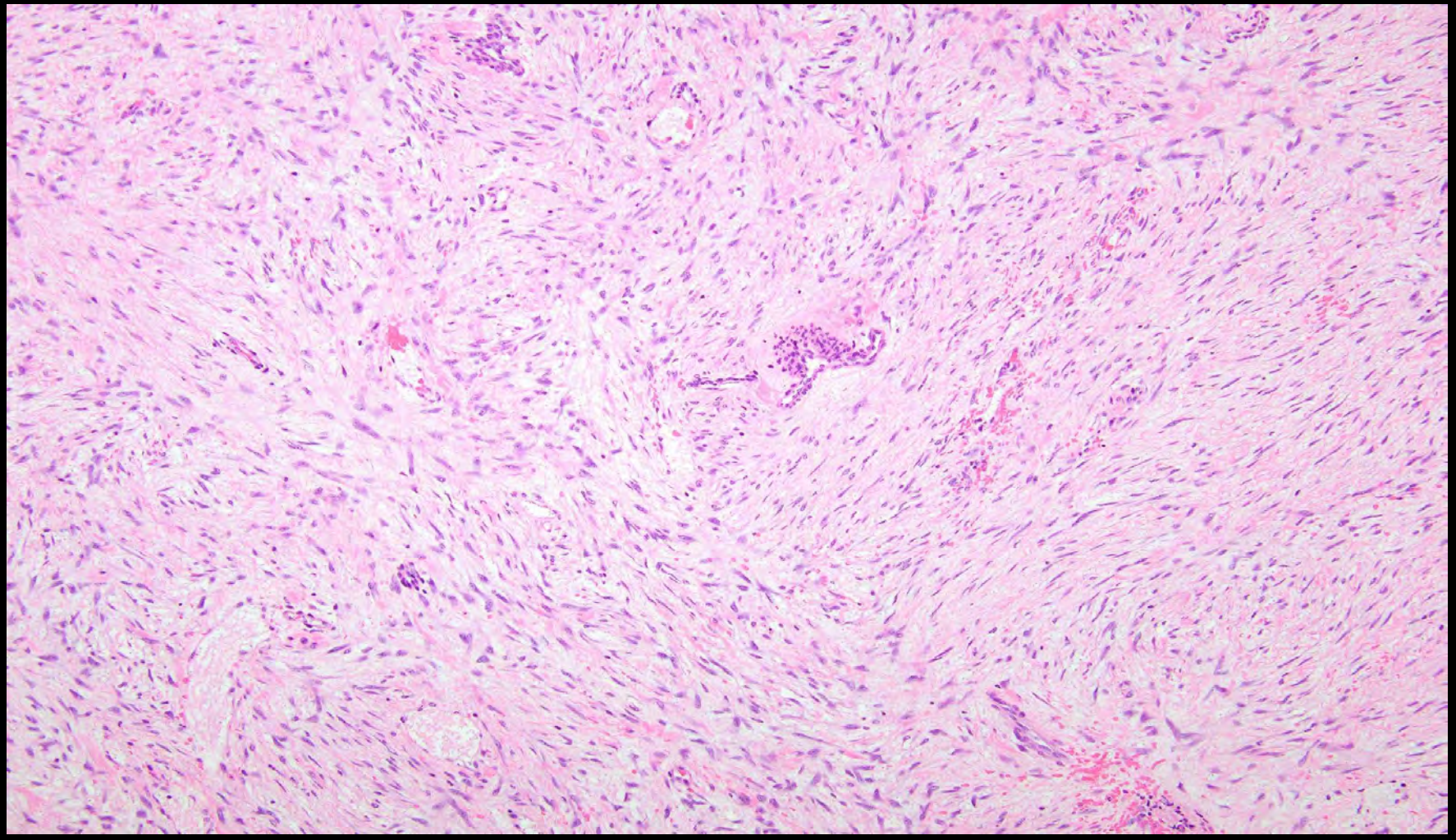


Infiltrative growth

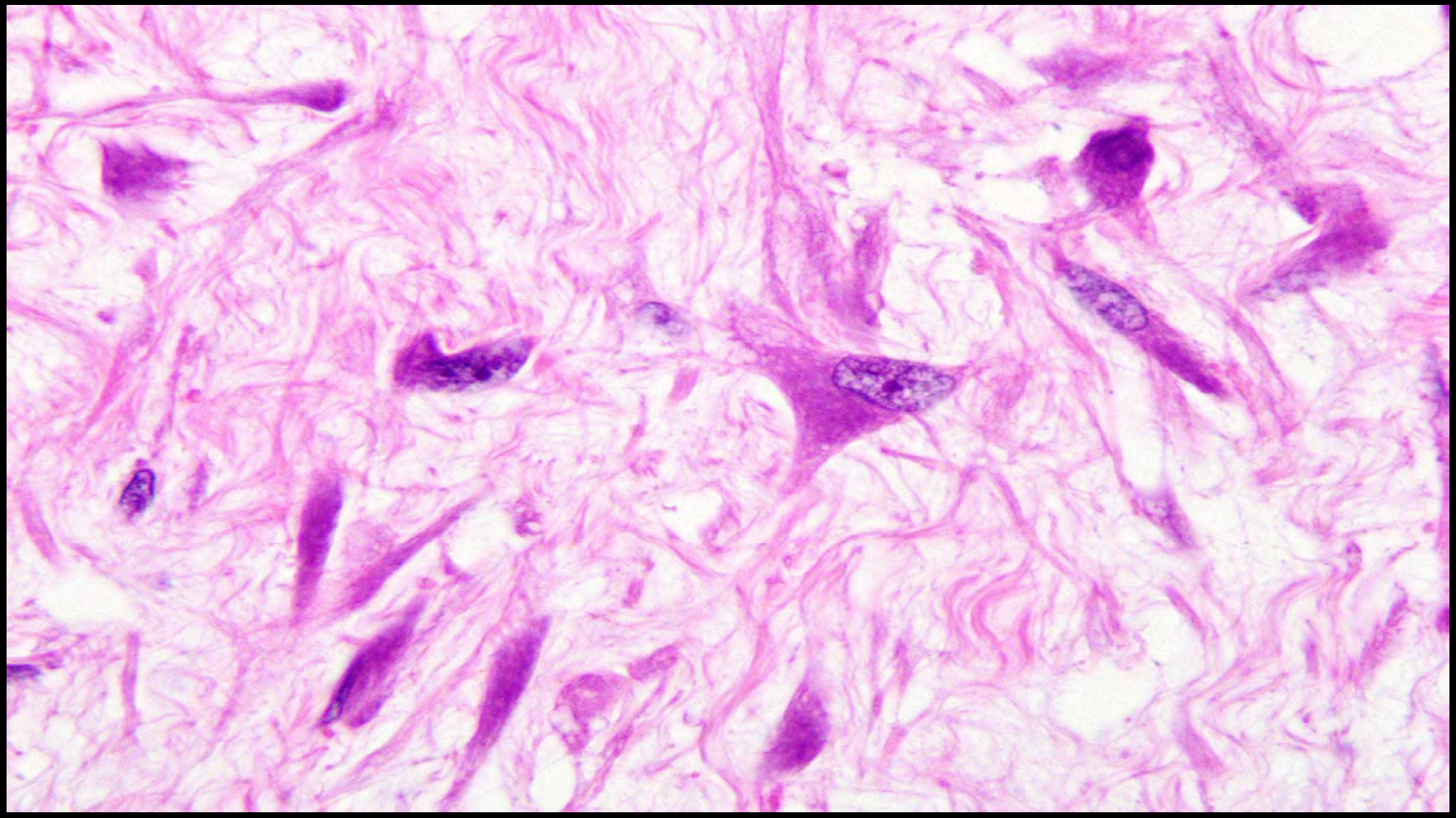


Hello,
Pancreas!

Vascular pattern

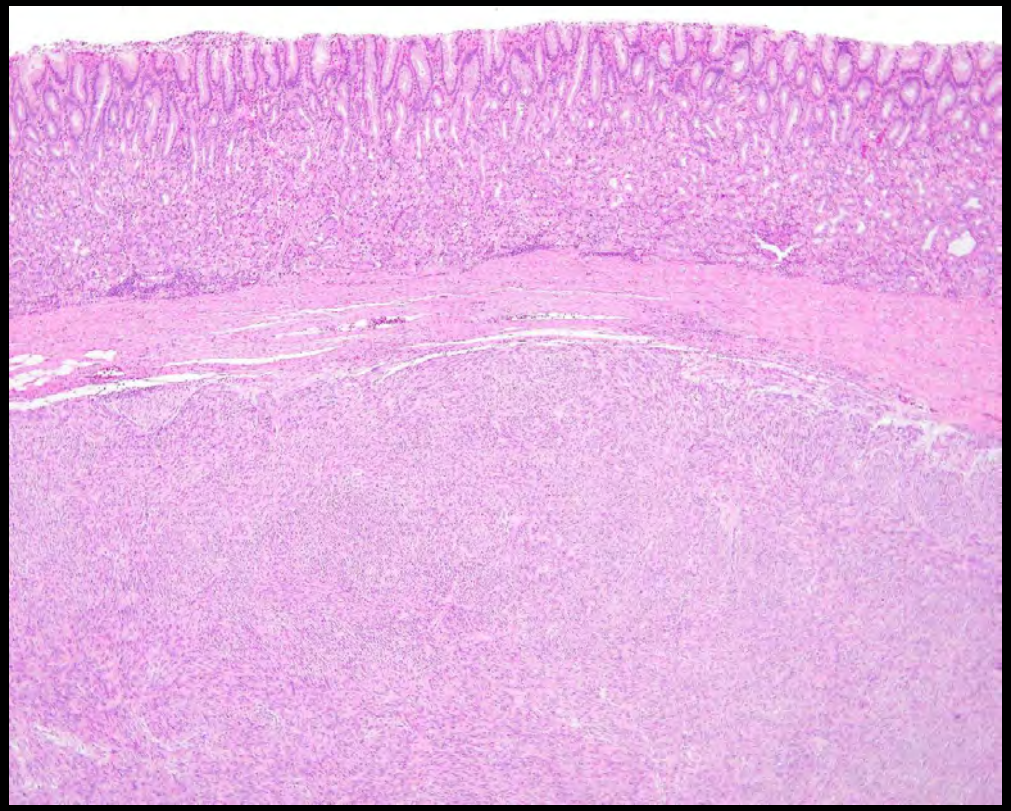


Characteristic cytologic features

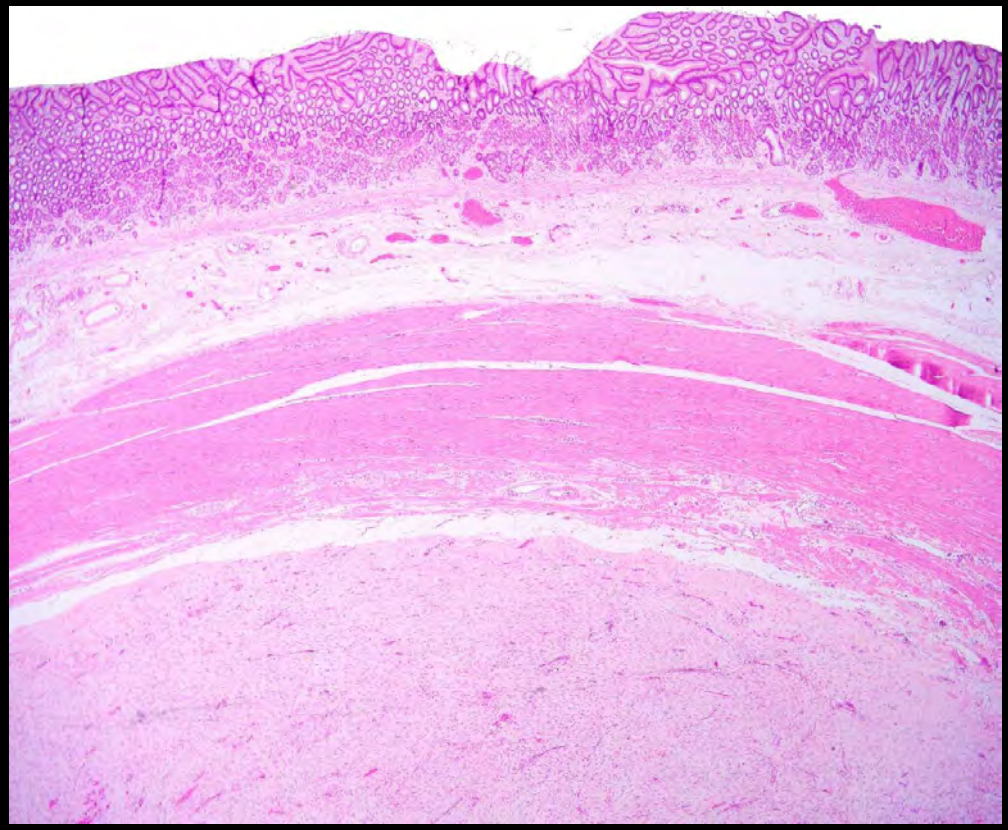


Beauty Contest

Gastrointestinal stromal tumor/GIST



Fibromatosis

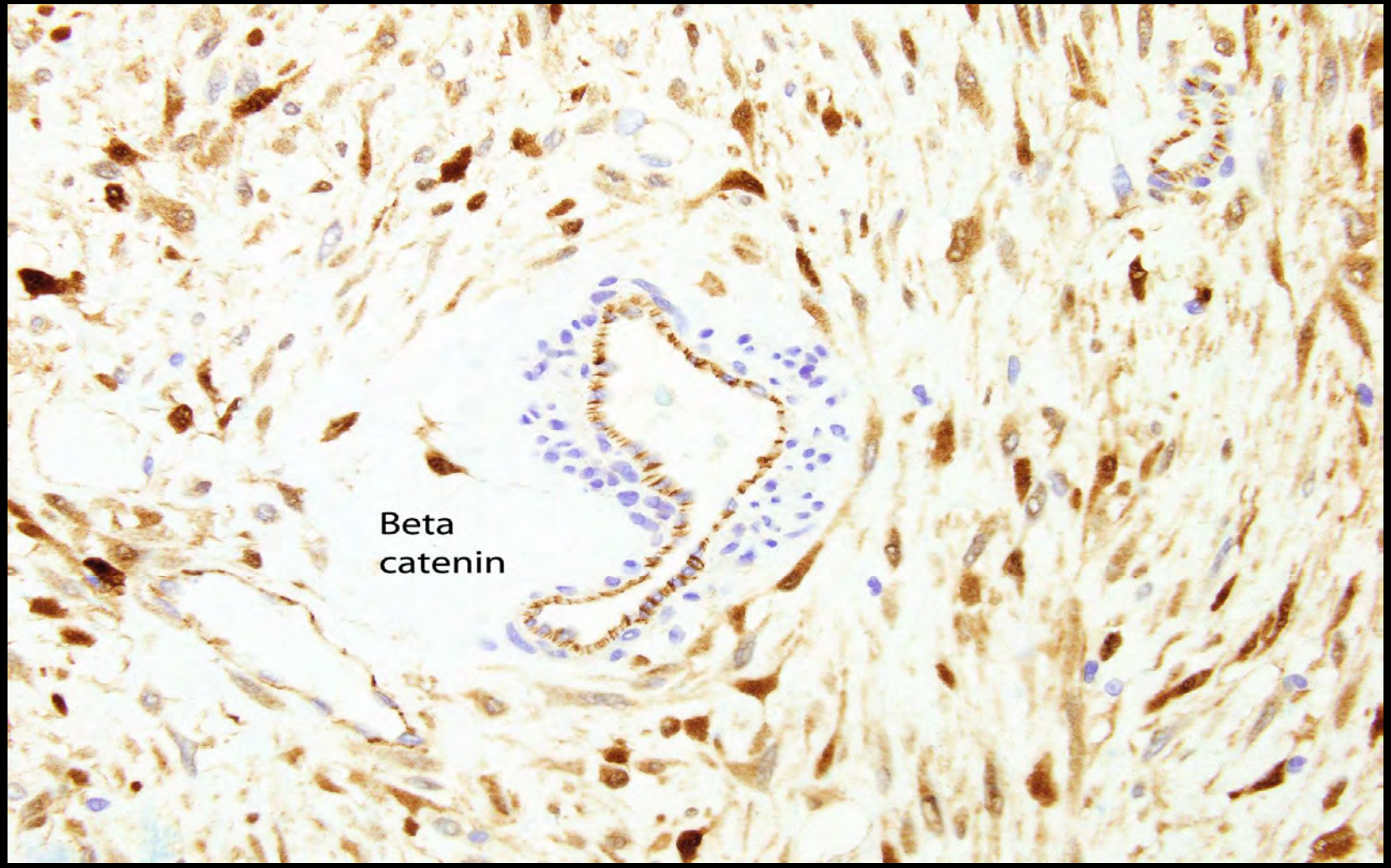


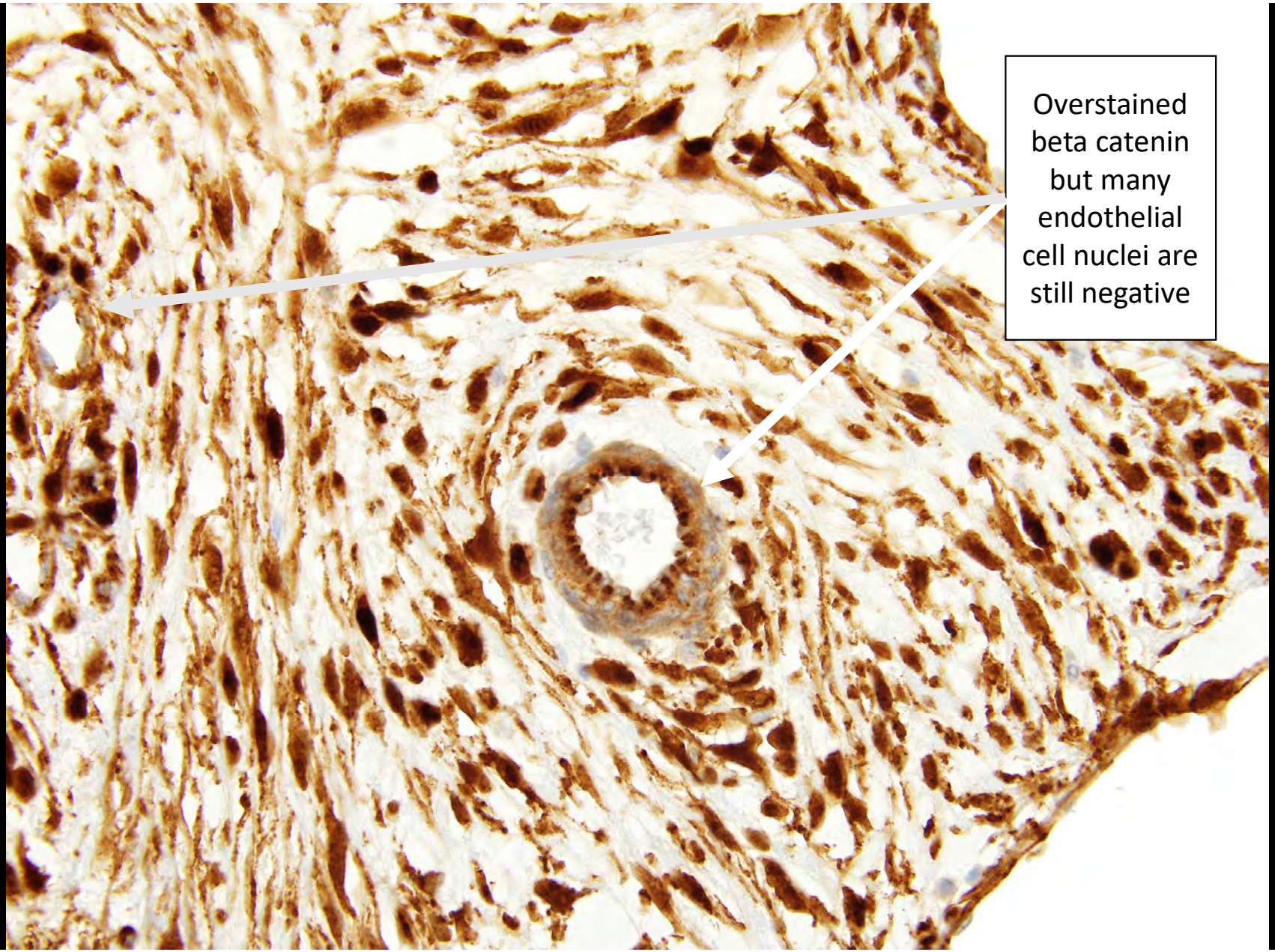
β catenin in Fibromatoses

- Accumulates in nucleus
- NOT detected in GISTs

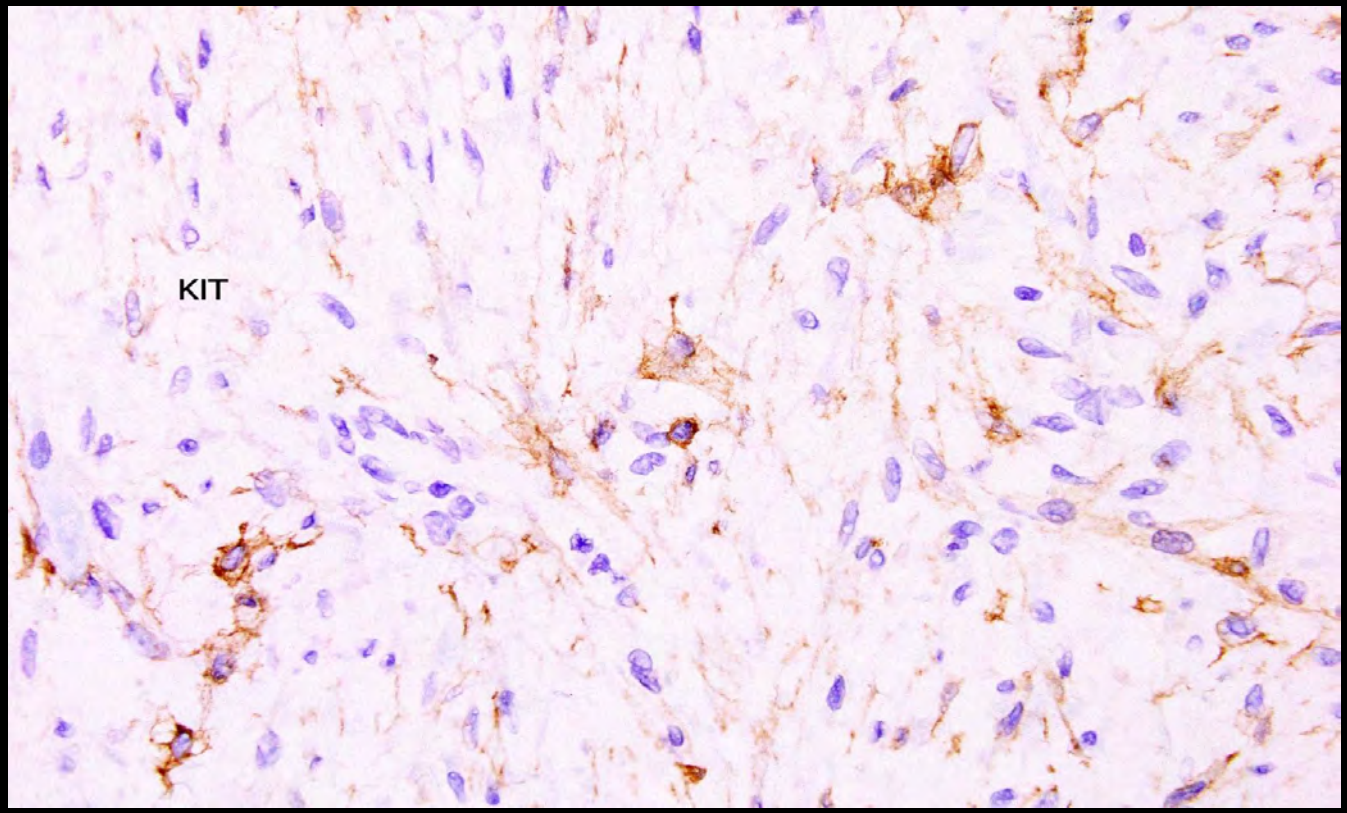
- 1: Montgomery E, Torbenson MS, Kaushal M, Fisher C, Abraham SC. Beta-catenin immunohistochemistry separates mesenteric fibromatosis from gastrointestinal stromal tumor and sclerosing mesenteritis. Am J Surg Pathol. 2002 Oct;26(10):1296-301. PMID: 12360044.
- 2: Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, Ricci F, Weber K, Furlong MA, Fisher C, Montgomery E. Nuclear beta-catenin expression distinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. Am J Surg Pathol. 2005 May;29(5):653-9. PMID: 15832090.

A perfect beta catenin preparation




Overstained beta catenin but many endothelial cell nuclei are still negative

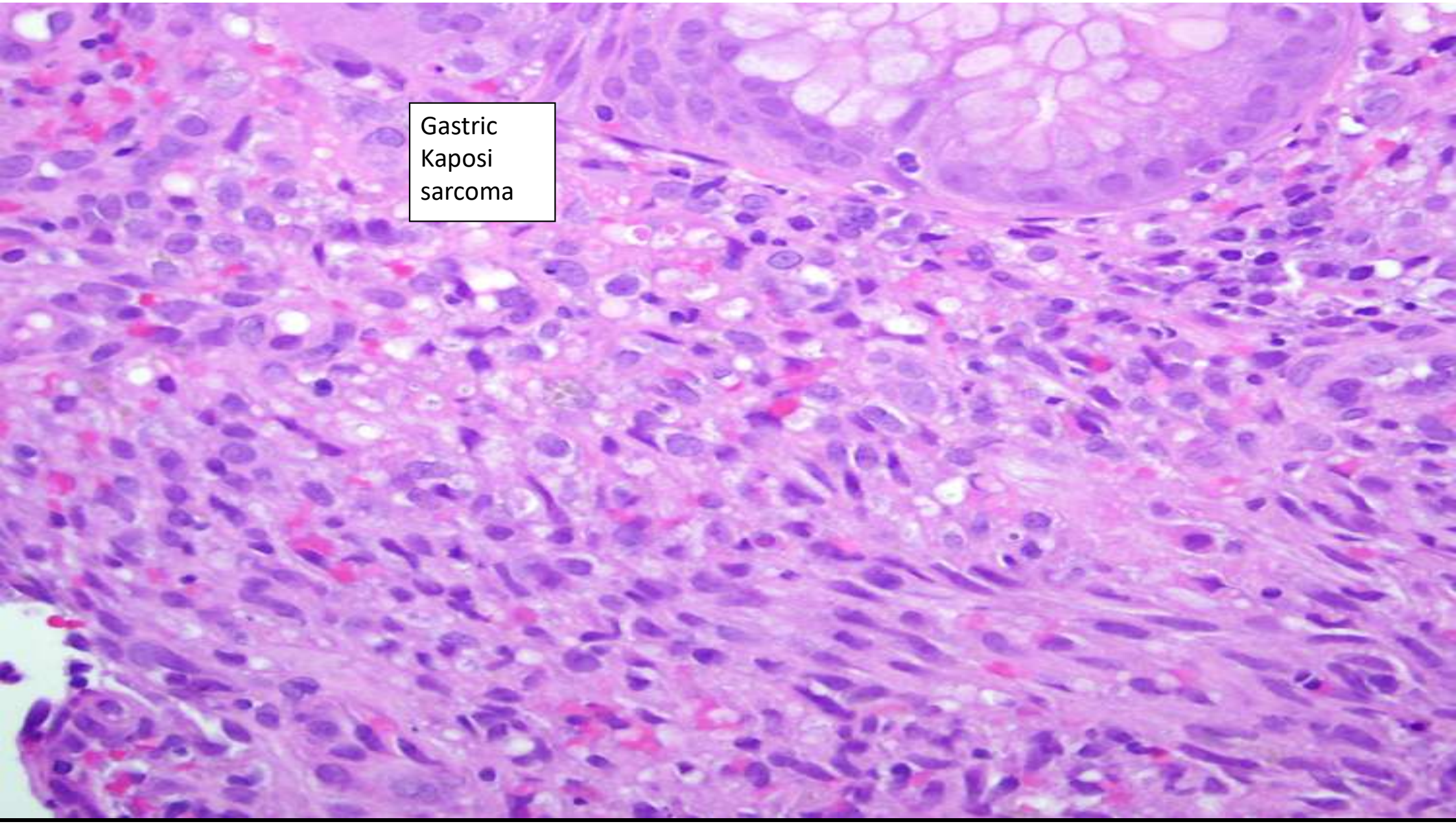
Pitfall alert – KIT in fibromatosis



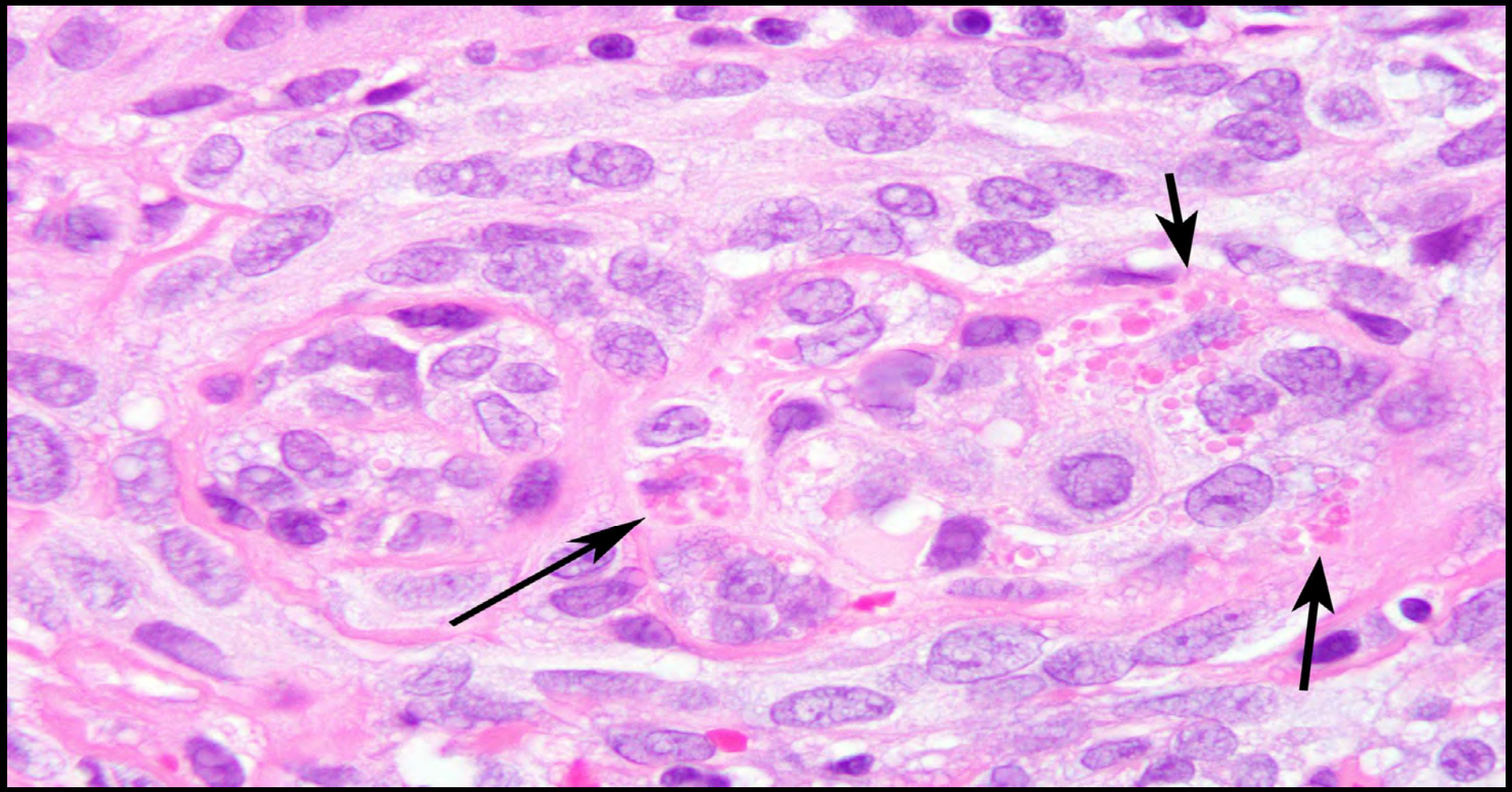
Too much antigen retrieval – no longer a common issue but this is a 2020 case!

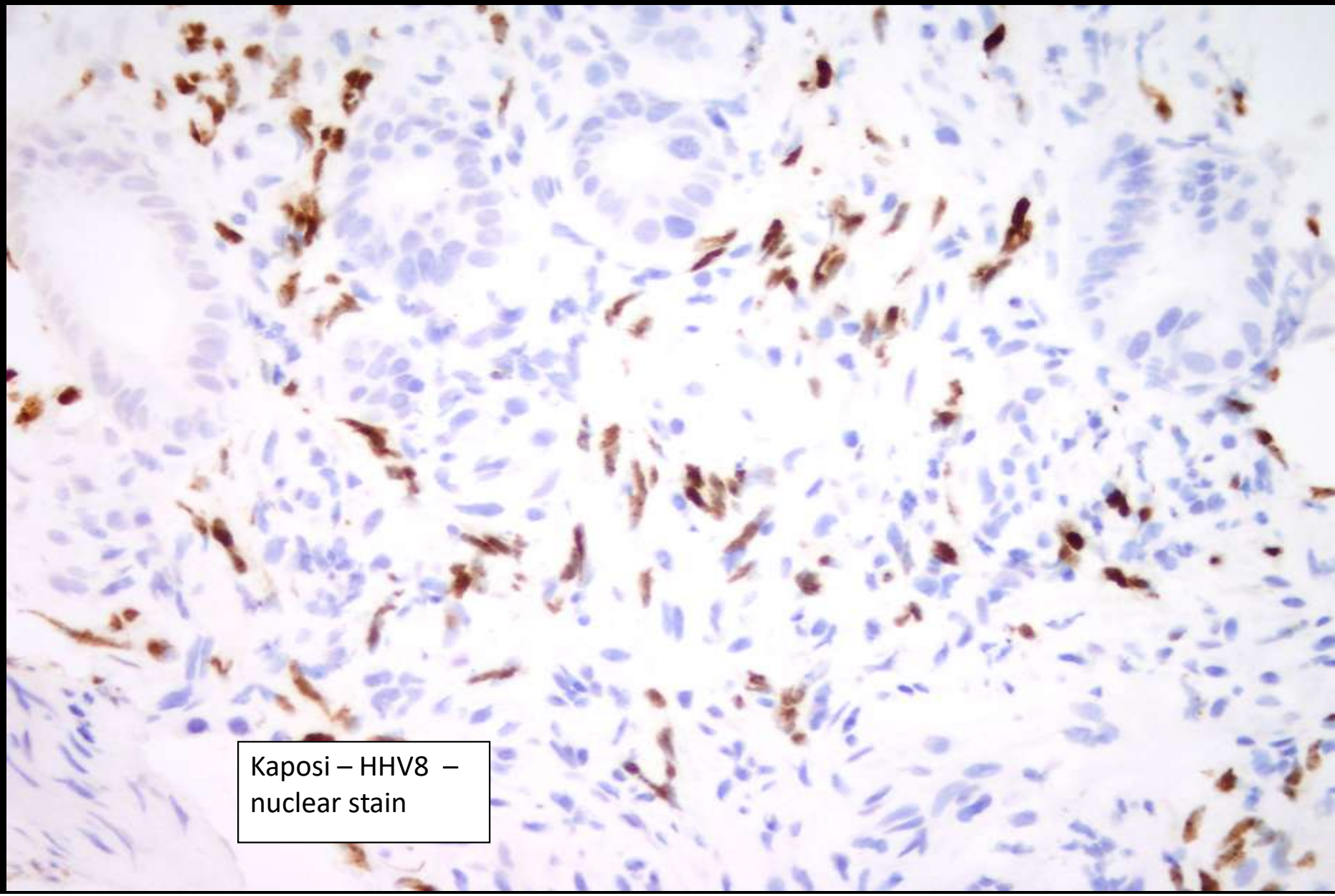
Yantiss RK, Spiro IJ, Compton CC, Rosenberg AE. Gastrointestinal stromal tumor versus intra-abdominal fibromatosis of the bowel wall: a clinically important differential diagnosis. Am J Surg Pathol. 2000 Jul;24(7):947-57. PMID: 10895817.

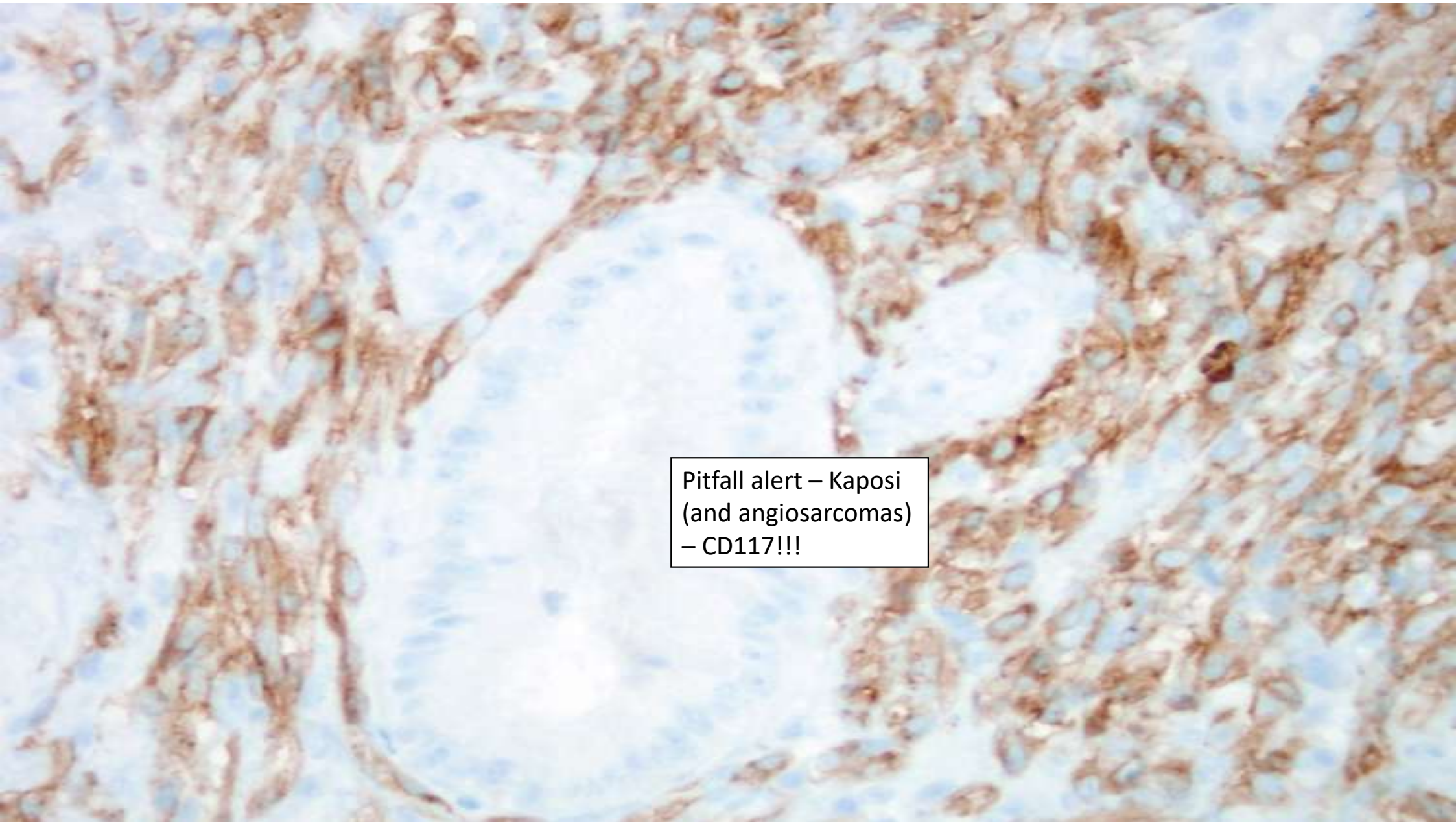
More “KITfalls”- immunostaining pitfalls (in addition to melanoma)

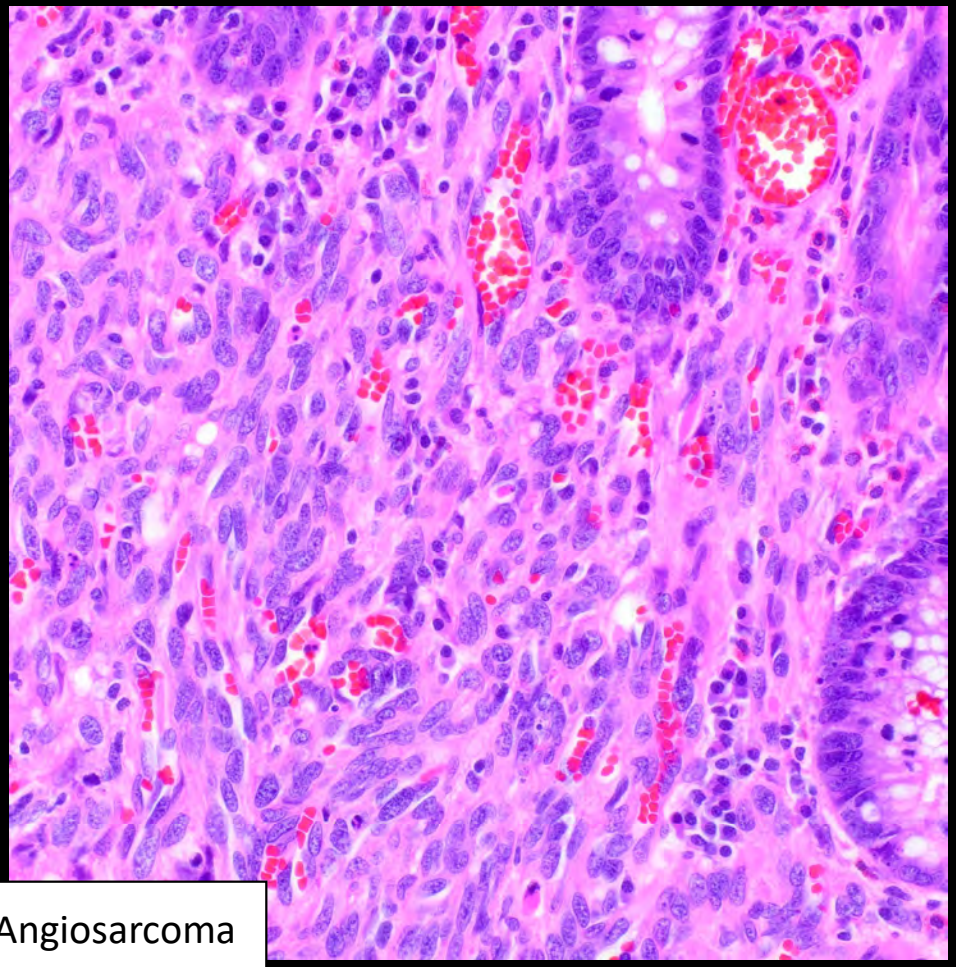

Gastric
Kaposi
sarcoma

Kaposi sarcoma – hyaline globules



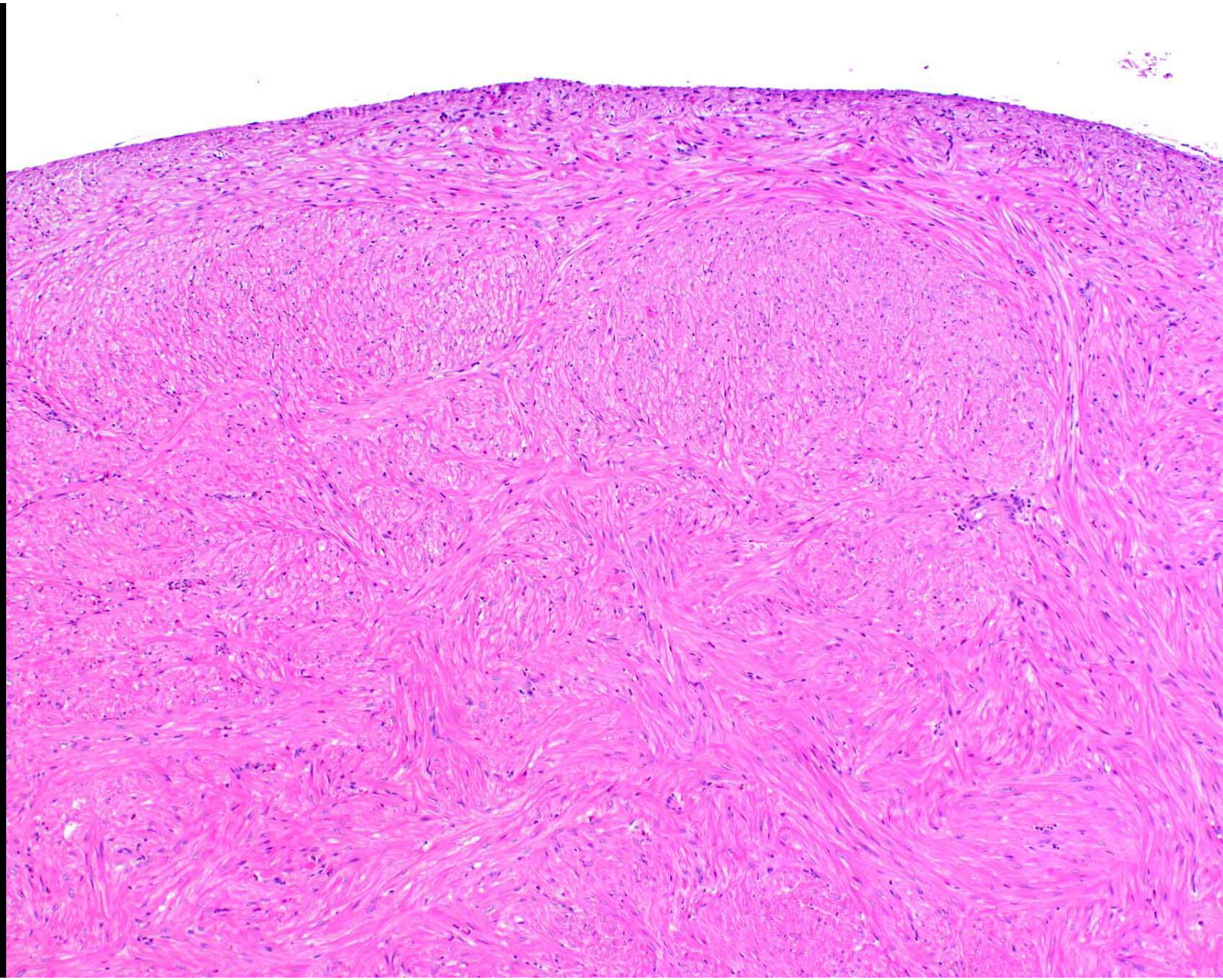

Kaposi – HHV8 –
nuclear stain

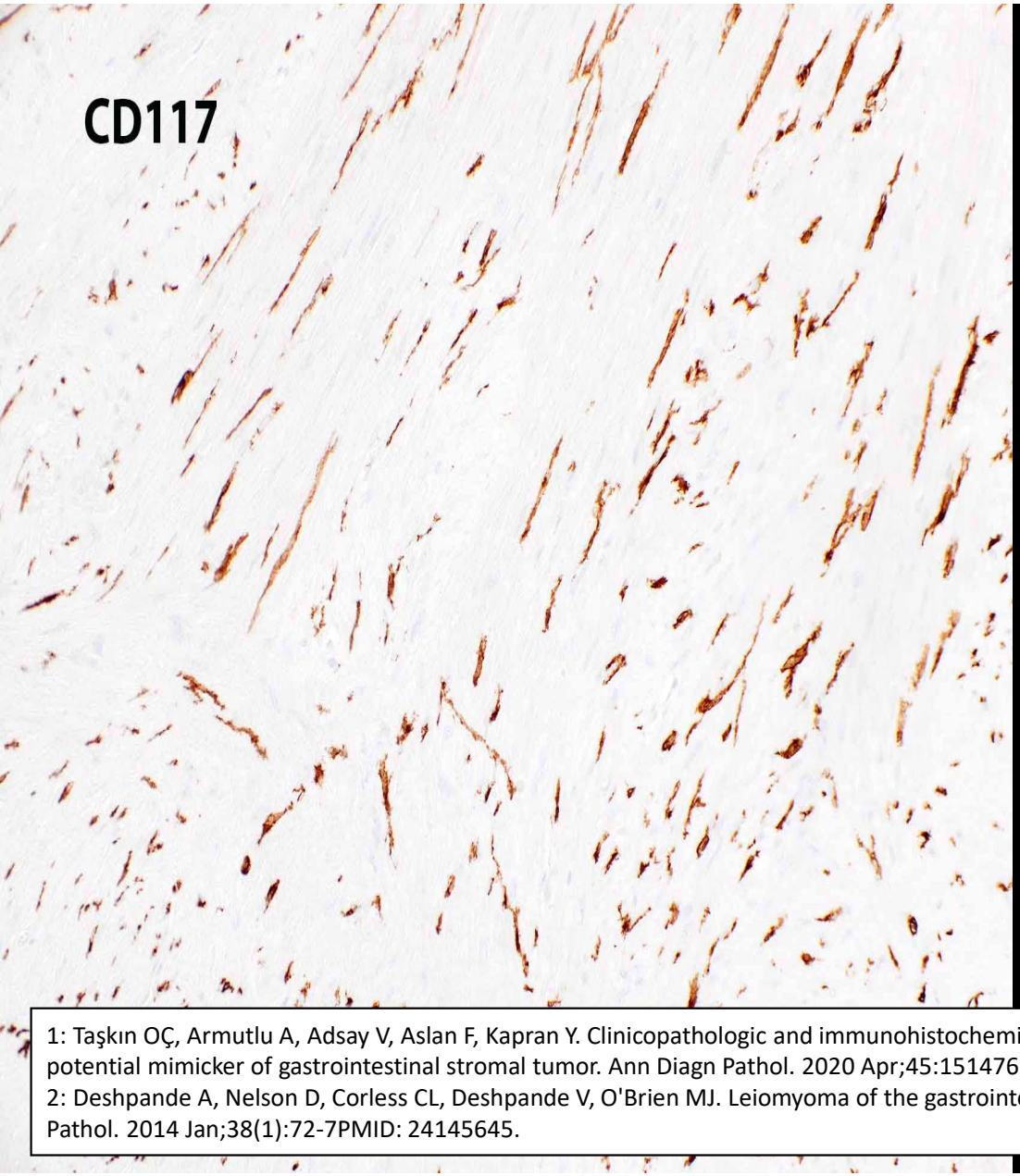

Pitfall alert – Kaposi
(and angiosarcomas)
– CD117!!!

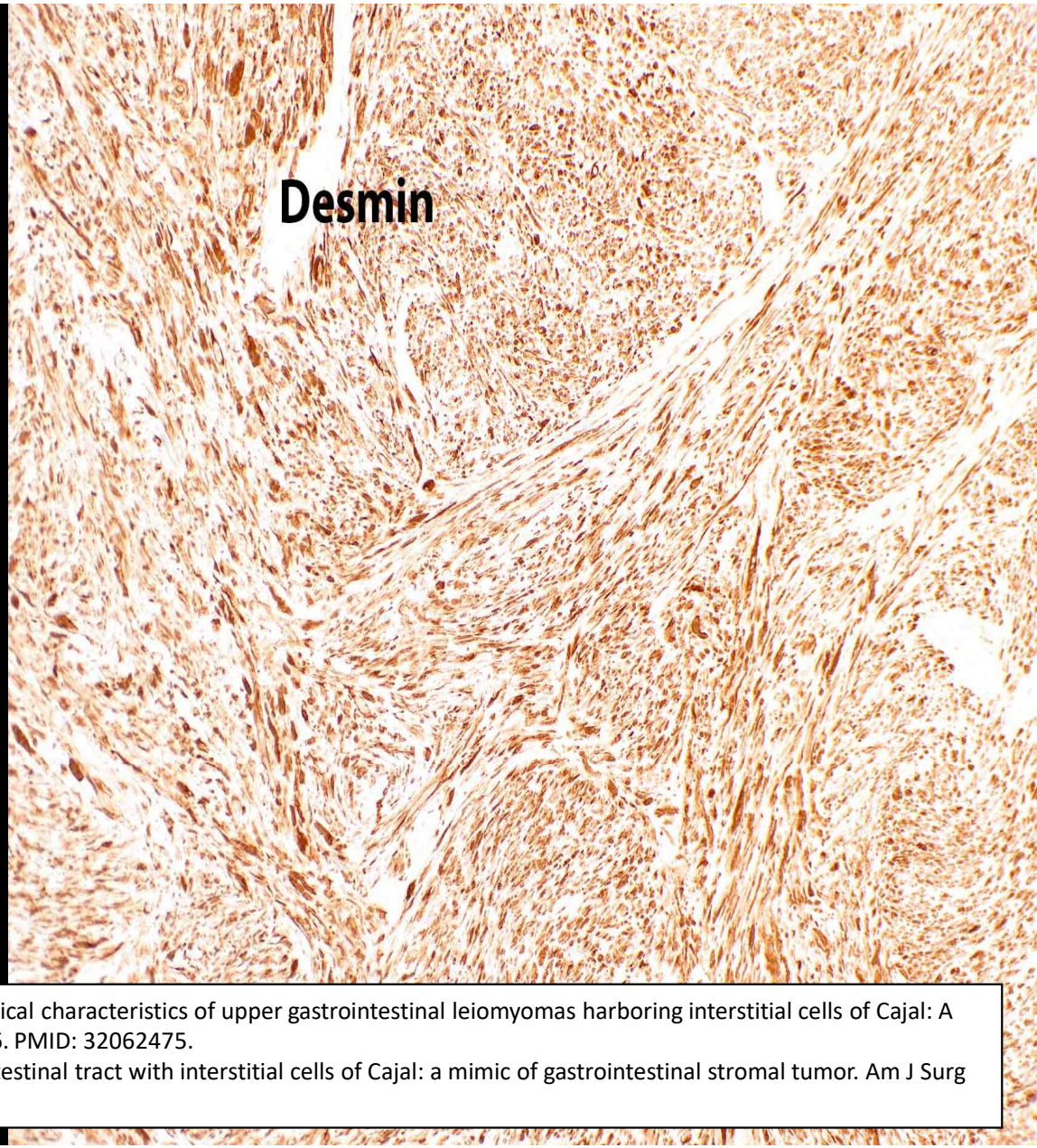


Angiosarcoma

Leiomyoma of gastroesophageal junction







1: Taşkın OÇ, Armutlu A, Adsay V, Aslan F, Kapran Y. Clinicopathologic and immunohistochemical characteristics of upper gastrointestinal leiomyomas harboring interstitial cells of Cajal: A potential mimicker of gastrointestinal stromal tumor. Ann Diagn Pathol. 2020 Apr;45:151476. PMID: 32062475.
2: Deshpande A, Nelson D, Corless CL, Deshpande V, O'Brien MJ. Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: a mimic of gastrointestinal stromal tumor. Am J Surg Pathol. 2014 Jan;38(1):72-7PMID: 24145645.

GIT “Schwannomas”

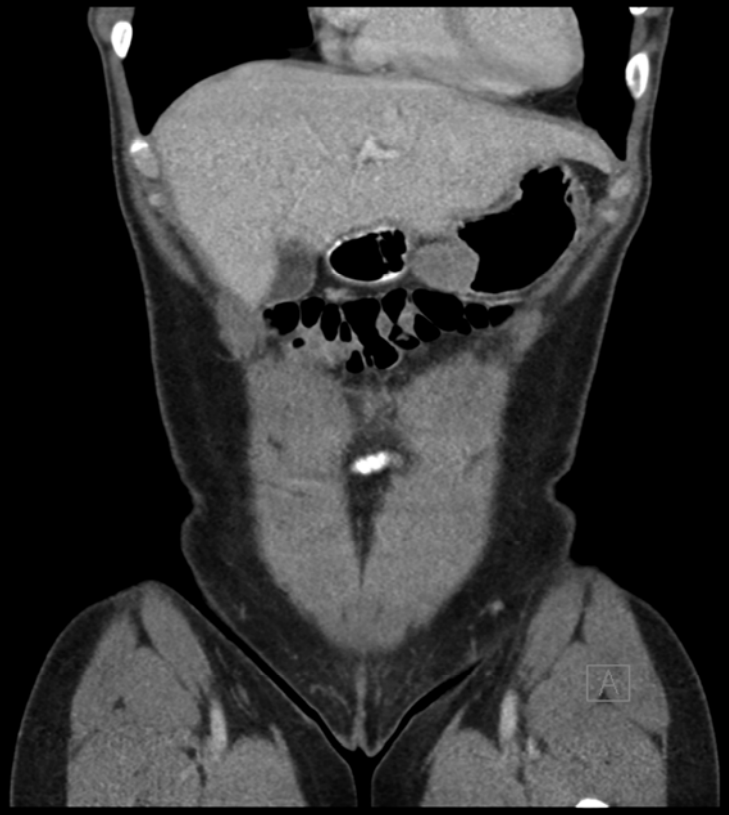
- Most schwannomas occur in the stomach involving submucosa and muscularis propria. They rarely arise in the esophagus or colon.
- Lesions classified as GI schwannomas differ from the conventional somatic soft tissue schwannomas histologically by having peripheral lymphoid cuffs, lacking fibrous capsules or vascular hyalinization, and rarely showing degenerative changes.

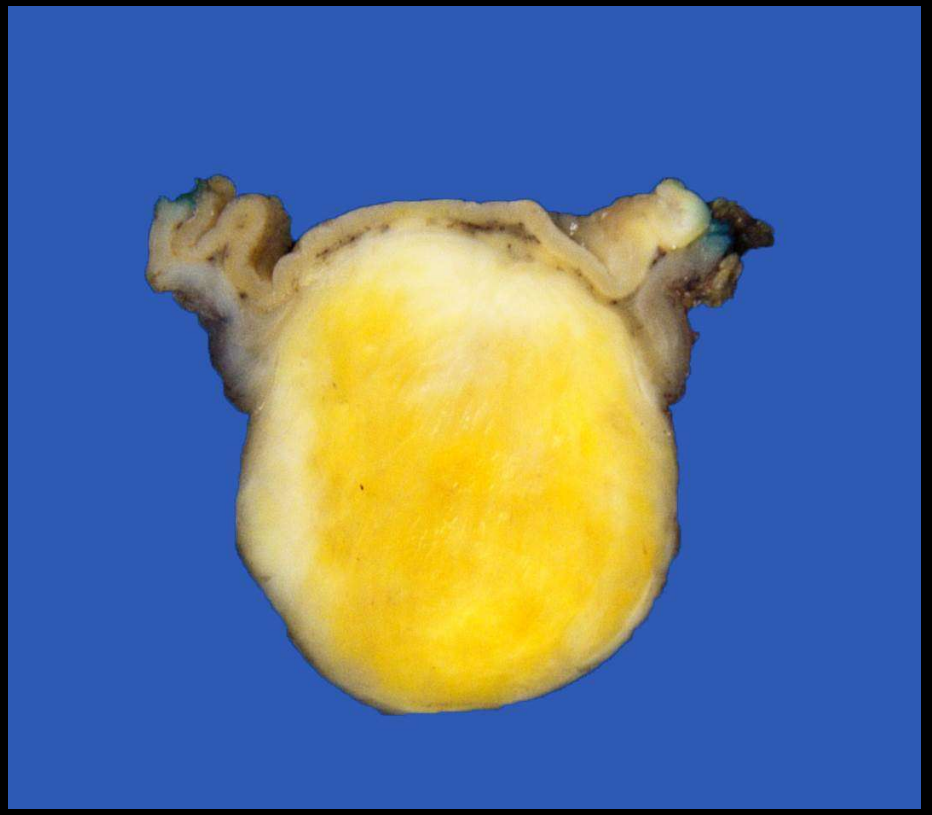
- Voltaggio L, Murray R, Lasota J, Miettinen M. Gastric schwannoma: a clinicopathologic study of 51 cases and critical review of the literature. Hum Pathol. 2012 May;43(5):650-9. PMID: 22137423; PMCID: PMC3305846.

GIT “Schwannomas”

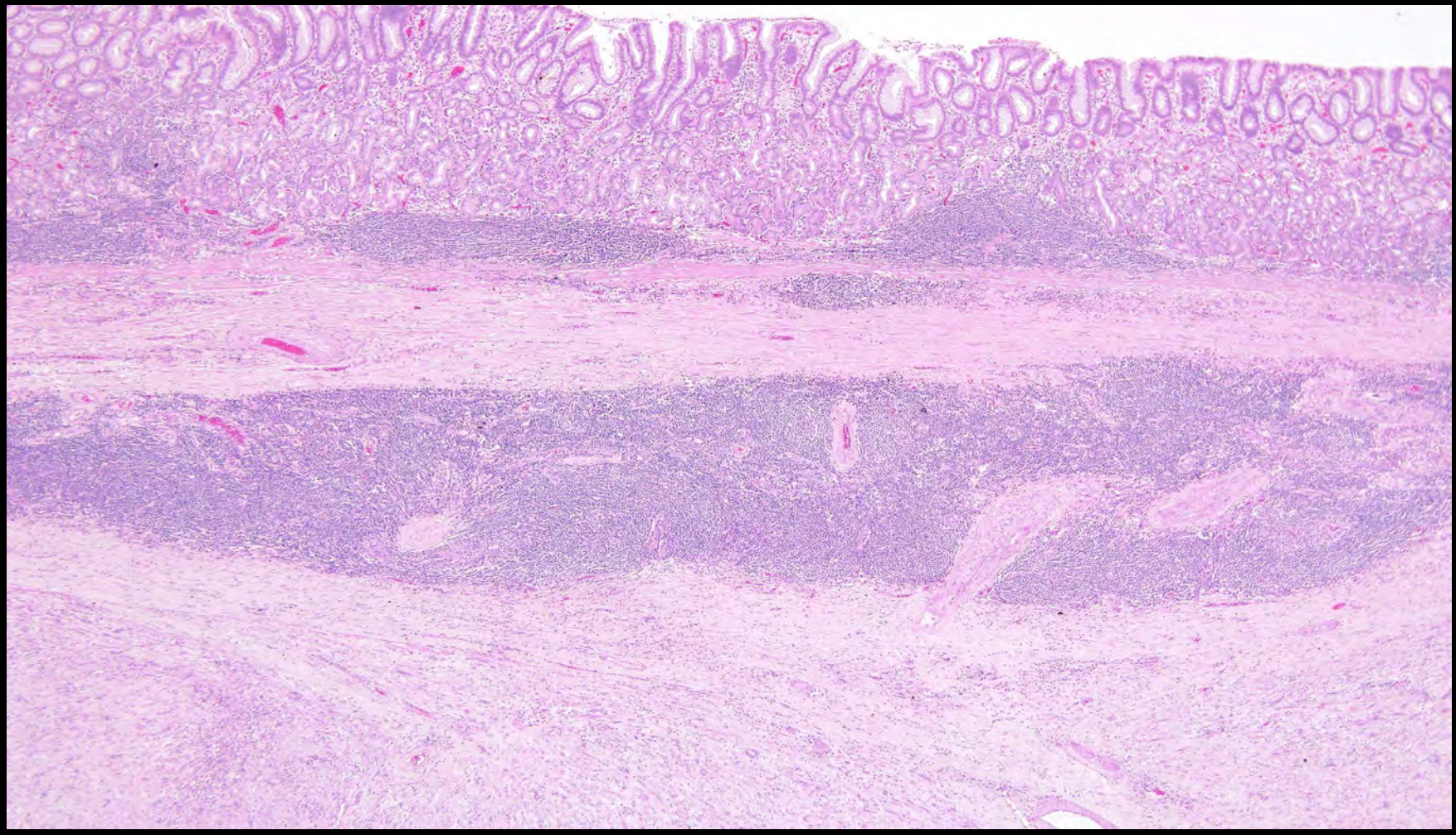
- GI “schwannomas” lack alterations in the *NF2* gene found in many sporadic, conventional schwannomas from other sites.

Gastric schwannoma – Arises in Muscularis Propria

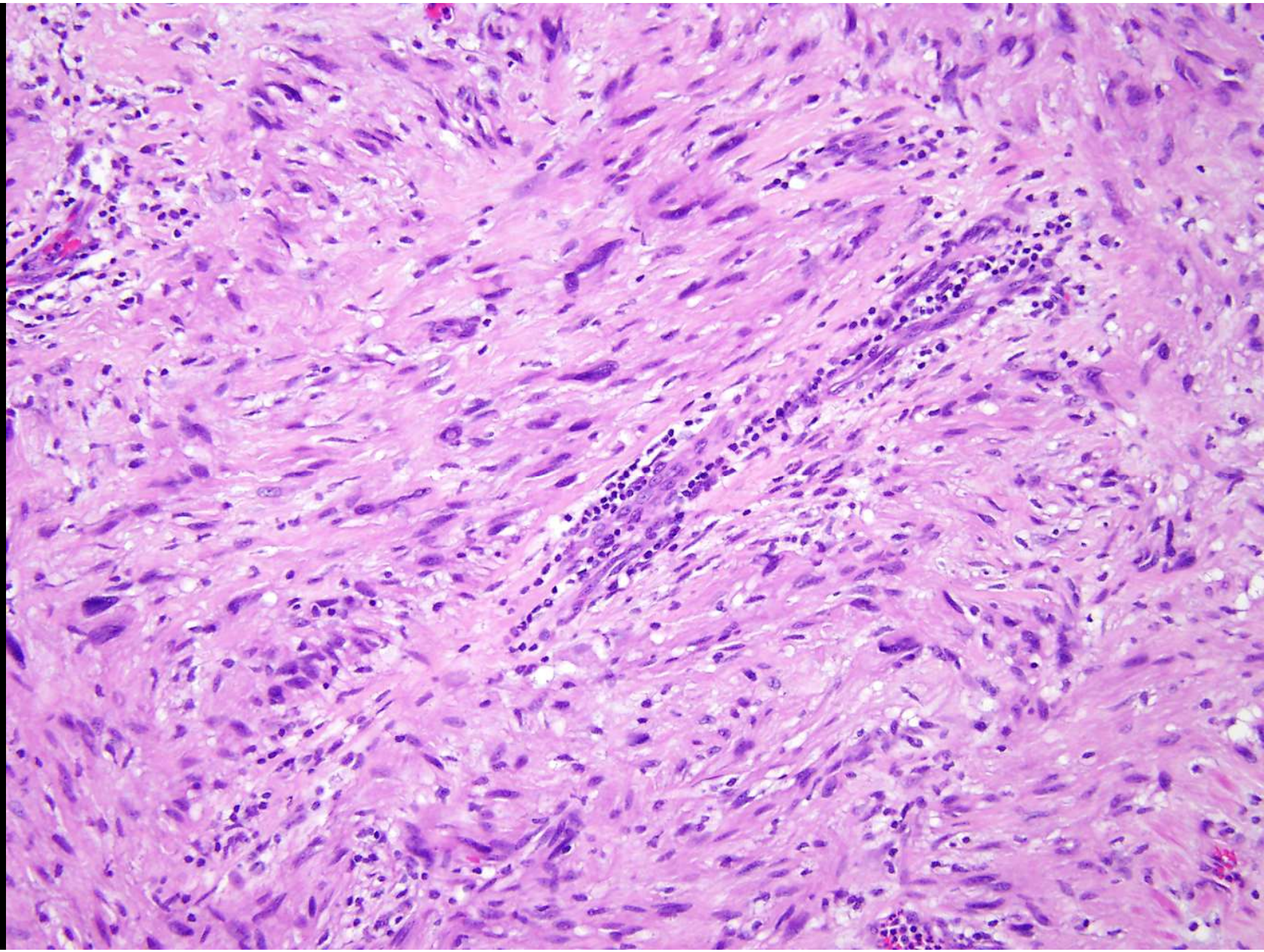


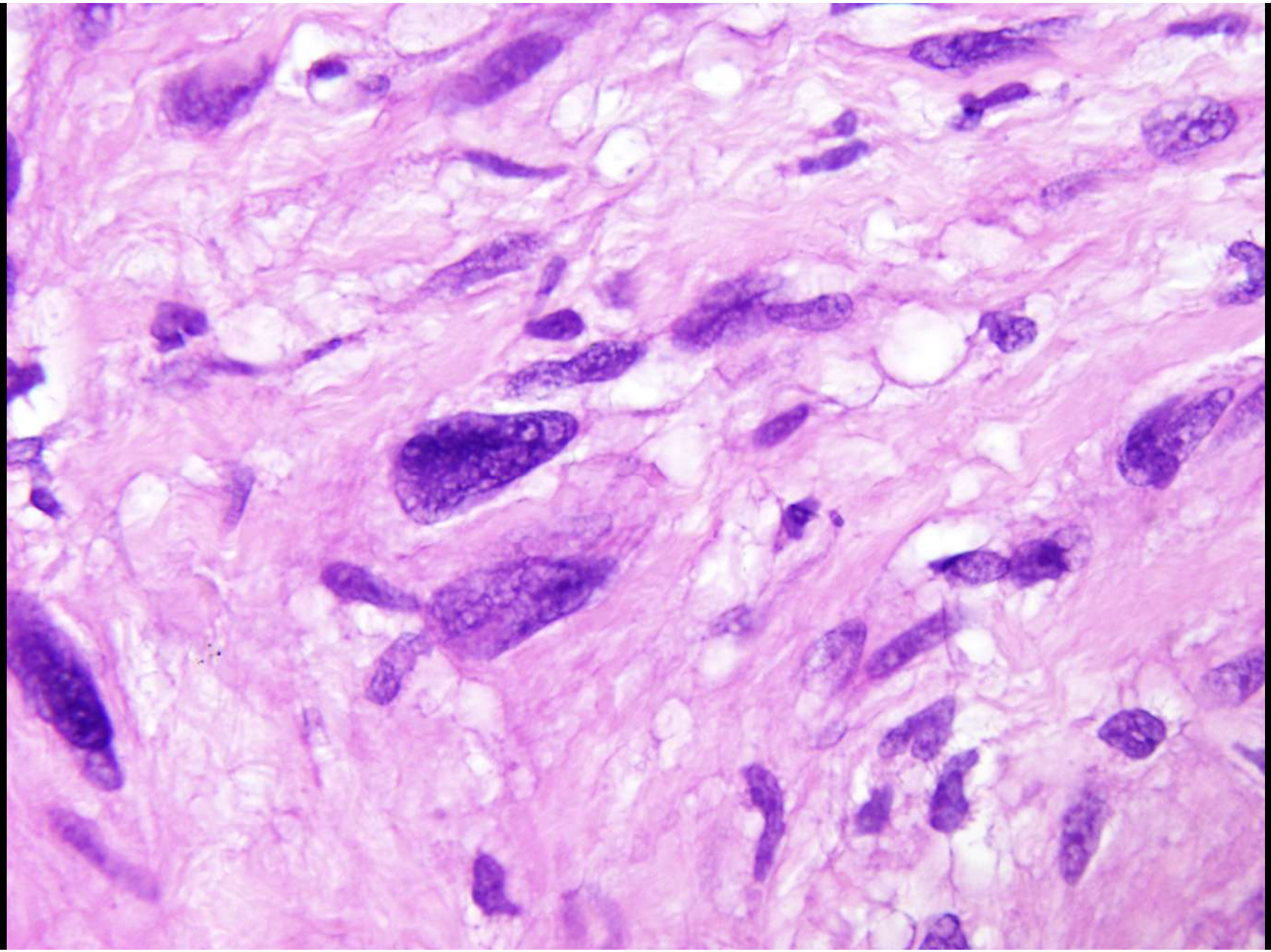


Gastric schwannoma - Thick lymphoid cuff

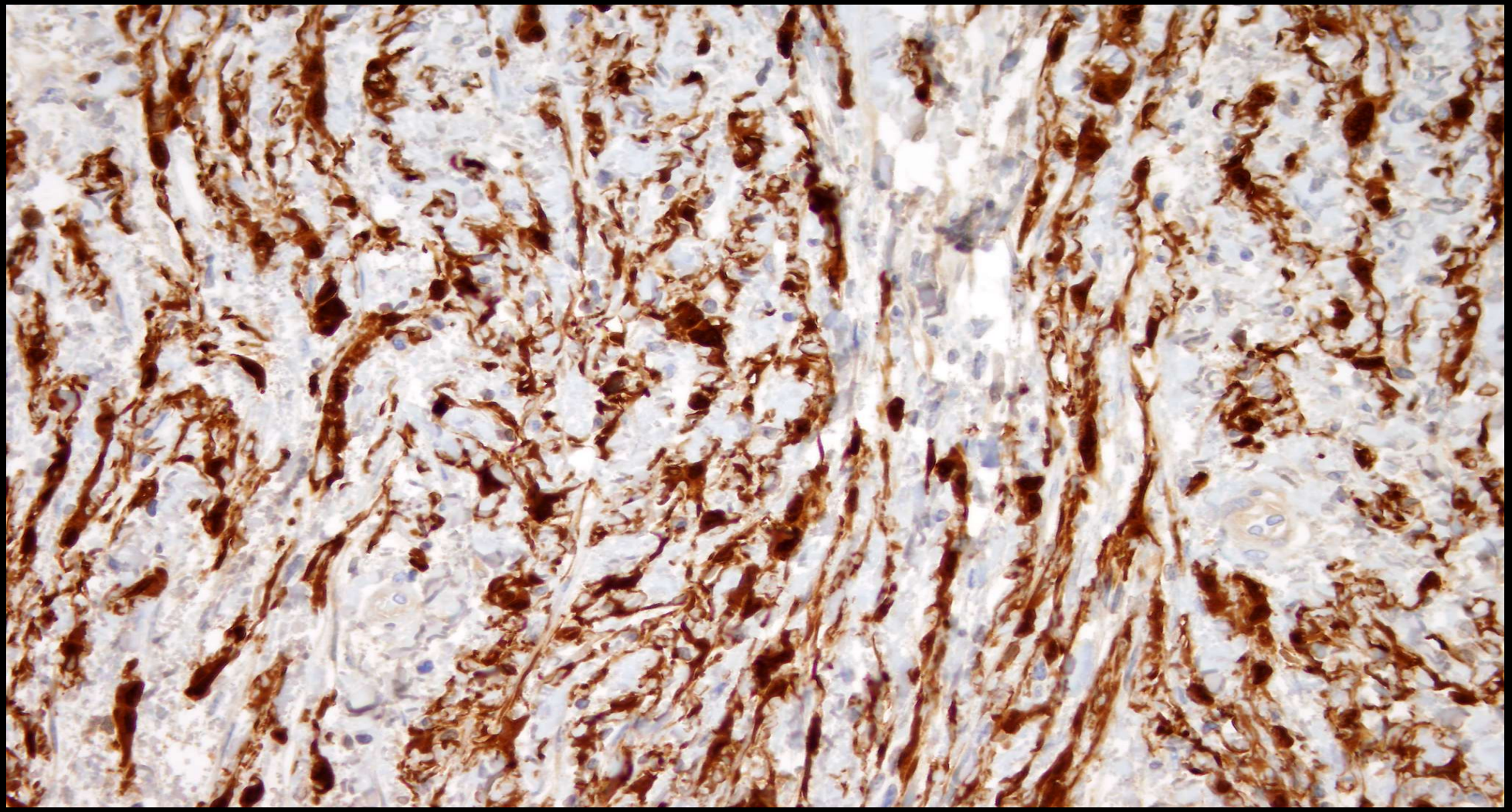


Vague palisading and plentiful inflammation



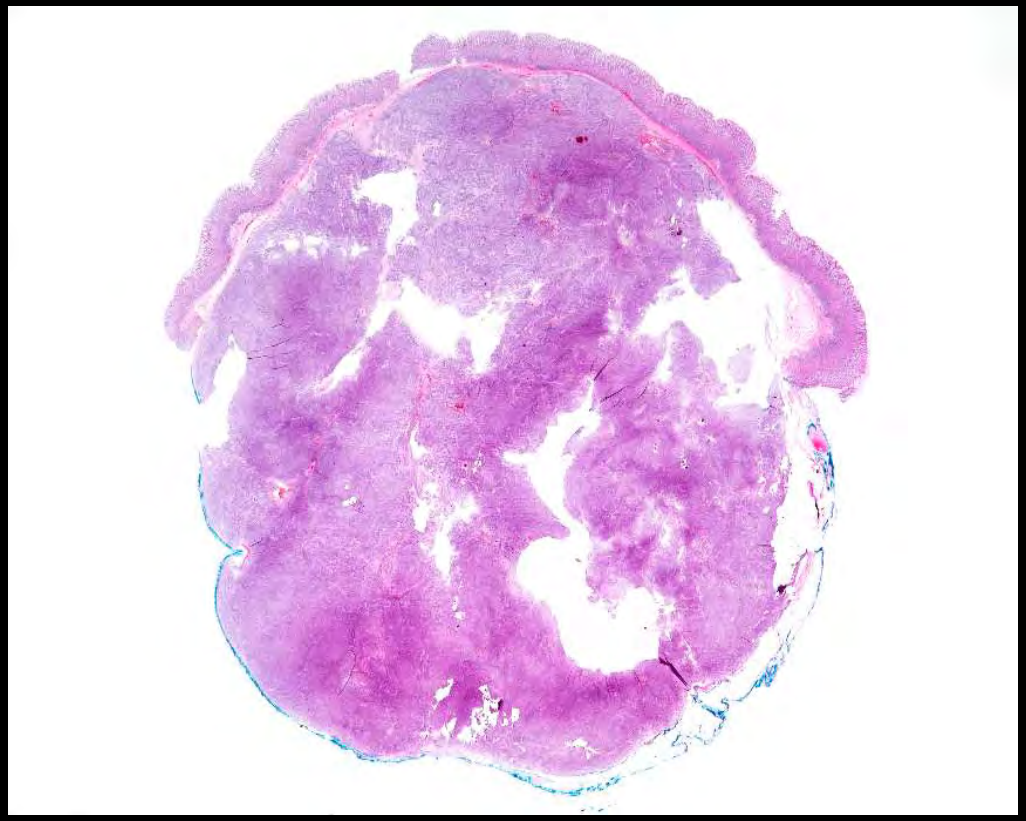


Gastric schwannoma – S100 protein for nervous souls

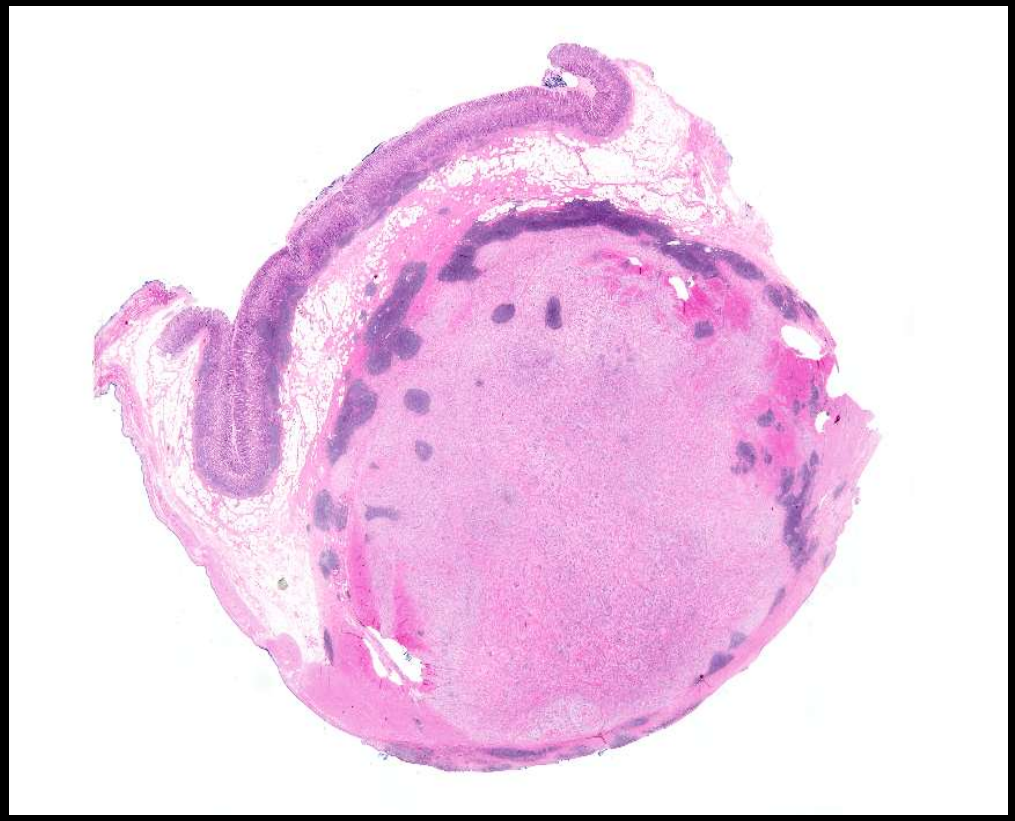


Gastric Beauty Contest

GIST



Schwannoma

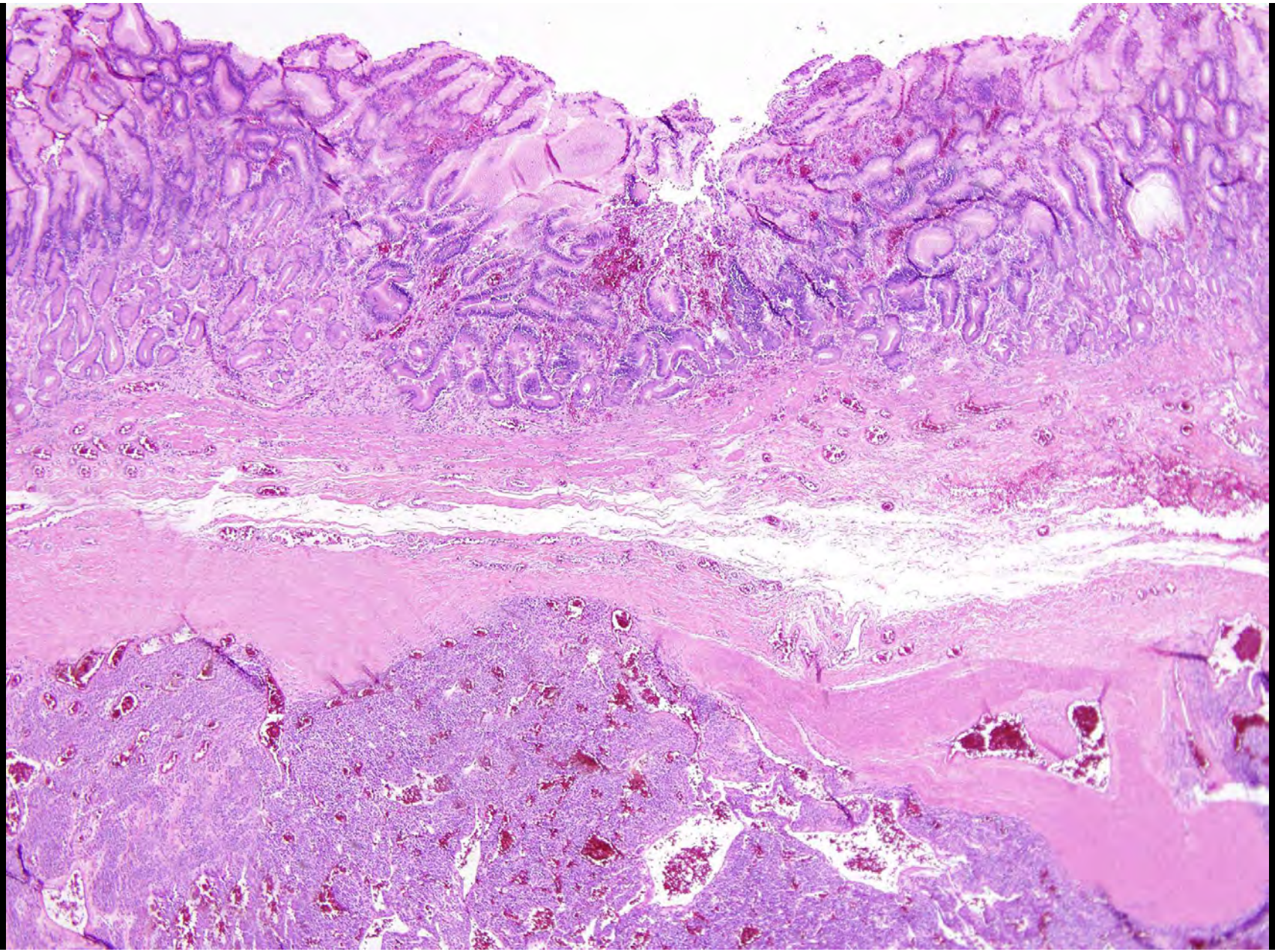


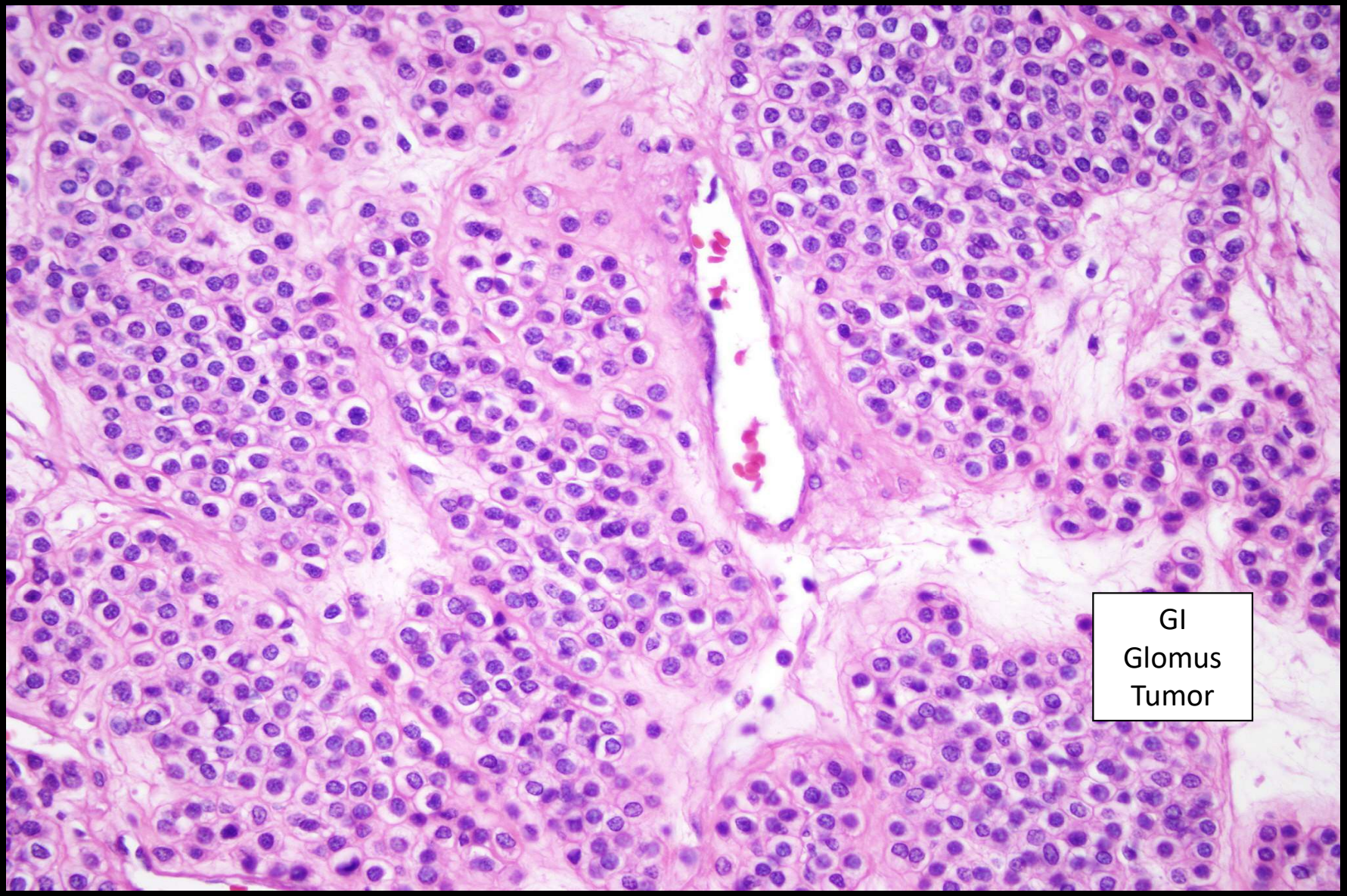
GI Glomus Tumors

- Rare in the GI tract.
- Largest series (AFIP); female predominance, median age at presentation of 55 years.
- Majority in stomach
- May present with severe bleeding producing melena.
- The vast majority behaves in a benign fashion.
- However, some examples are lethal with metastases.
- *Difficult to predict which will have an unfavorable outcome – proposal of ≥ 5cm with ≥2 mitoses/10 hpf as malignant.*
- **Esophageal examples (rare) seem to be aggressive**

- Birkness-Gartman JE, Wangsiricharoen S, Lazar AJ, Gross JM. Oesophageal glomus tumours: rare neoplasms with aggressive clinical behaviour. Histopathology. 2023 Jun;82(7):1048-1055. PMID: 36788021.)
- Papke DJ Jr, Sholl LM, Doyle LA, Fletcher CDM, Hornick JL. Gastroesophageal Glomus Tumors: Clinicopathologic and Molecular Genetic Analysis of 26 Cases With a Proposal for Malignancy Criteria. Am J Surg Pathol. 2022 Oct 1;46(10):1436-1446. PMID: 35703141.

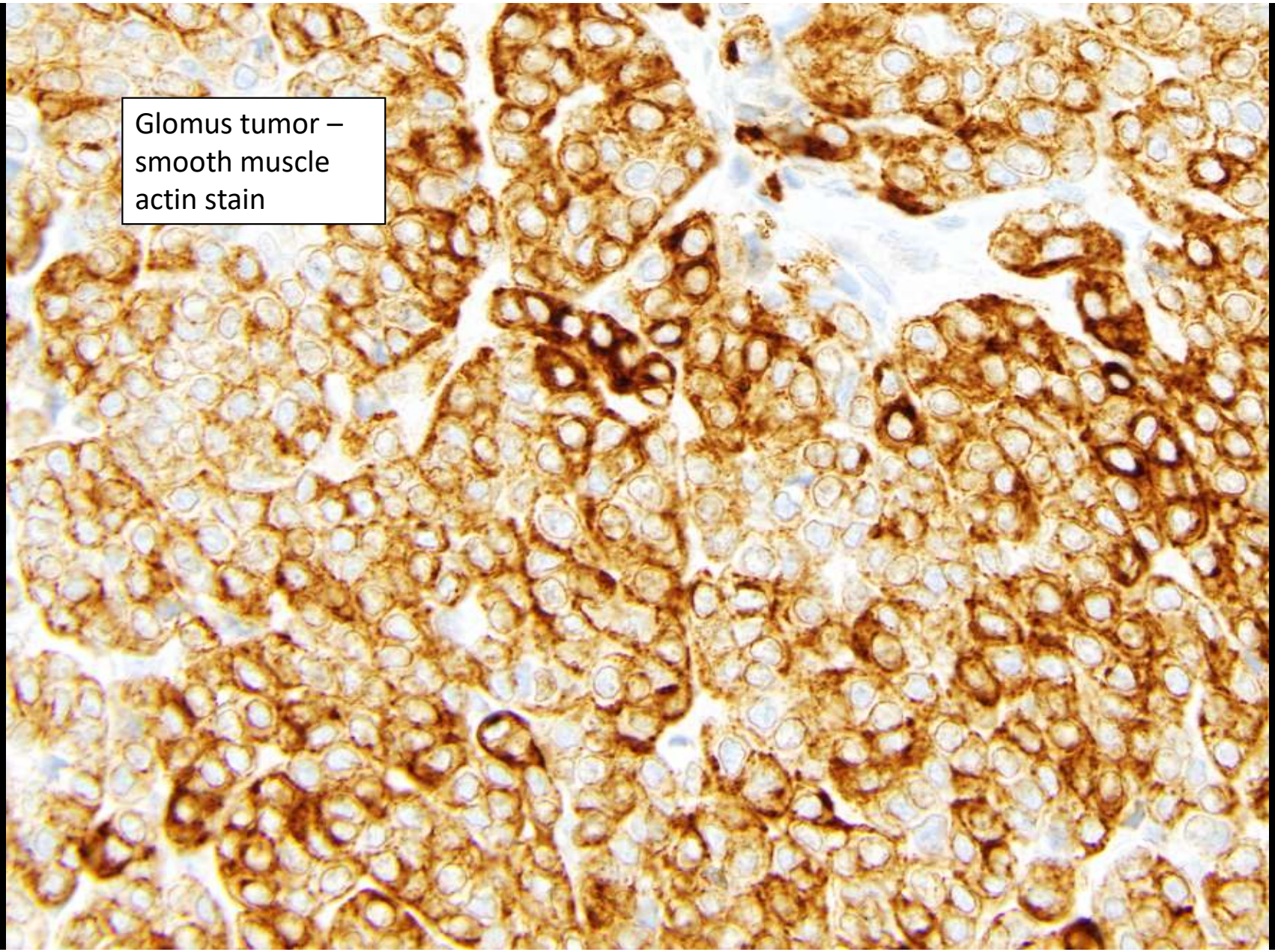
GI Glomus Tumors
Denizens of muscularis propria

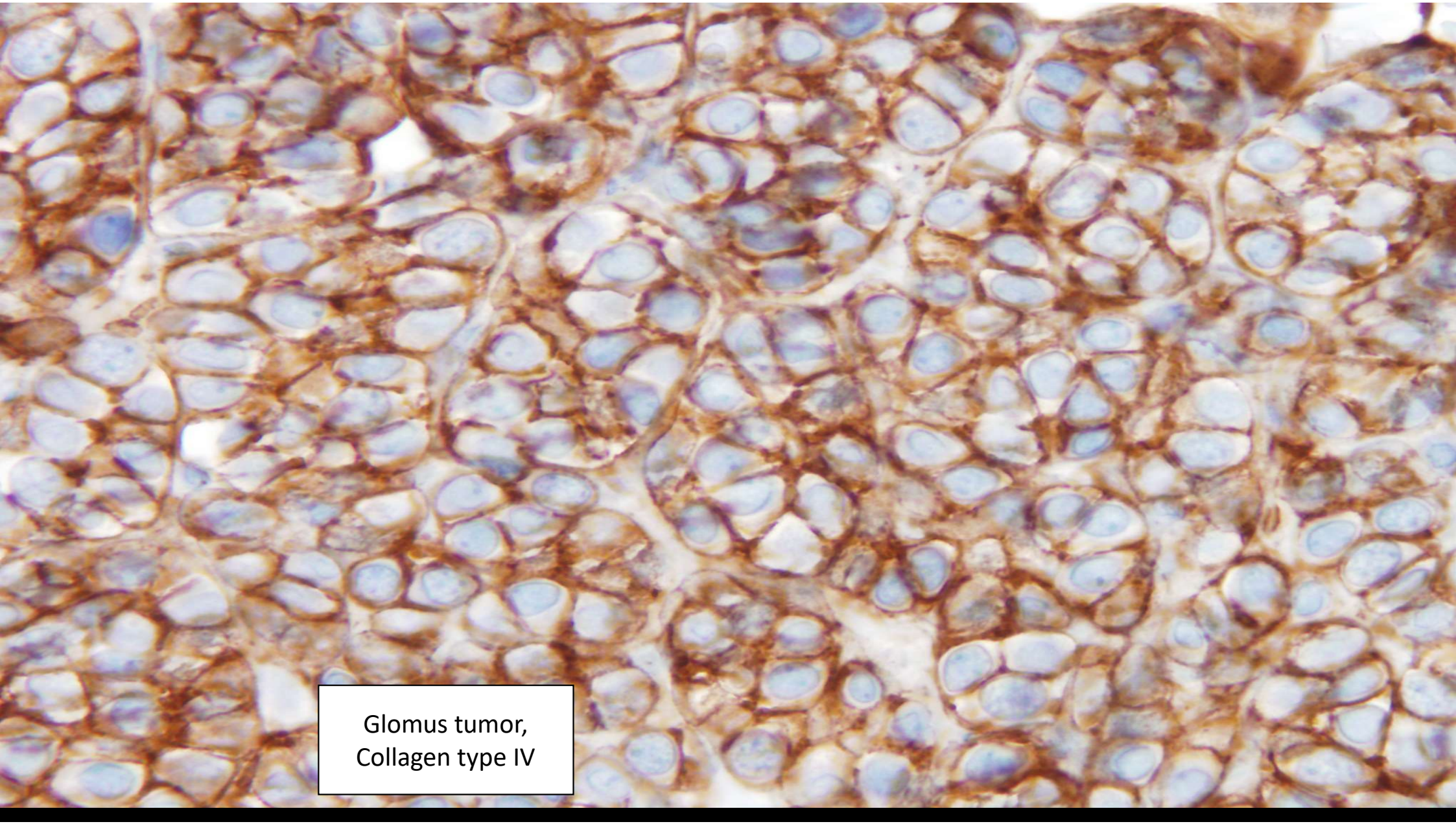


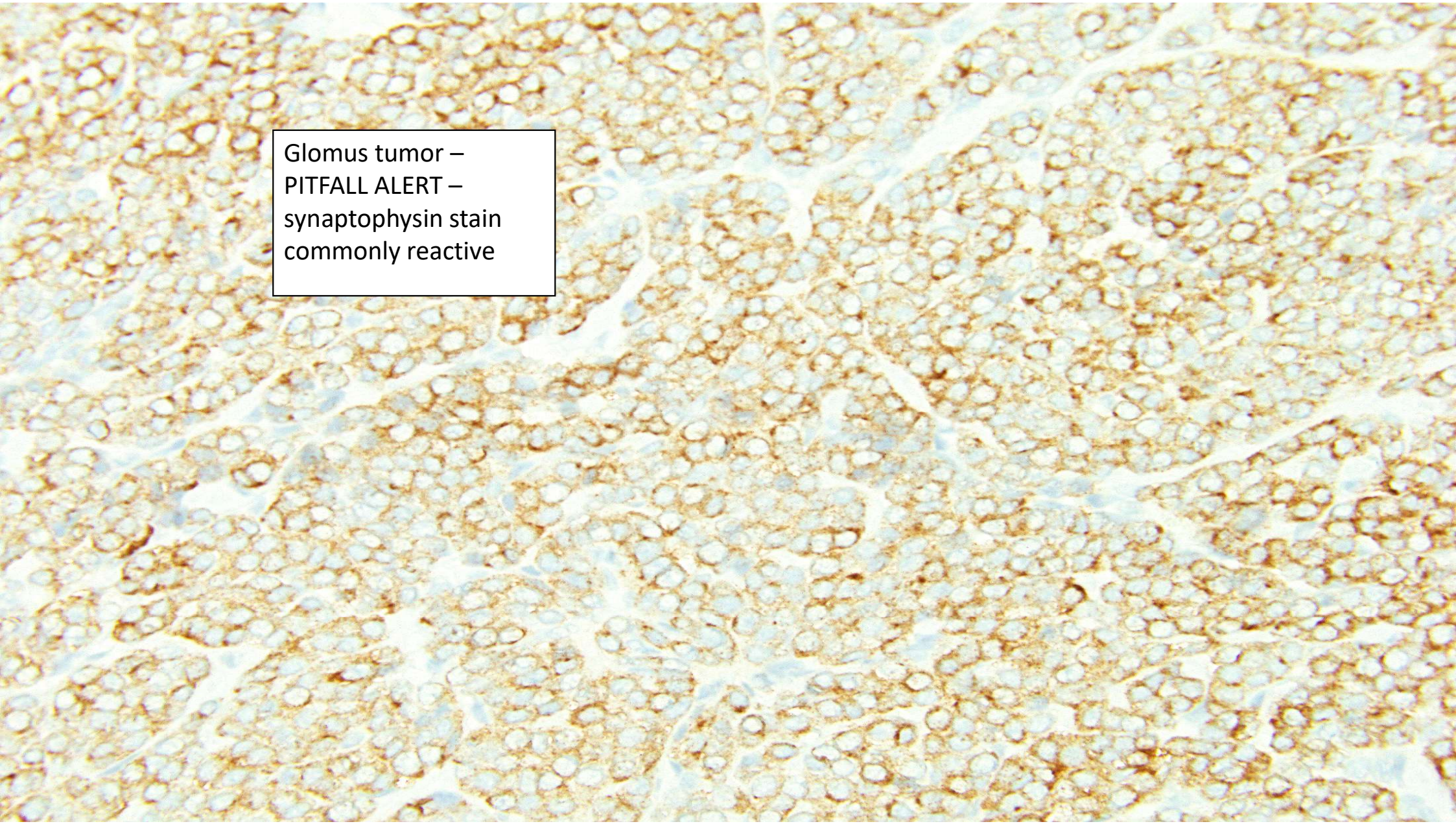

GI
Glomus
Tumor

GI Glomus Tumors, Ancillary Studies

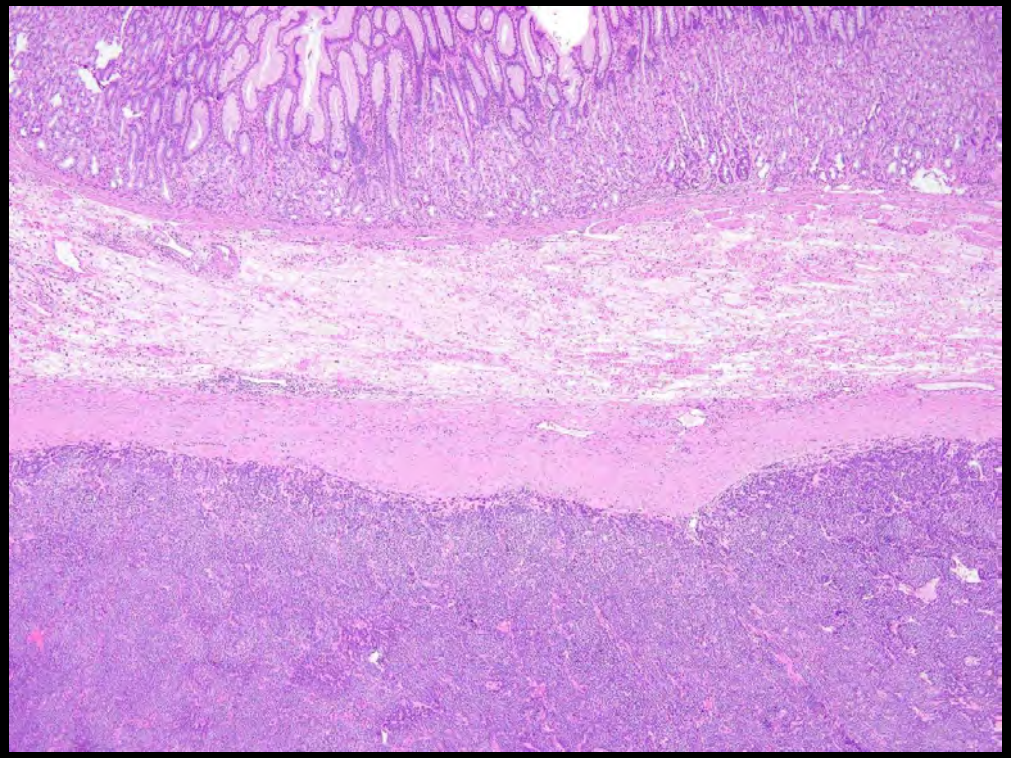
- Express smooth muscle actin, calponin, and h-caldesmon but lack desmin.
- Pericellular net-like positivity is seen with basement membrane proteins (laminin and collagen type IV).
- Some cases have focal CD34.
- No CD117/kit expression – No *KIT* mutations.
- Some cases express synaptophysin but these tumors lack chromogranin and they lack keratin.
- *MIR143::NOTCH* fusion Genes Chromosomes and Cancer 2013; 52:1075

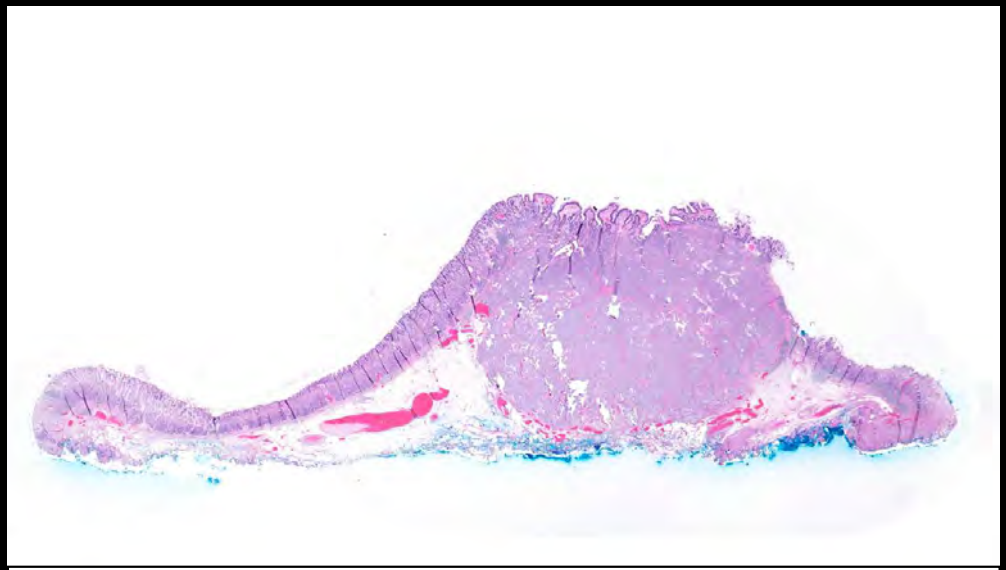

Glomus tumor –
smooth muscle
actin stain


Glomus tumor,
Collagen type IV


Glomus tumor –
PITFALL ALERT –
synaptophysin stain
commonly reactive

Glomus Tumor (L) versus NET (R)



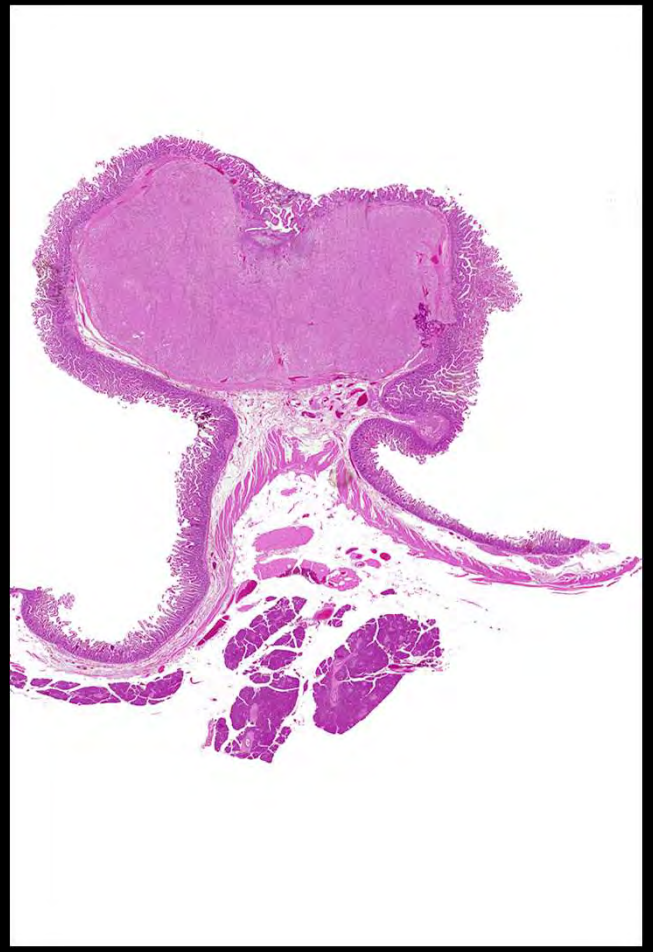


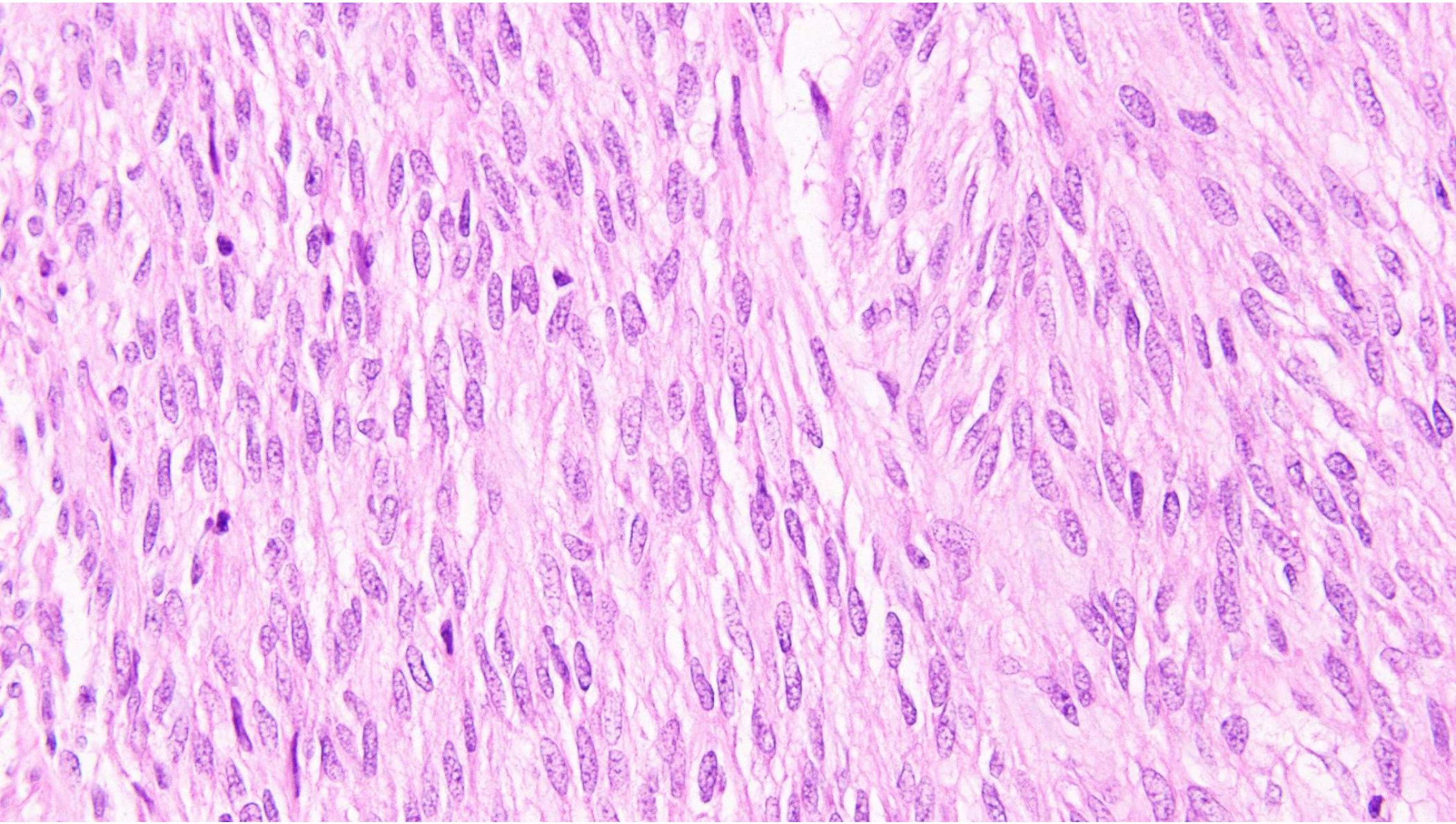
Well differentiated neuroendocrine (carcinoid tumor – lives at the junction of the mucosa and submucosa – this is an endoscopic mucosal resection specimen

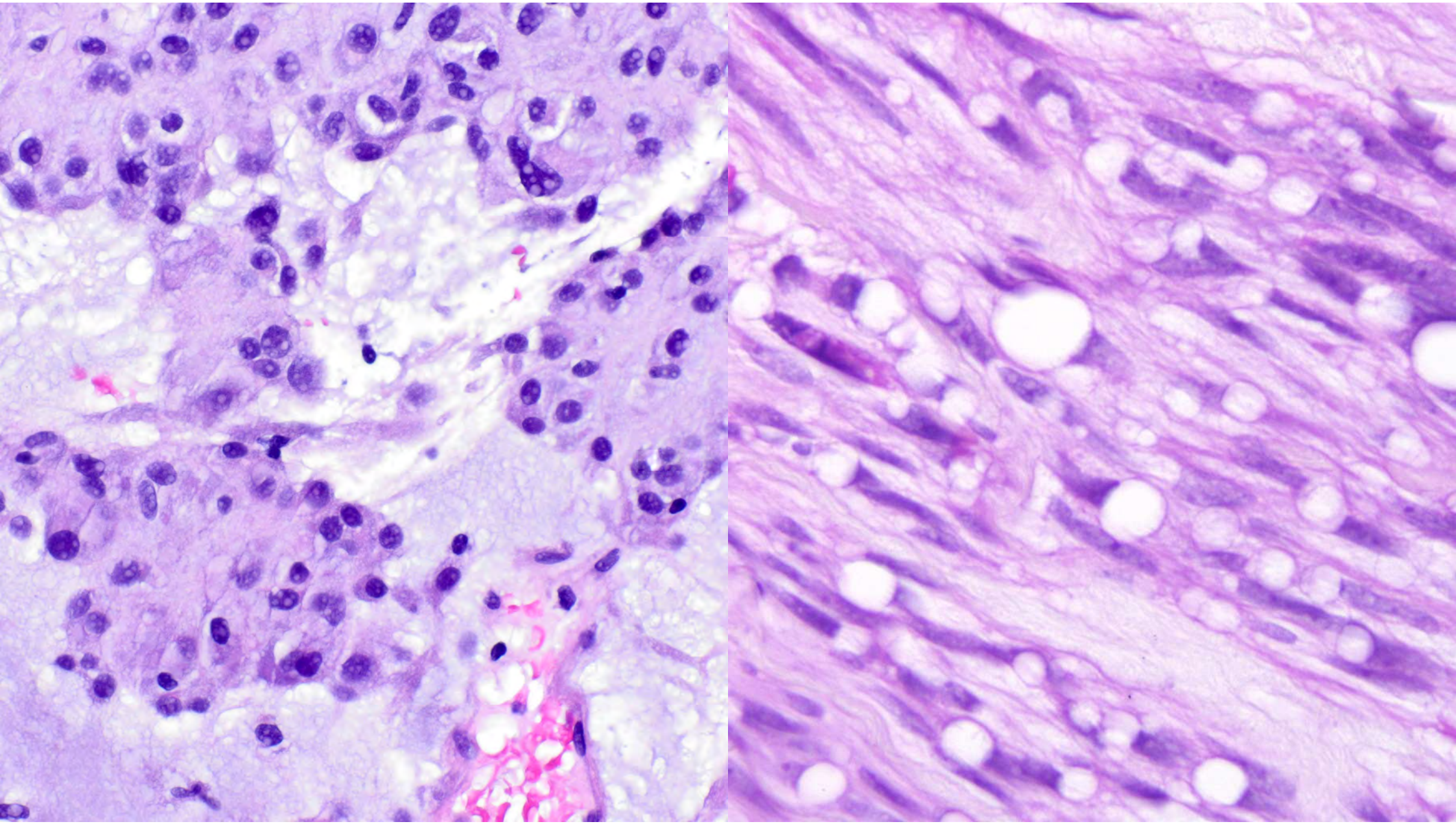
Emperor of The Muscularis Propria

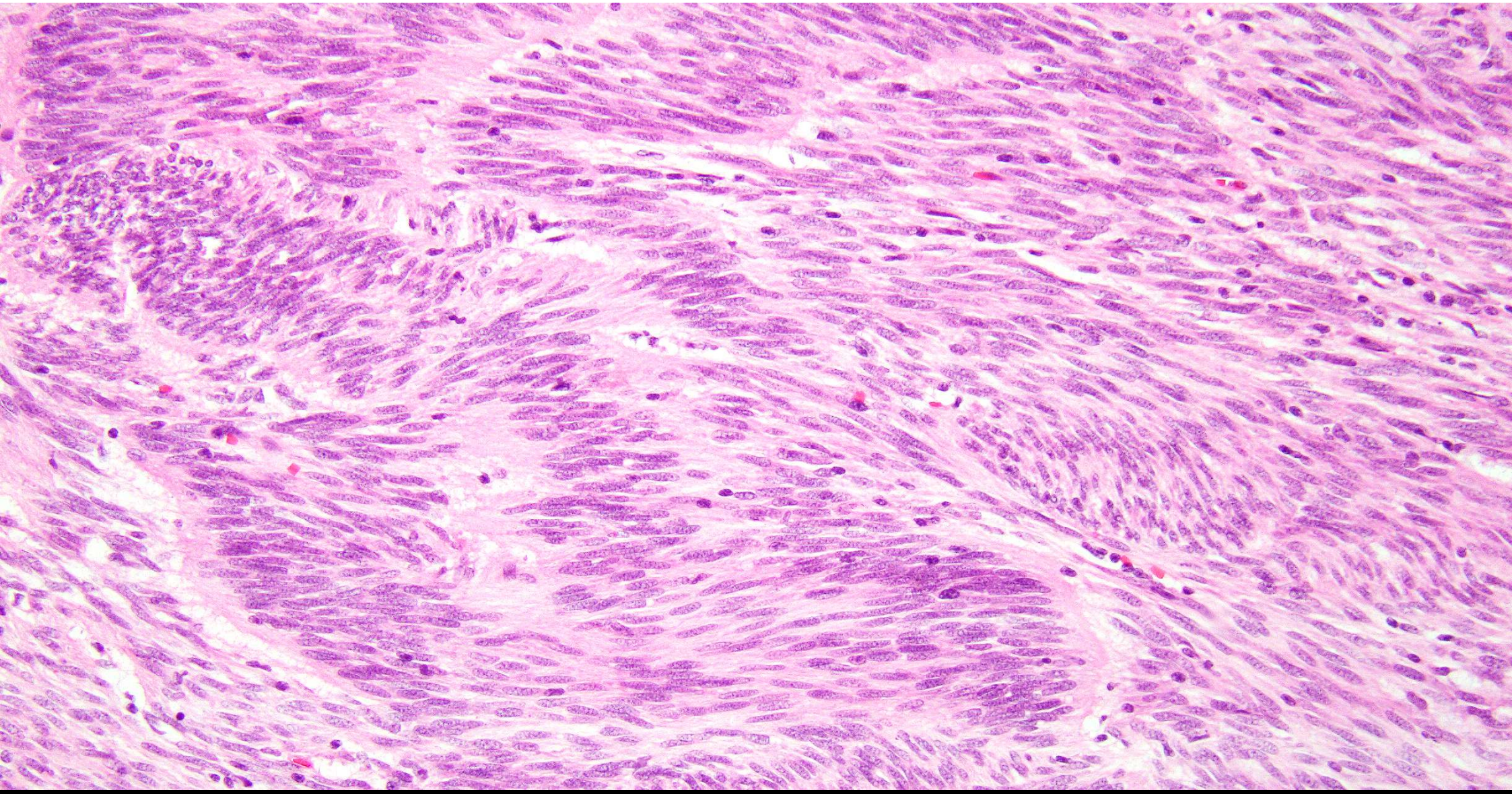
GIST

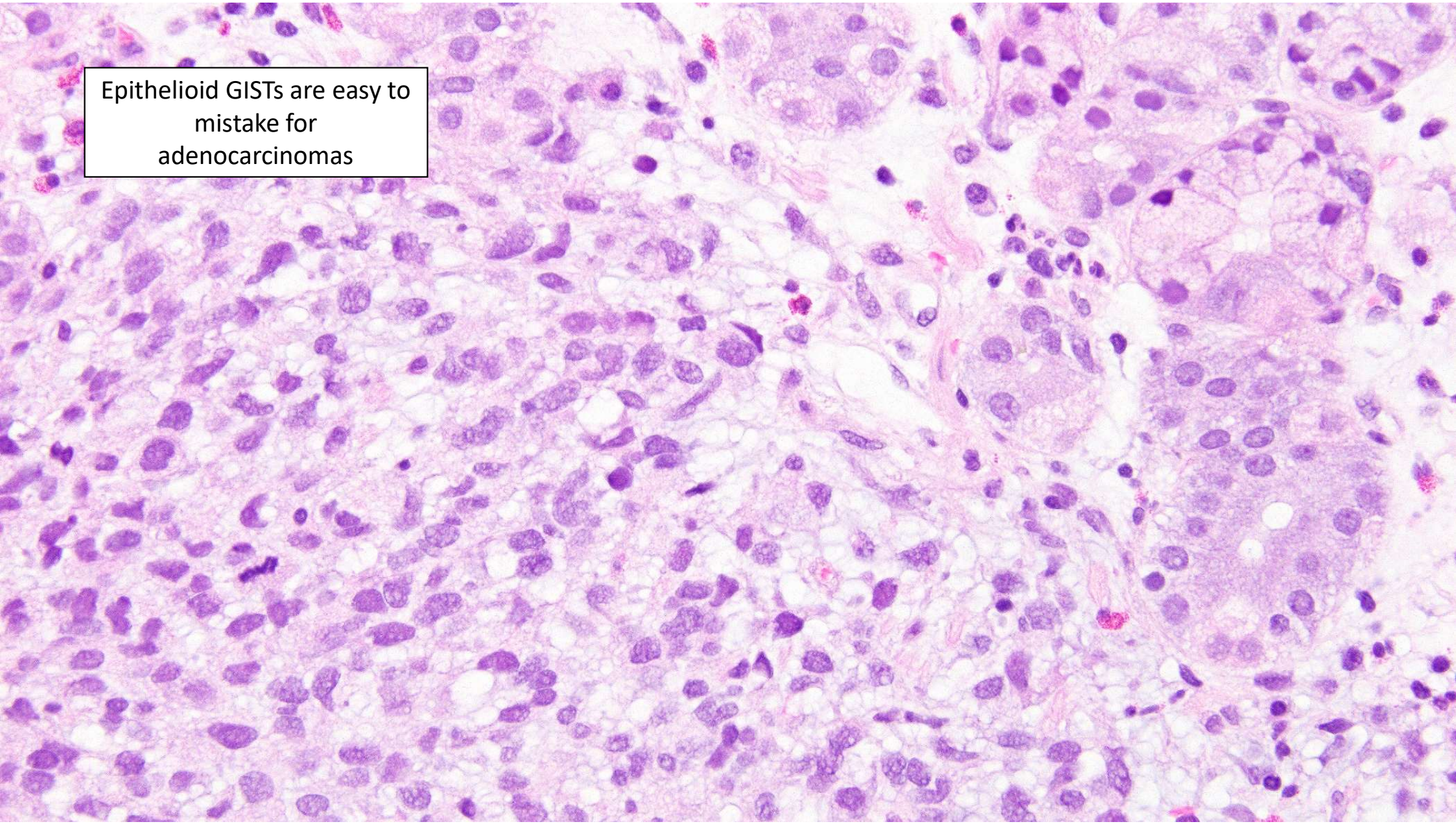
- 5-10% of all sarcomas
- 5,000/yr. in US
- 1% of GI malignancy
- M > F >50 yrs.
- Pain, bleeding, mass
- Incidental
- Metastasis



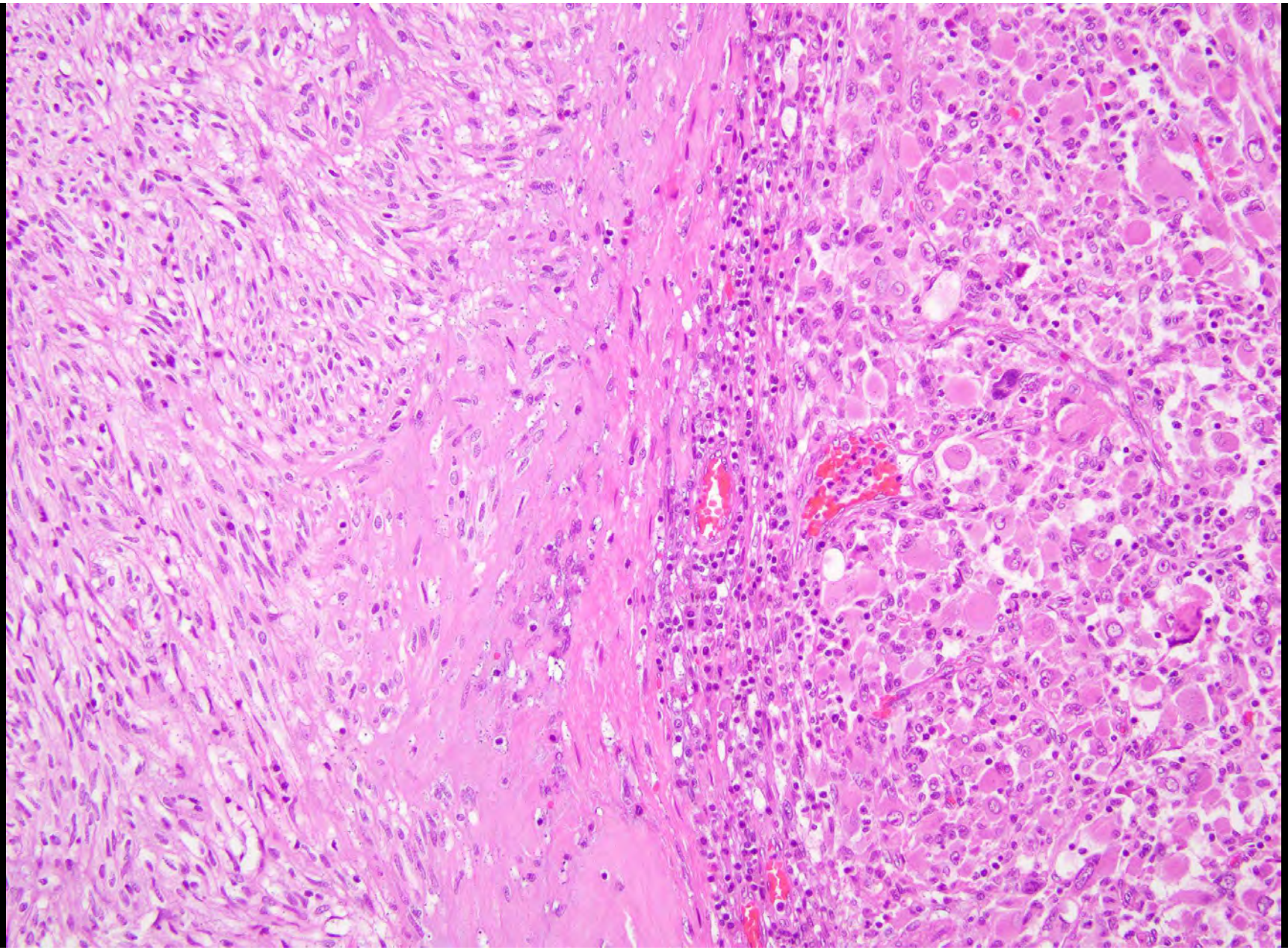







Epithelioid GISTs are easy to mistake for adenocarcinomas

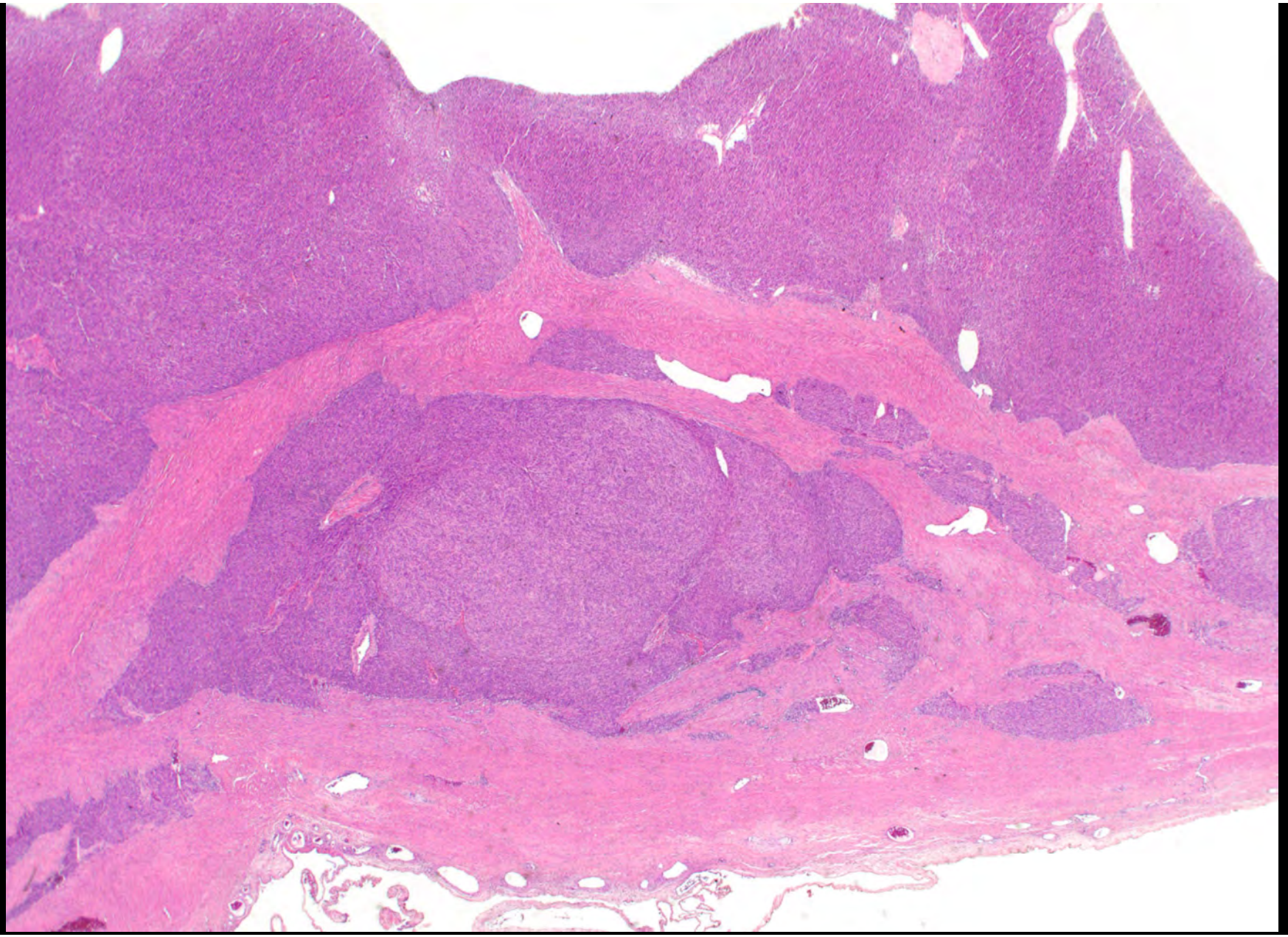
Dedifferentiated GIST

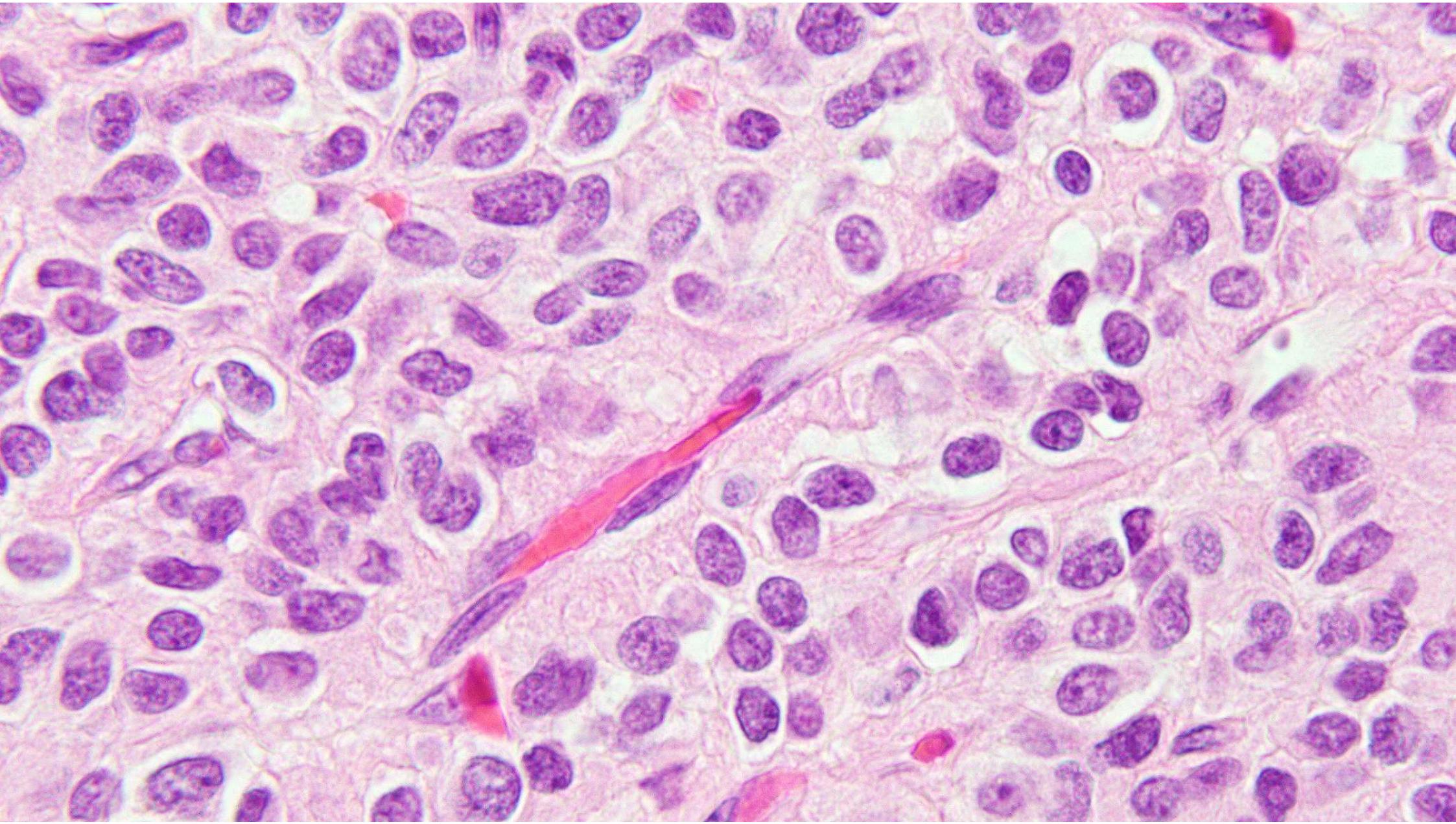


Family of *KIT* wild type GISTS – All Stain With KIT/DOG1 Immunostains

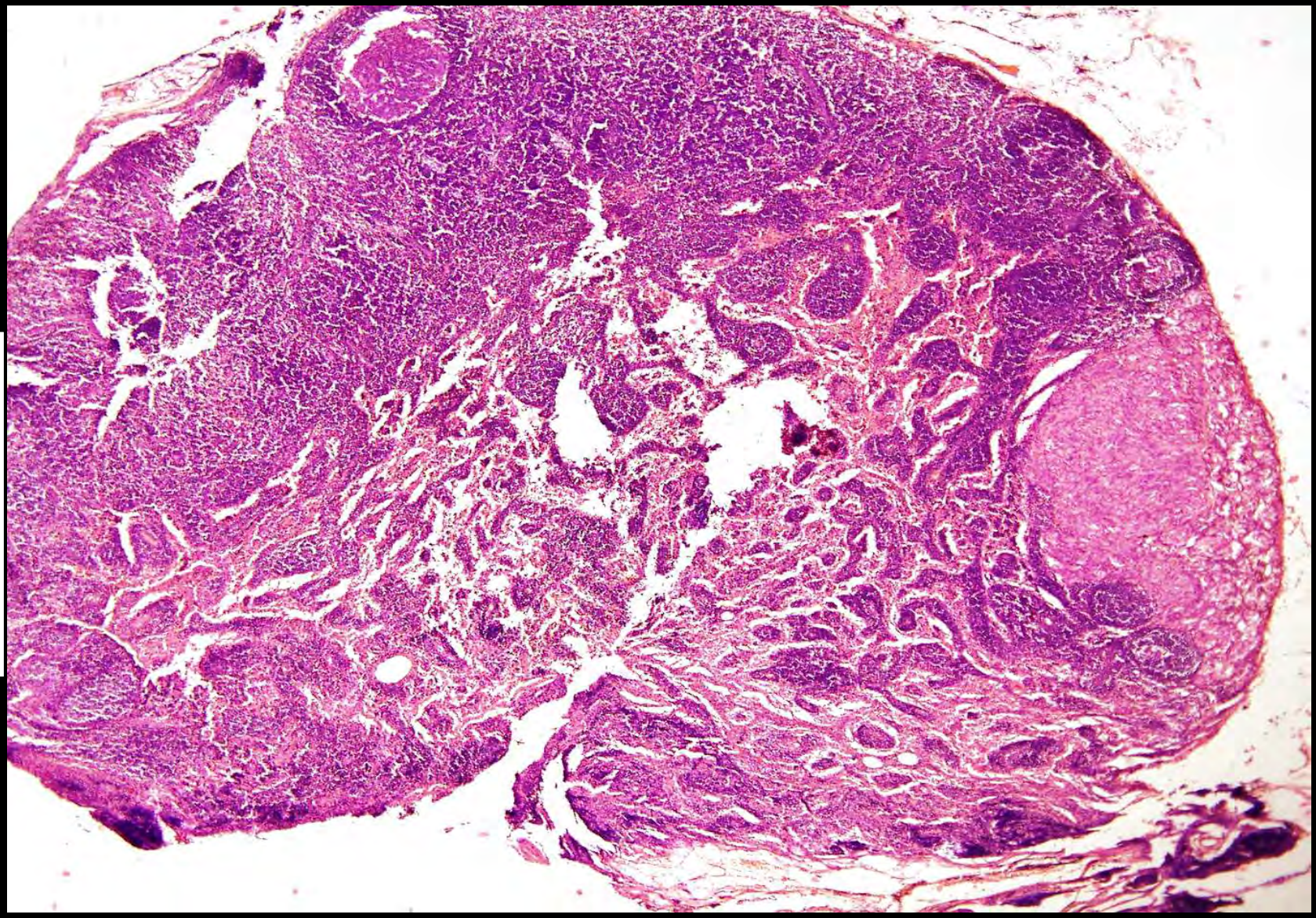
- NF1-associated
- Succinate dehydrogenase deficient ones:
  - About 7% of all GISTS (one study says 15% - referral bias)
  - Most pediatric cases
  - Gastric location
  - Often epithelioid with plexiform growth; LN mets; indolent course; no response to imatinib
  - Associated with Carney triad (GIST, paraganglioma, pulmonary chondroma – promotor methylation of *SDH* genes), Carney-Stratakis syndrome (GISTs and paraganglioma; affected families with germline mutations in either *SDHB, SDHC* or *SDHD*)

Succinate dehydrogenase deficient GIST
Plexiform pattern

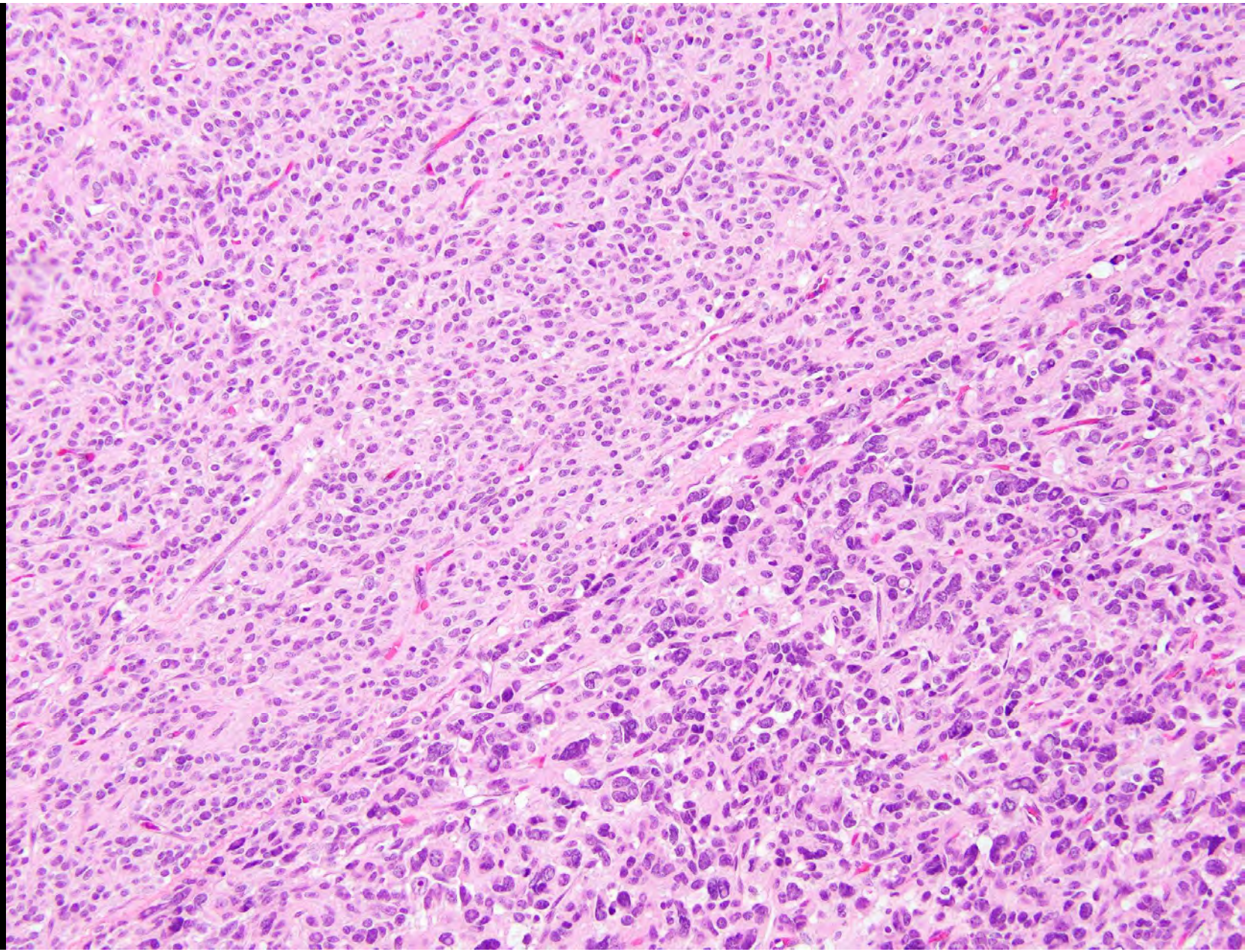


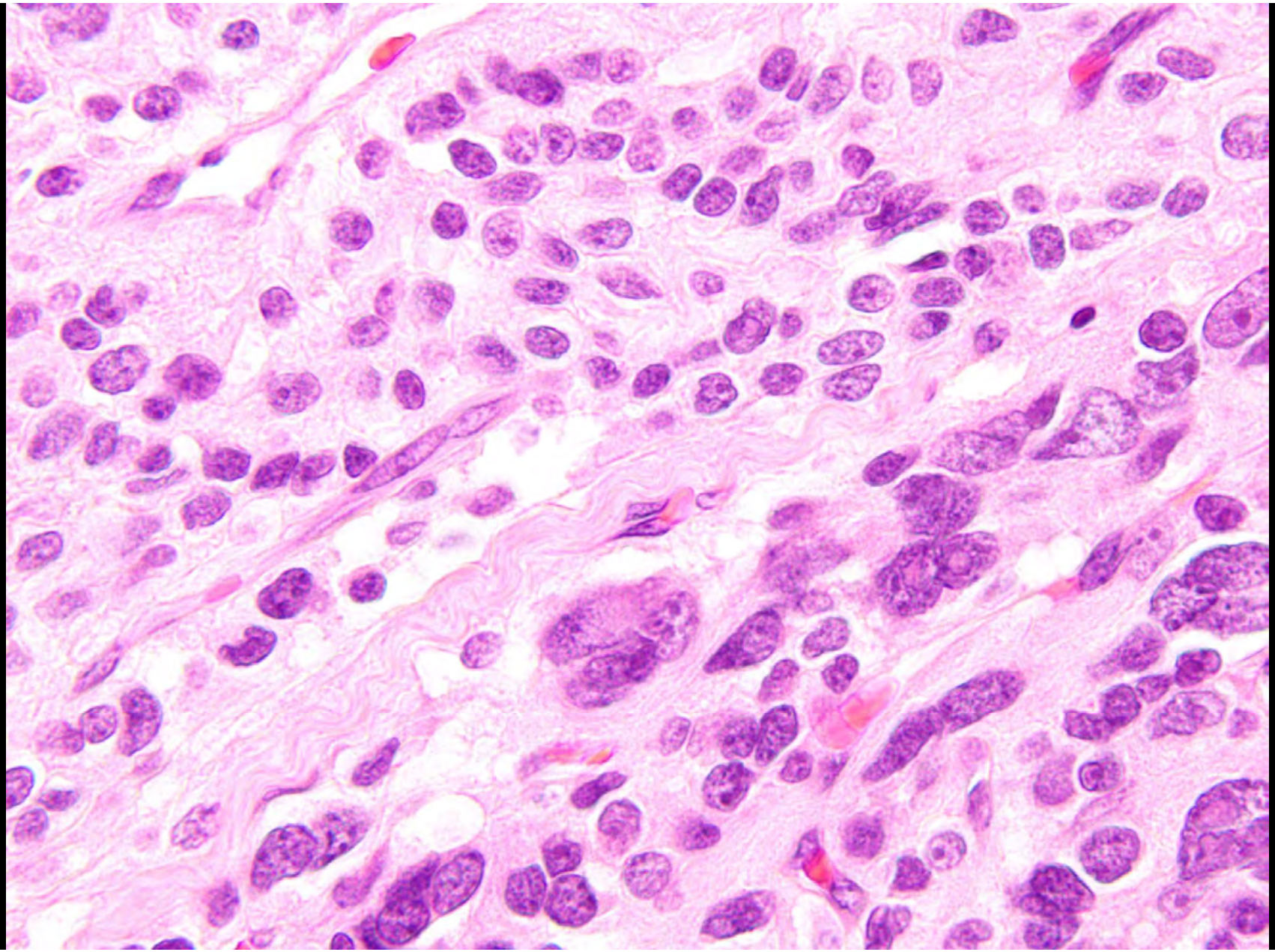


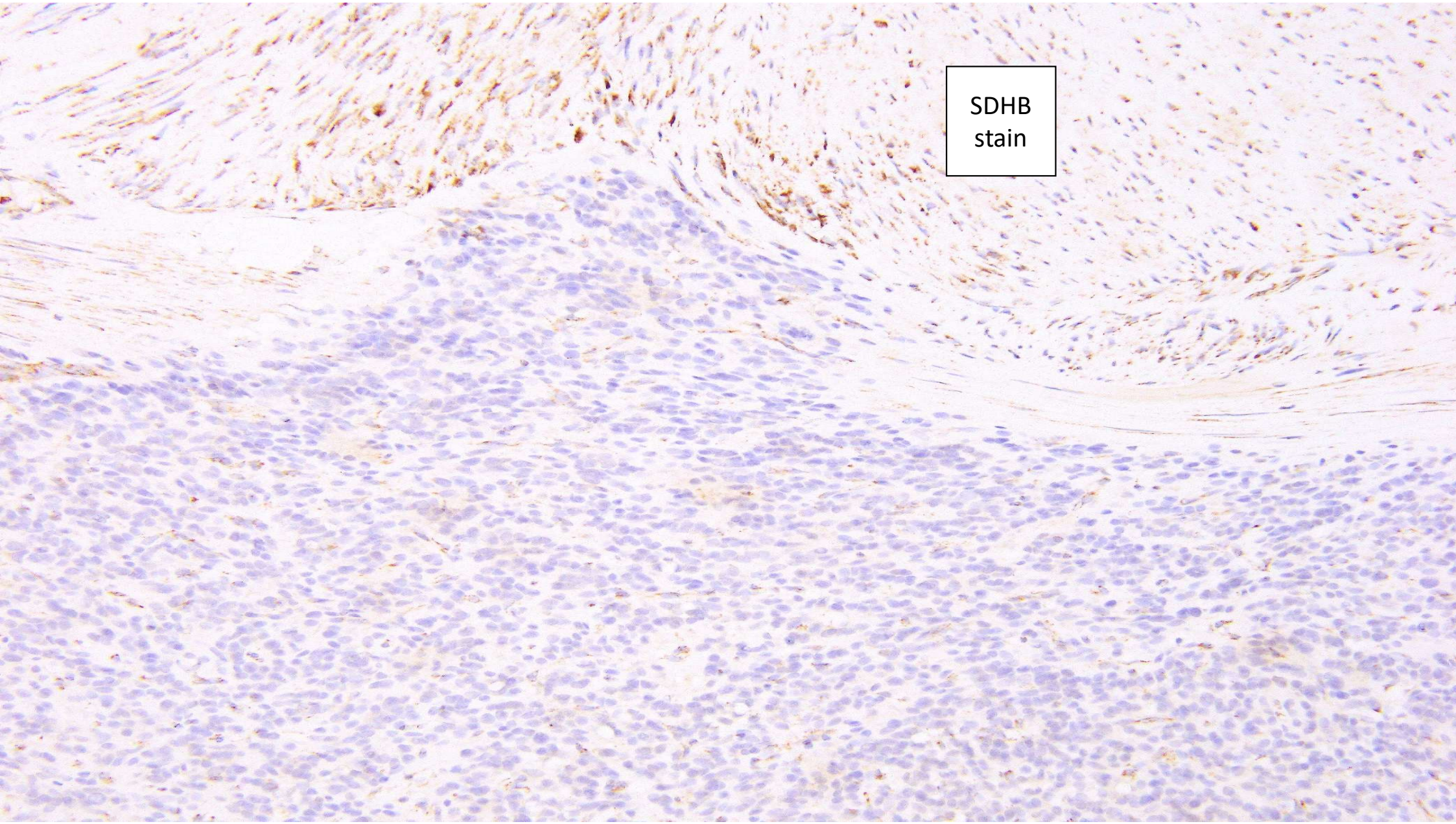
Succinate dehydrogenase deficient GIST – spread to lymph nodes but indolent behavior



Succinate dehydrogenase deficient GIST – some have bizarre nuclei or plasmacytoid features






SDHB
stain

Something submucosal

Inflammatory Fibroid Polyp (IFP)

- First described by J Vaněk
- 6 lesions, all in stomach (antrum/pylorus-5)

Vaněk J. Gastric submucosal granuloma with eosinophilic infiltration. *Am J Pathol* 1949;**25**;397-411.

IFP

- Present term coined in early 1950's

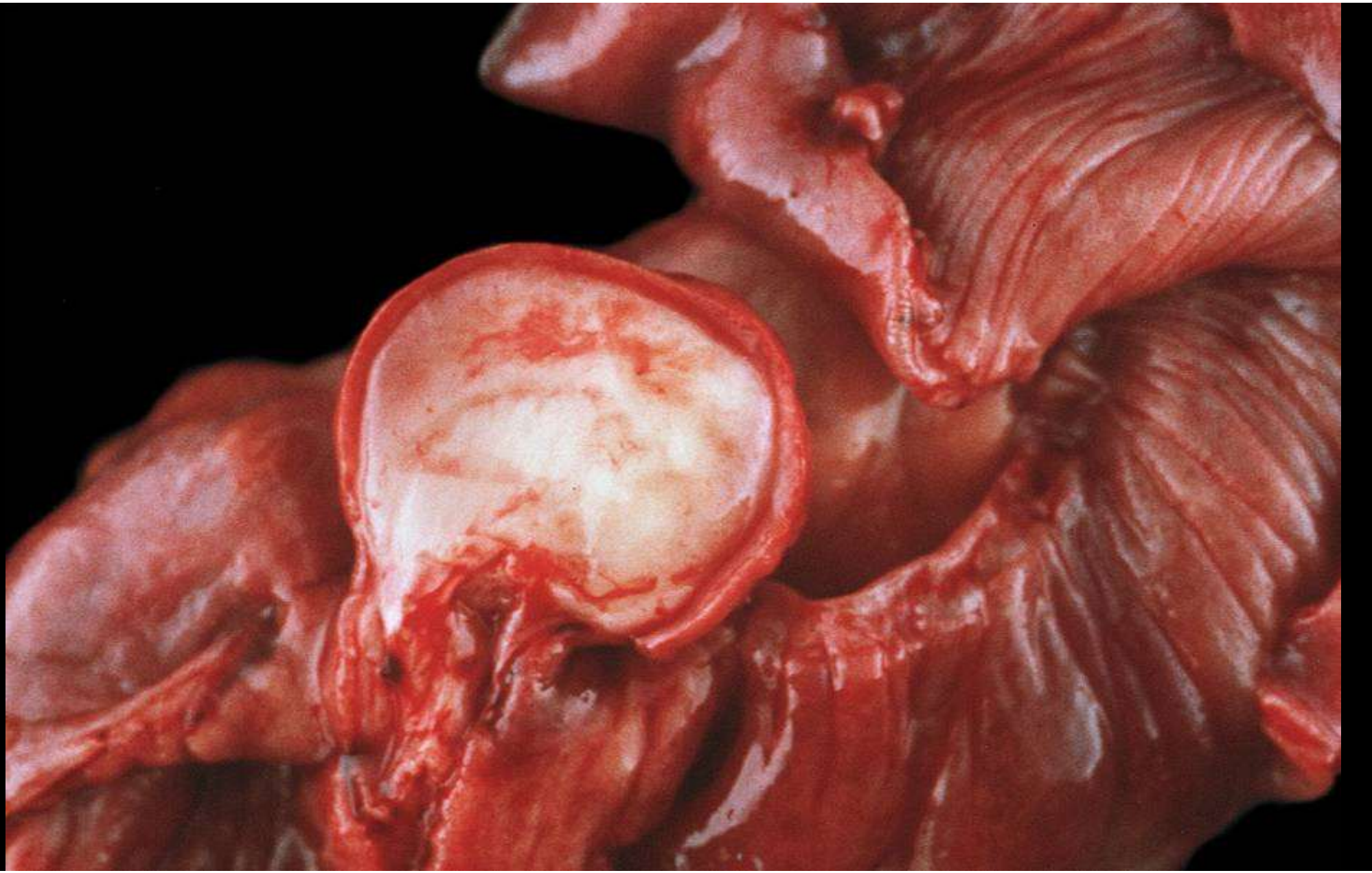
Helwig E, Ranier A. Inflammatory fibroid polyps of the stomach. *Surg Gynecol Obstets* 1953;**96**;355-67.

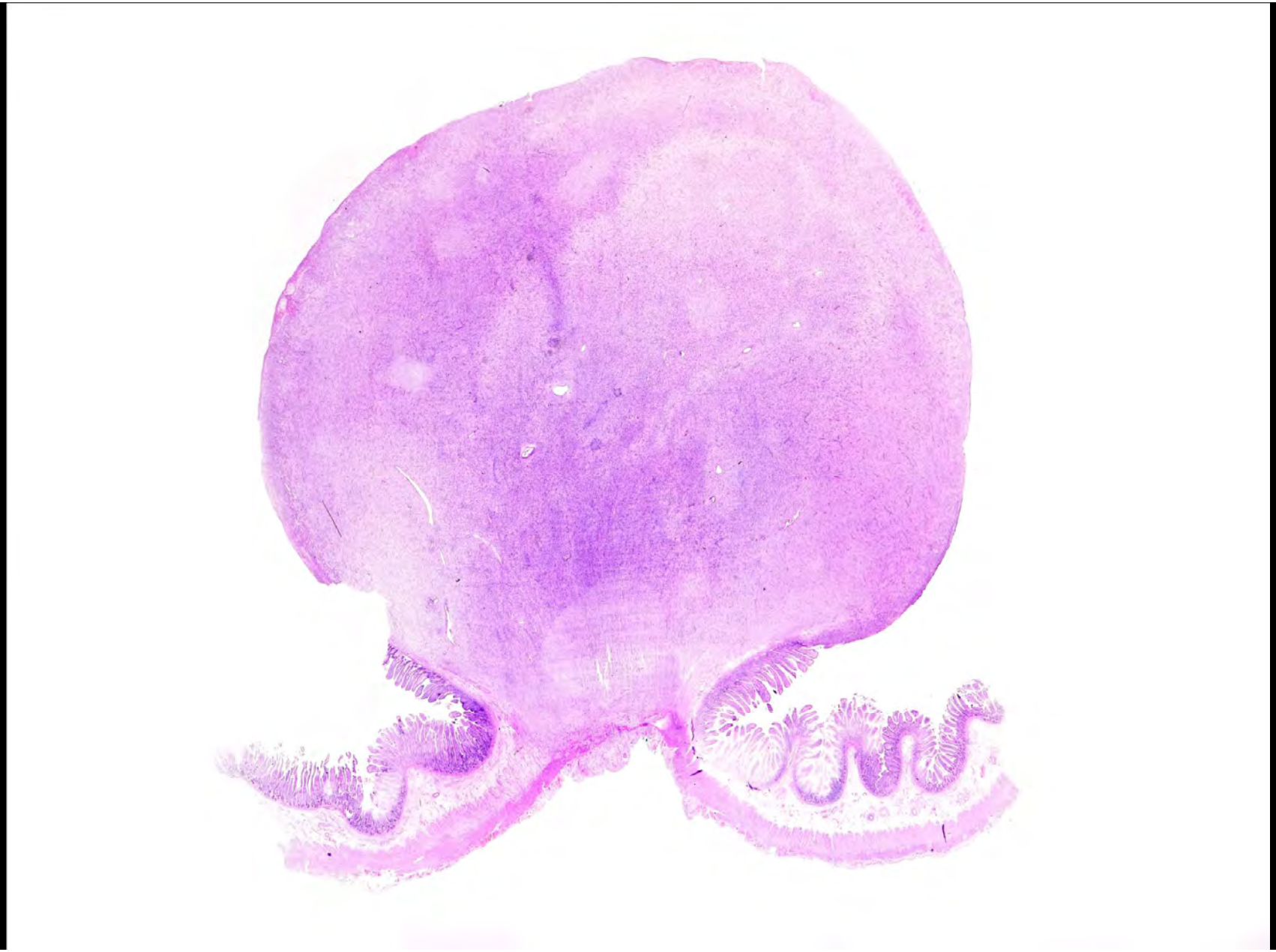
IFP Location

- Vast majority in stomach
- @1% of all gastric polyps (once fundic gland polyps removed from the mix)
- Nearly always in adults (60-80yrs)

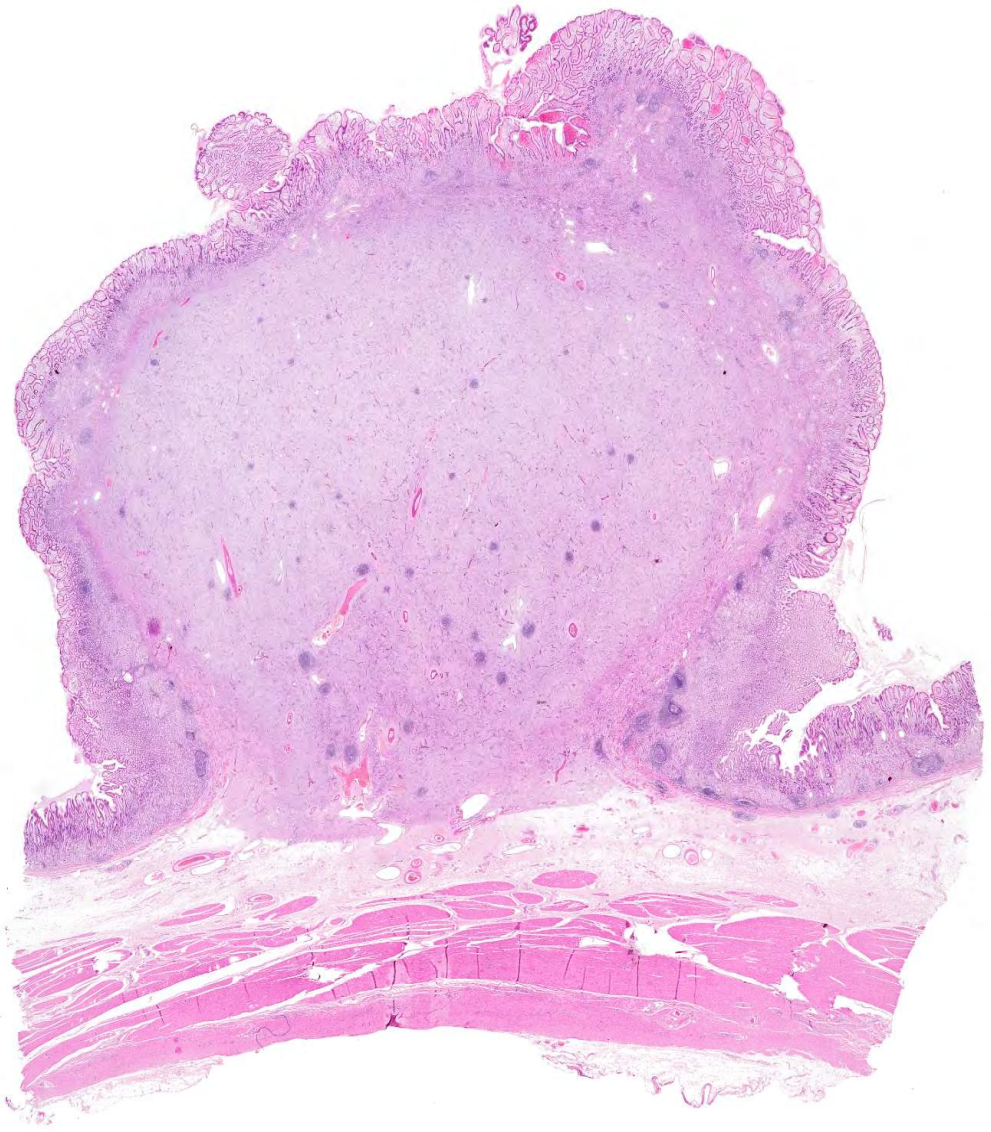
IFP- Endoscopic Appearance

- Smooth submucosal lesions
- Surface ulceration/erosion in about 1/3 of cases
- Presentation is site specific

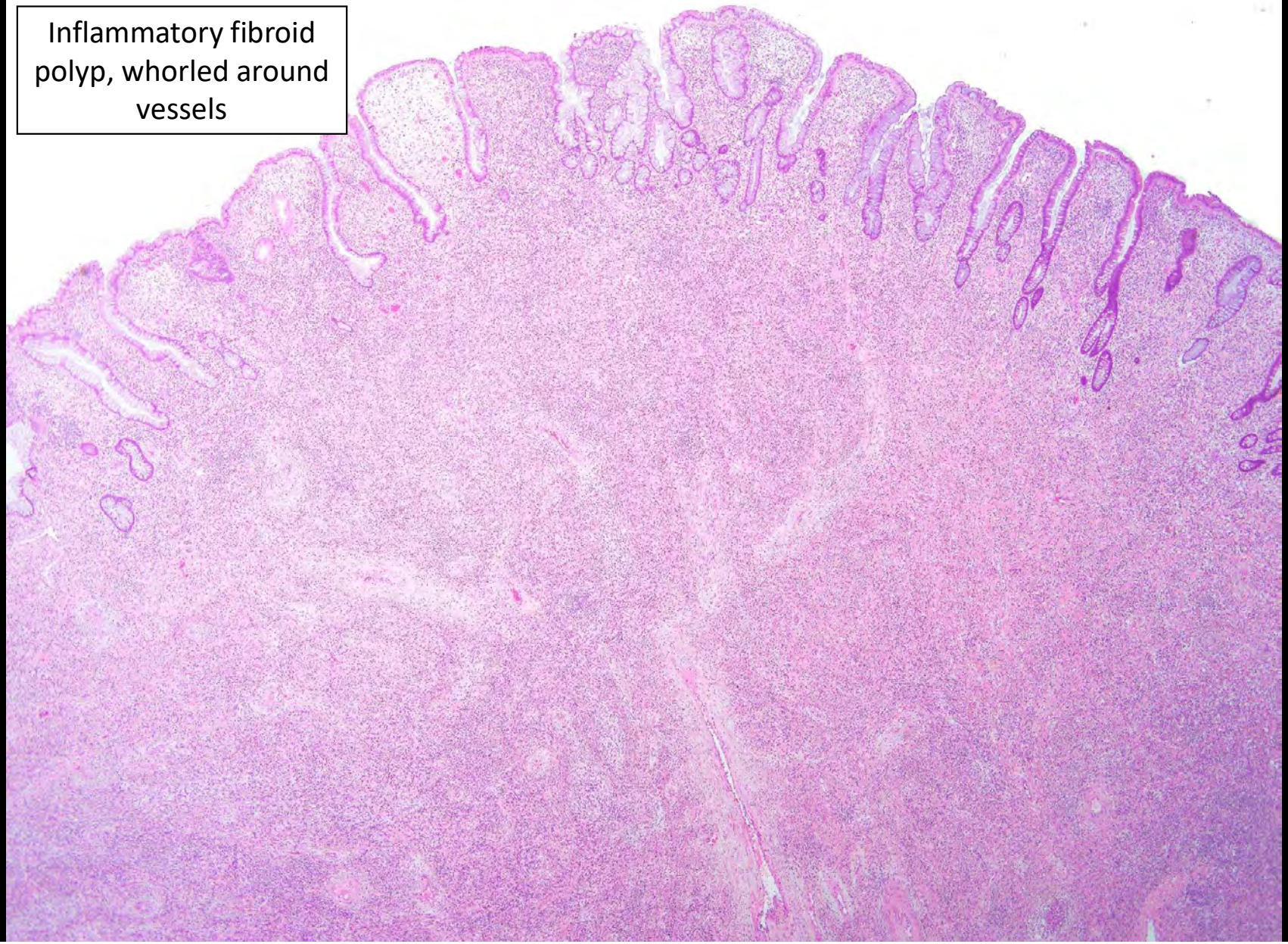


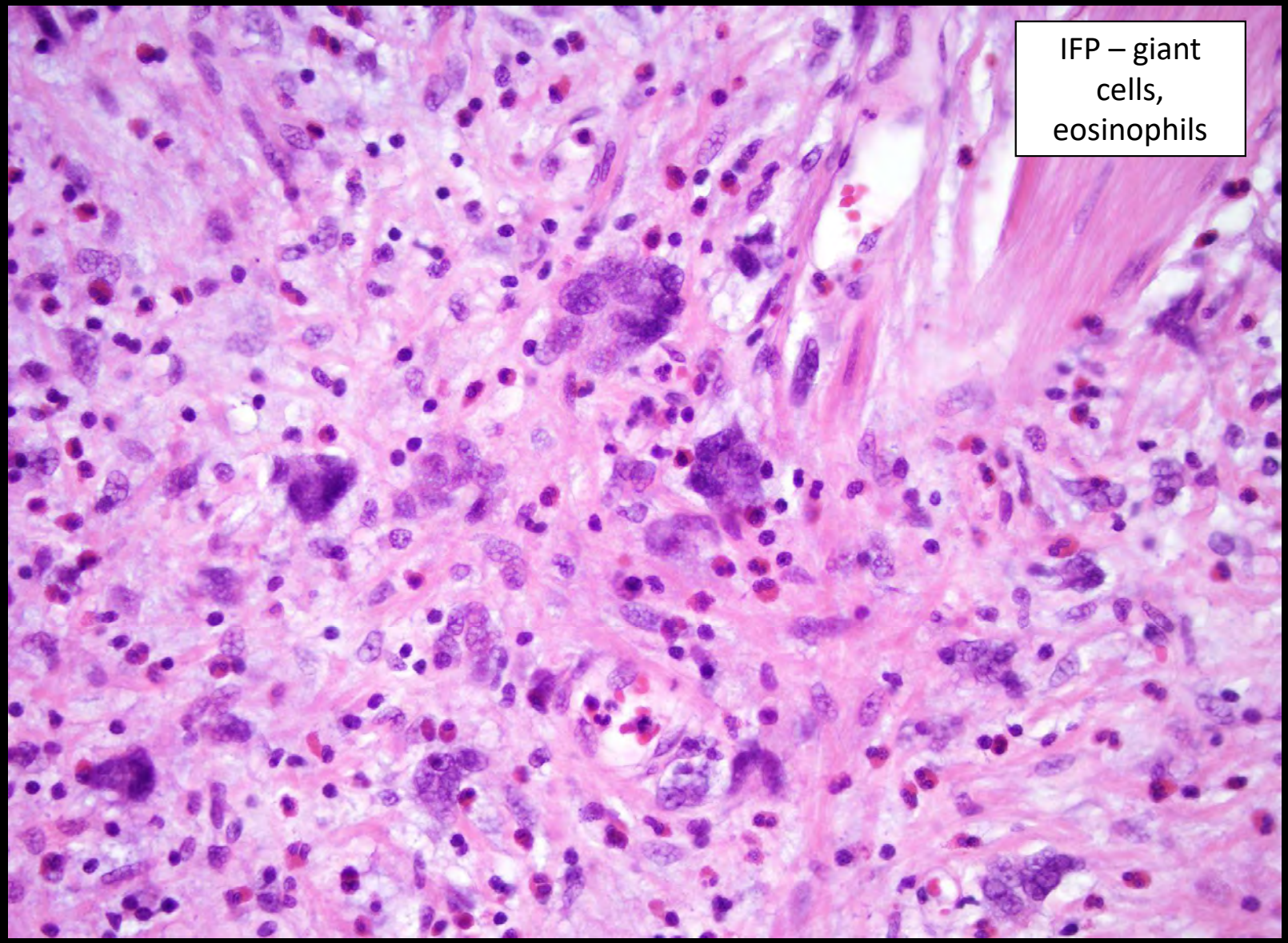


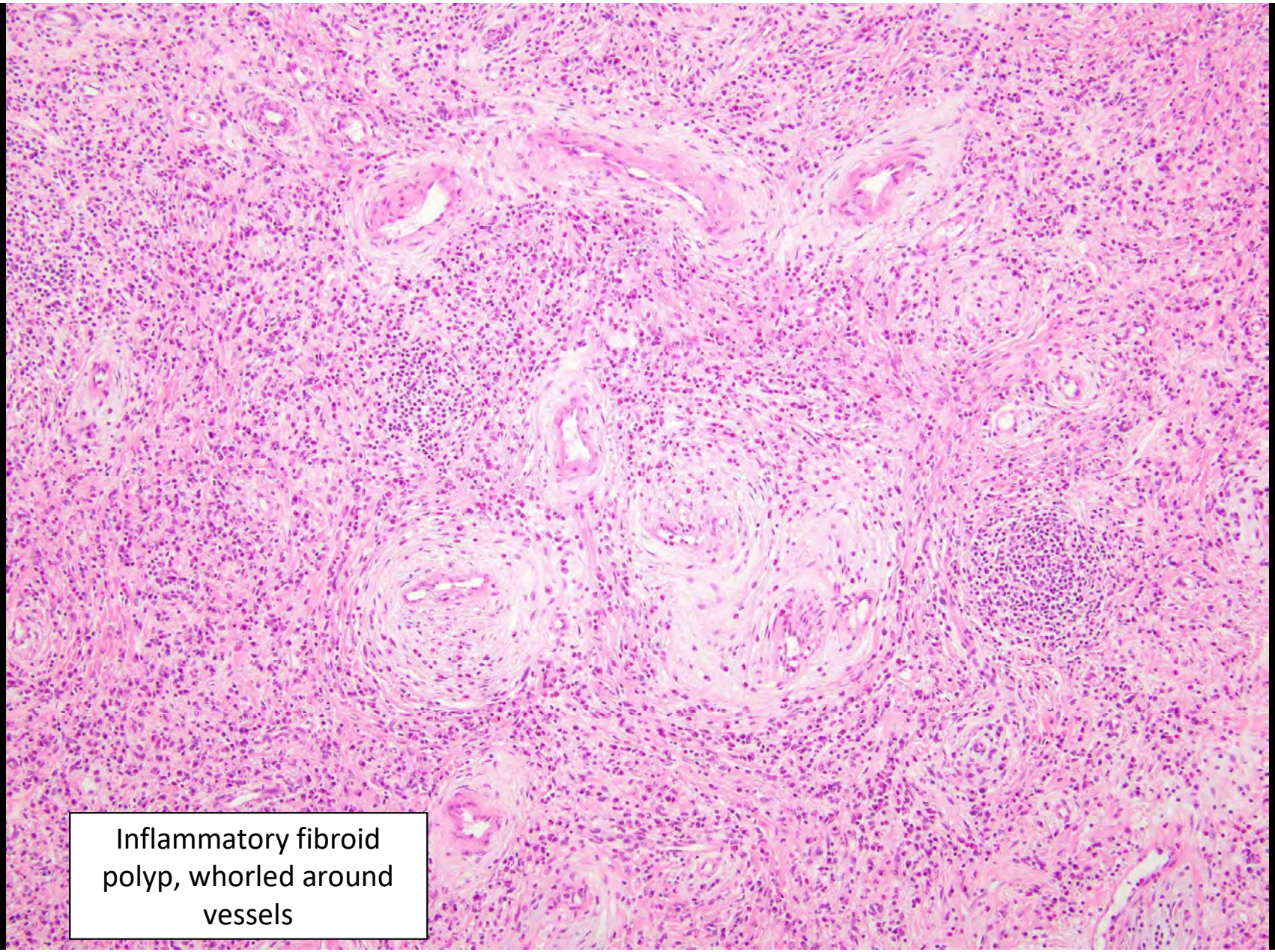
Gastric inflammatory fibroid polyp – note the characteristic submucosal location



Inflammatory fibroid polyp, whorled around vessels




IFP – giant cells, eosinophils

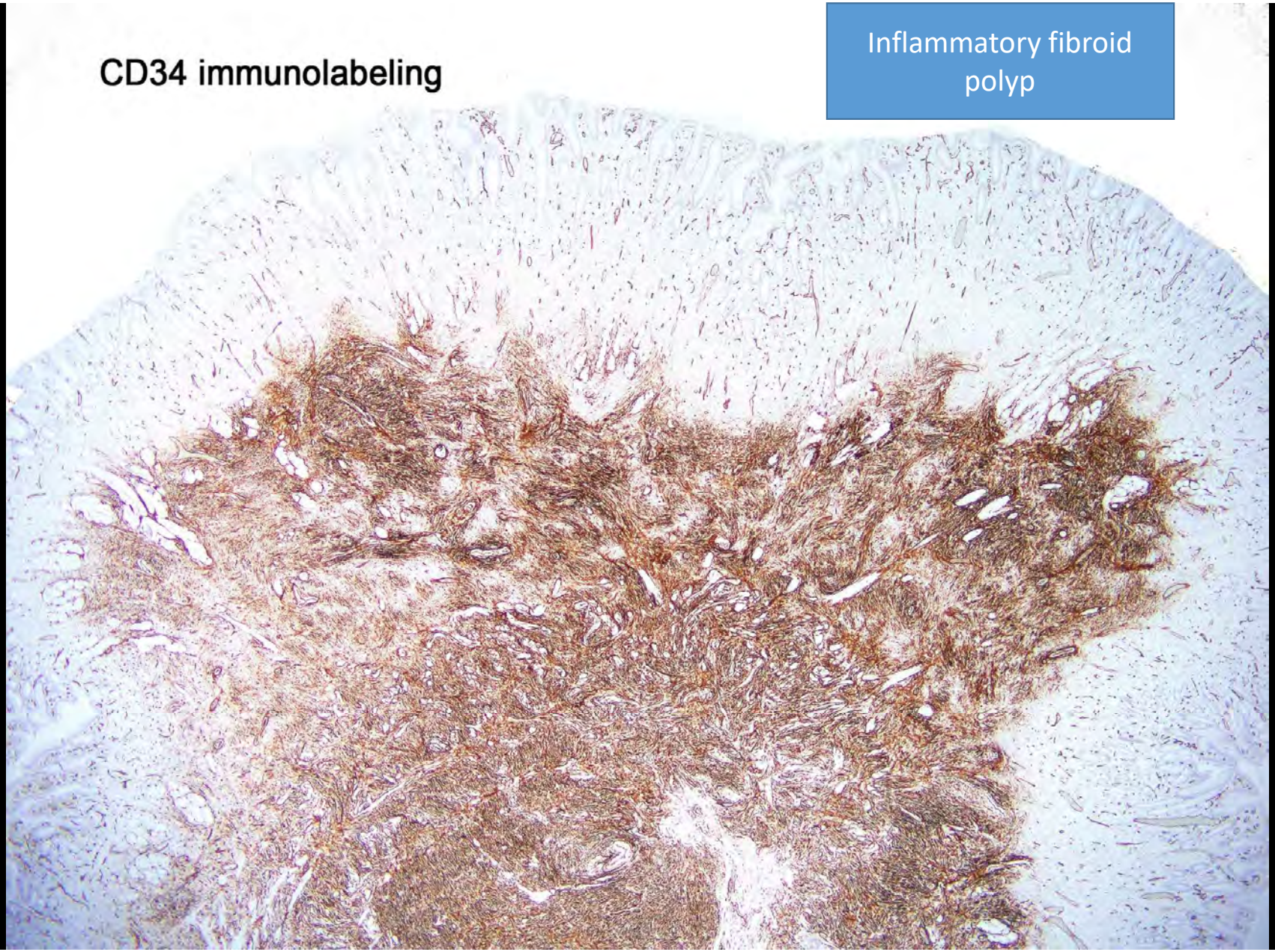

Inflammatory fibroid polyp, whorled around vessels

IFP- Pathogenesis

- Believed reactive in past – now known to have *PDGFRA* mutations (just like some GISTs – but ALWAYS benign)

IFP- Immunohistochemistry

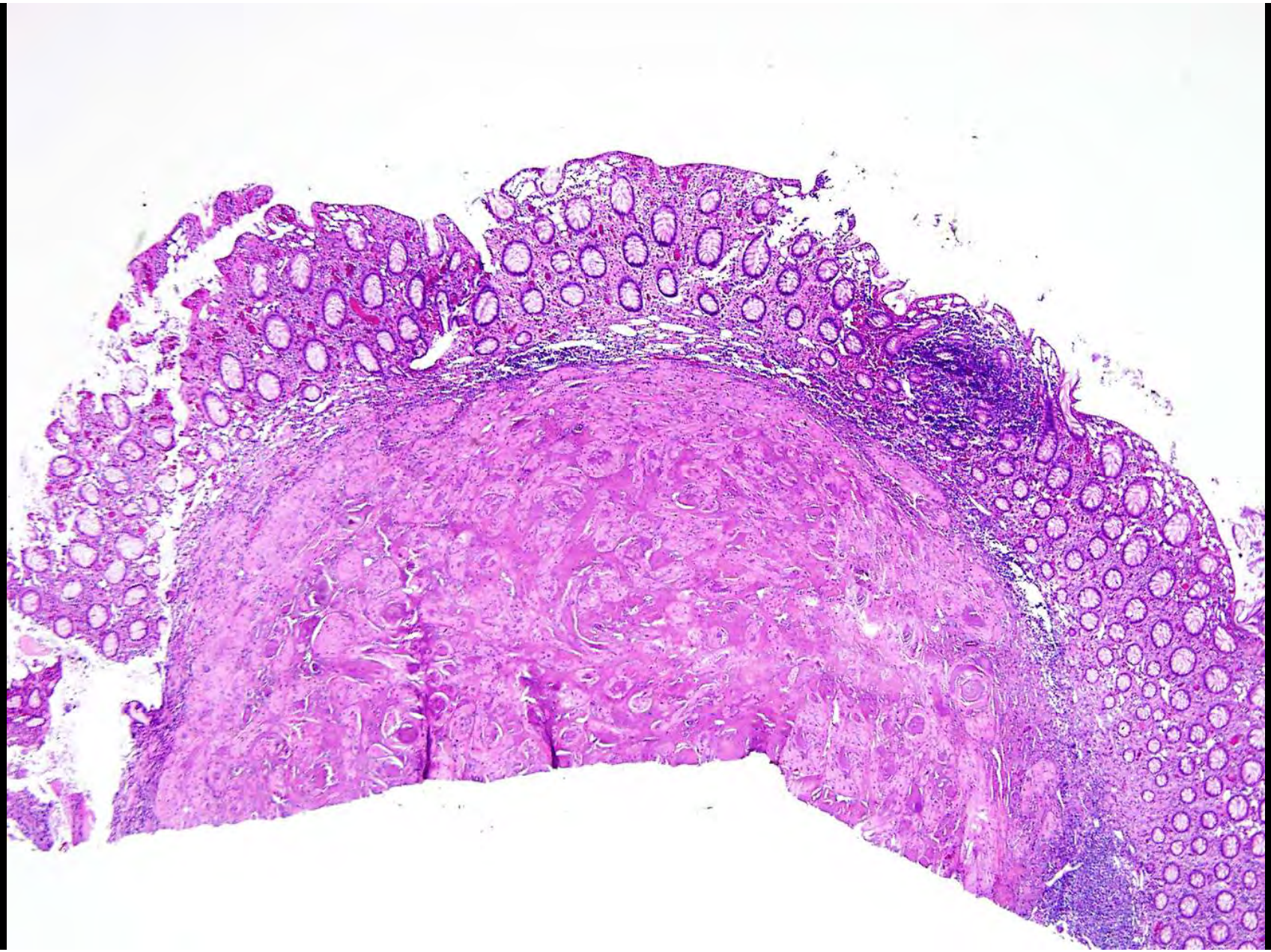
- Fibroblastic/myofibroblastic
- Variable actin, negative S100
- Consistent CD34 (less striking in large tumors)
- NO CD117/KIT or DOG1

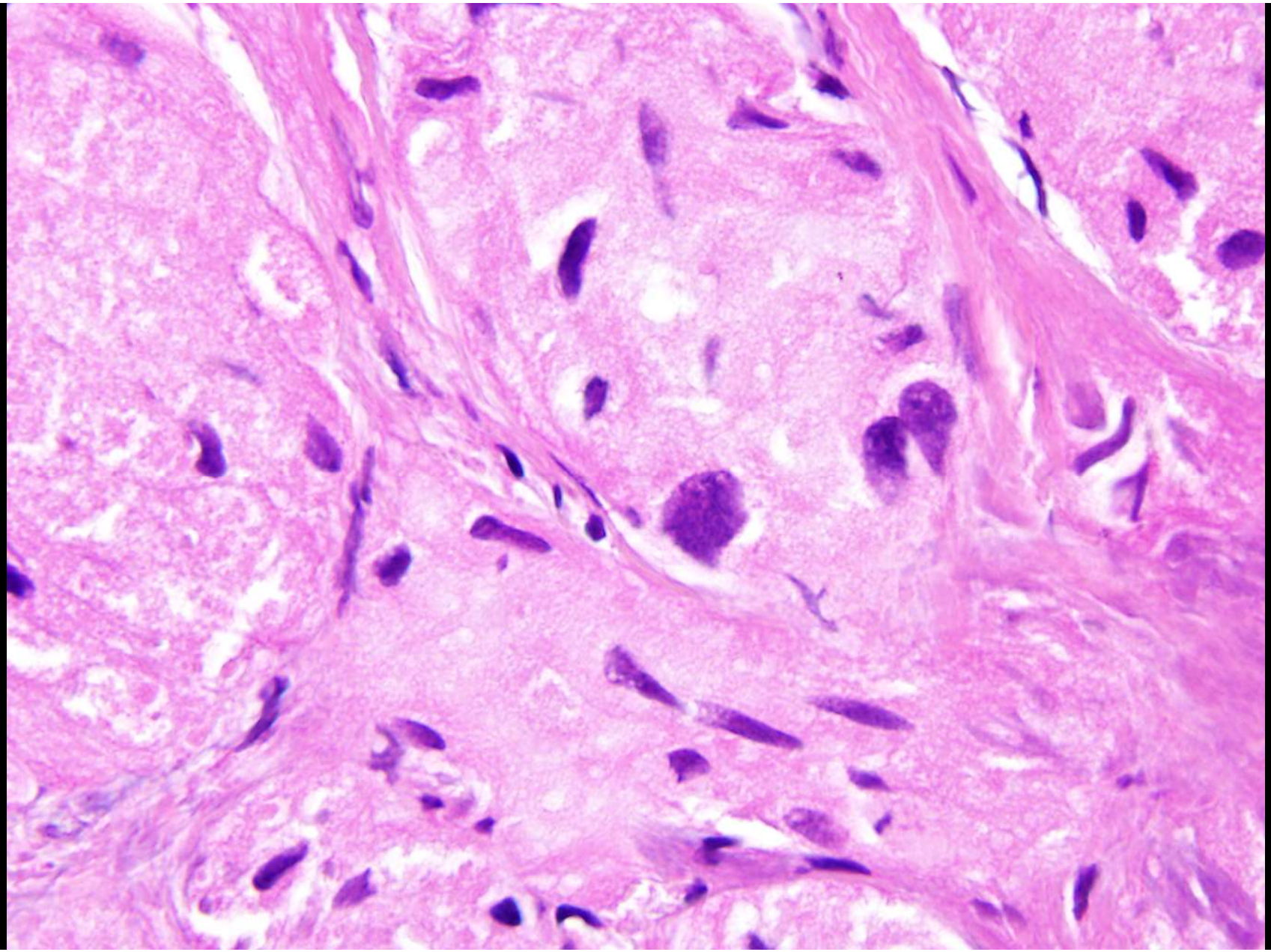

CD34 immunolabeling
Inflammatory fibroid polyp

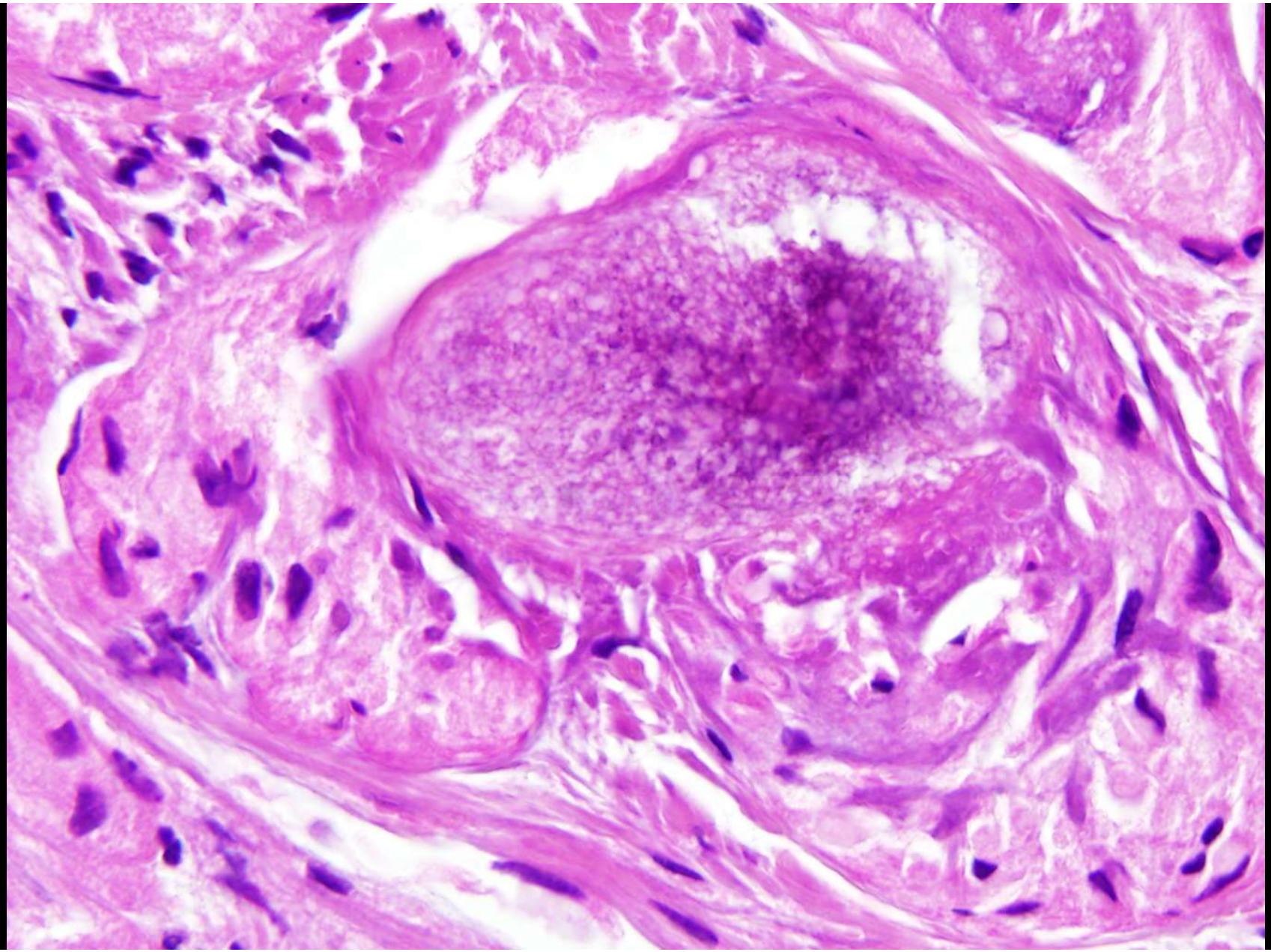
Some mucosal nerve sheath tumors

Colon Granular Cell Tumor

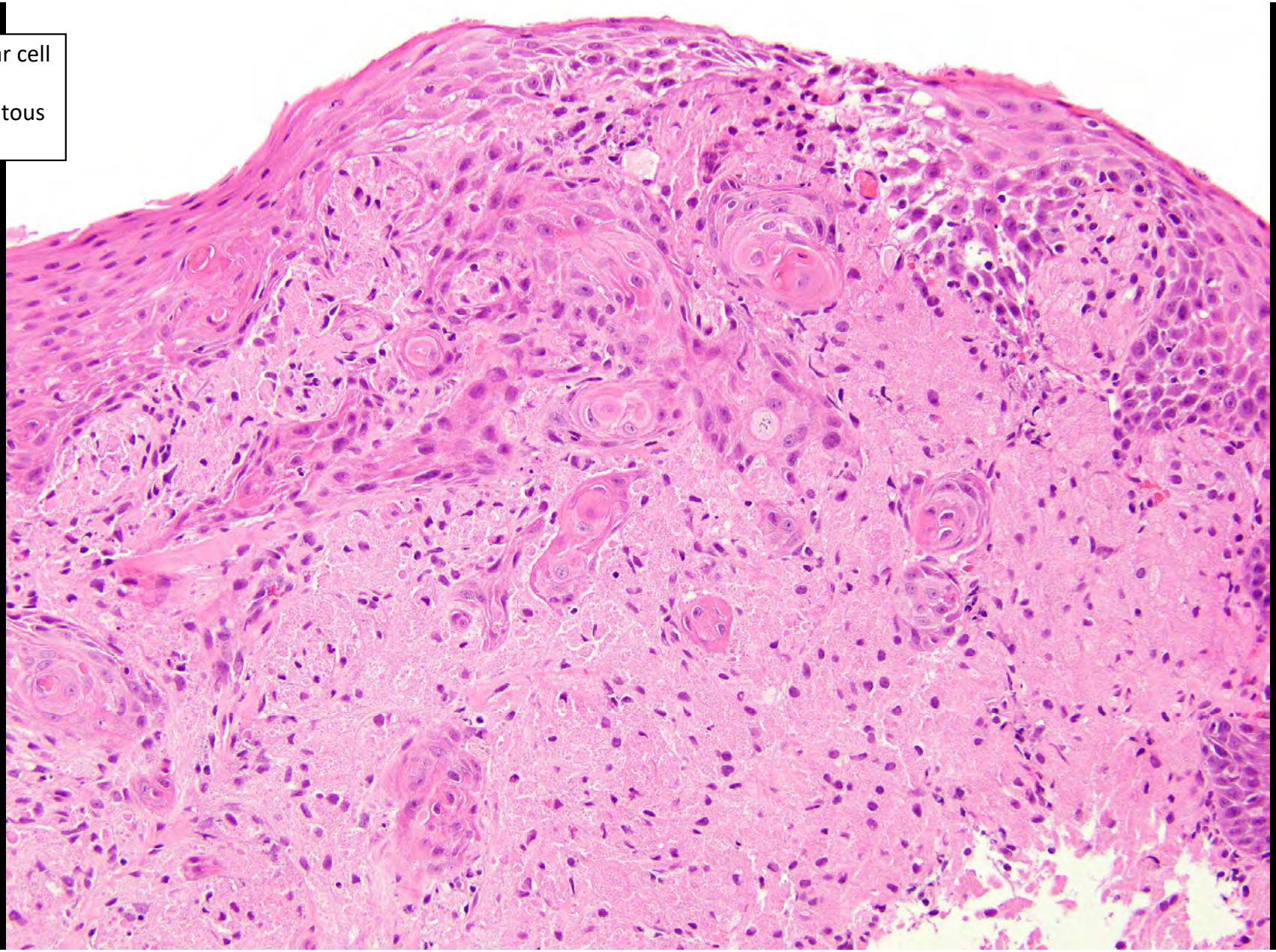
- Most GI tract granular cell tumors are in esophagus (or anus)
- Rare colon examples
- Tend to be on right side and often have large nuclei, mineralization, can recur as difficult to totally remove
- No CONVINCING malignant examples reported to date in colon – rare in esophagus

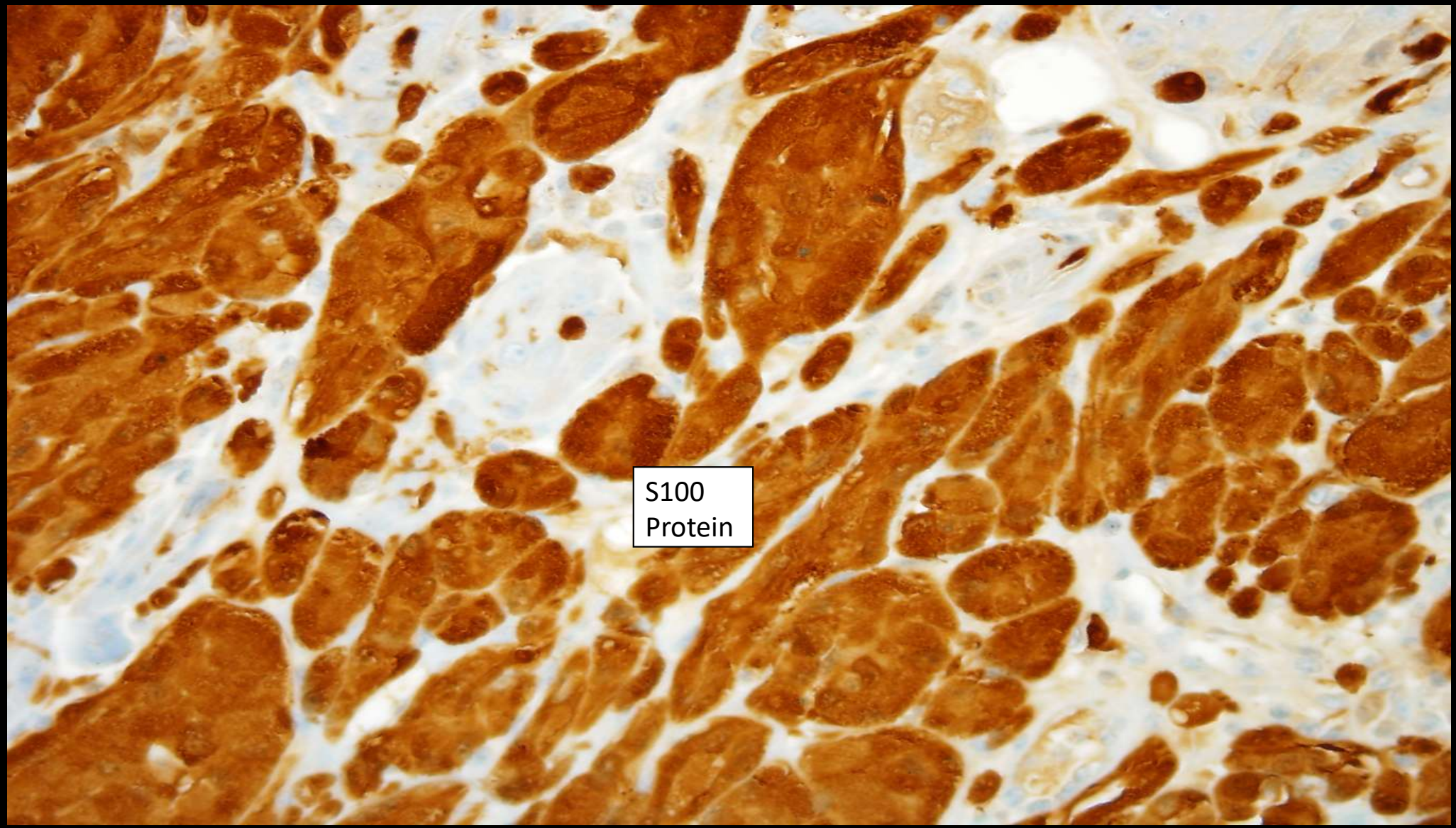






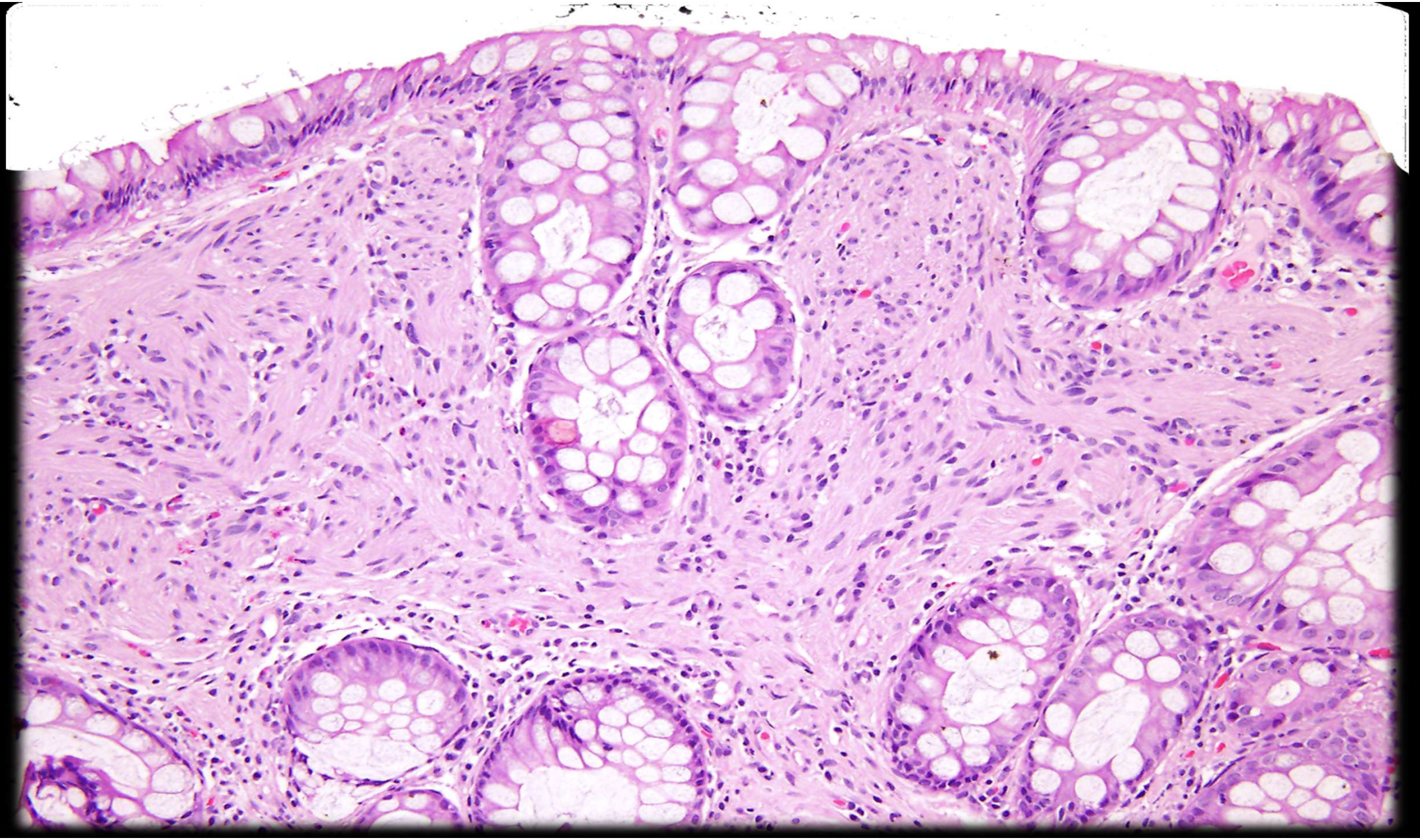
Esophageal granular cell tumor with striking pseudoepitheliomatous hyperplasia

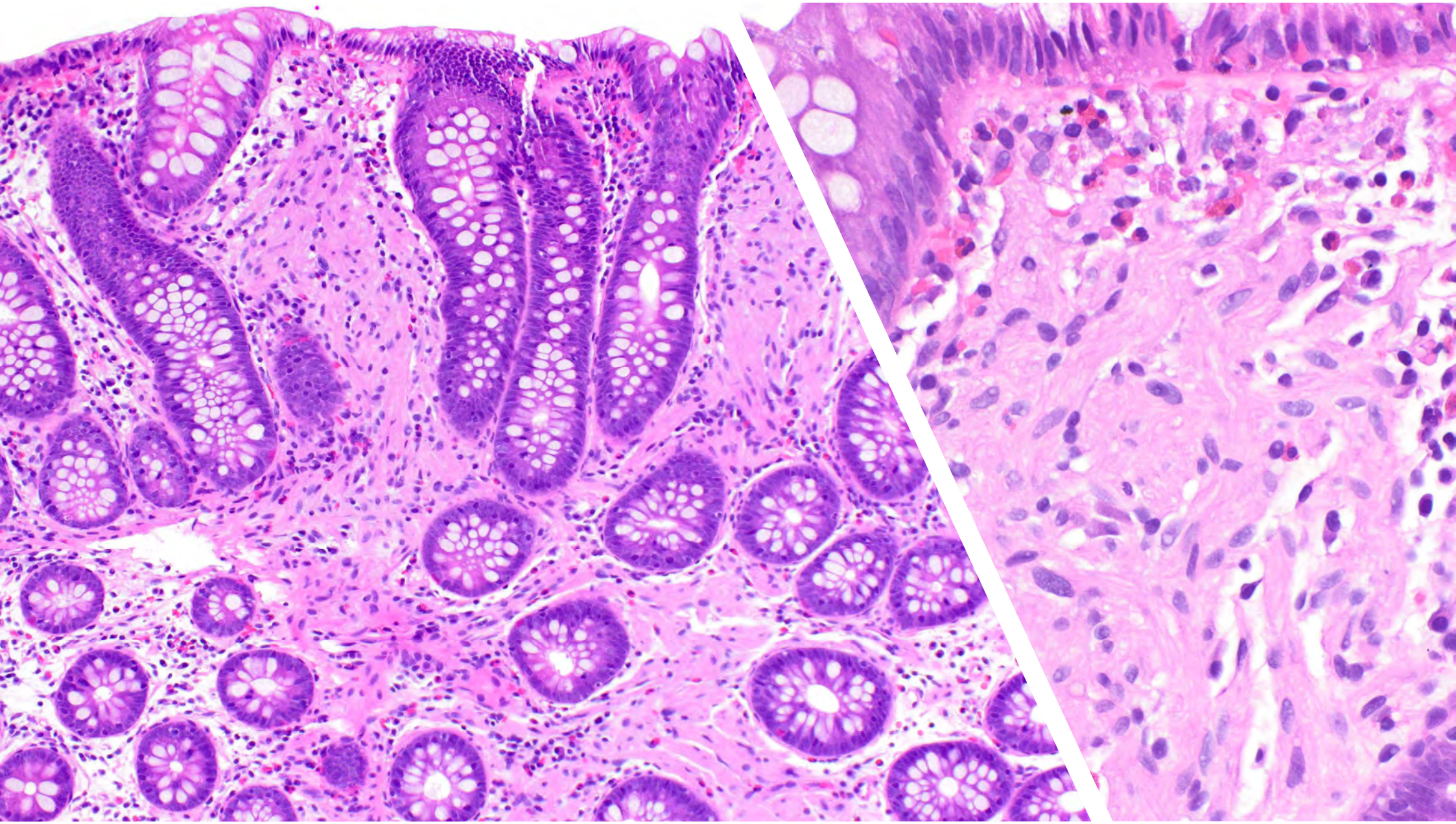


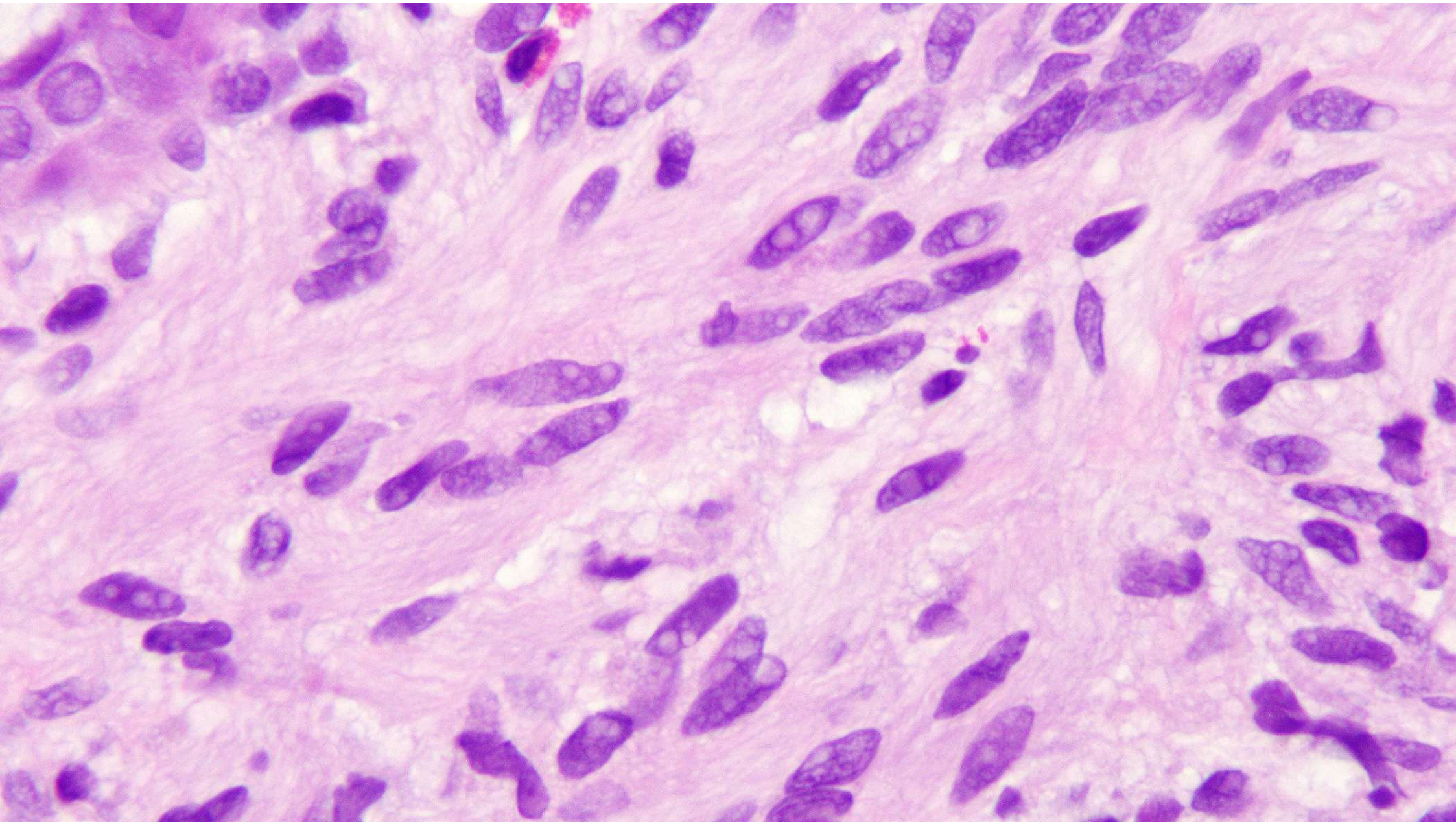

S100
Protein

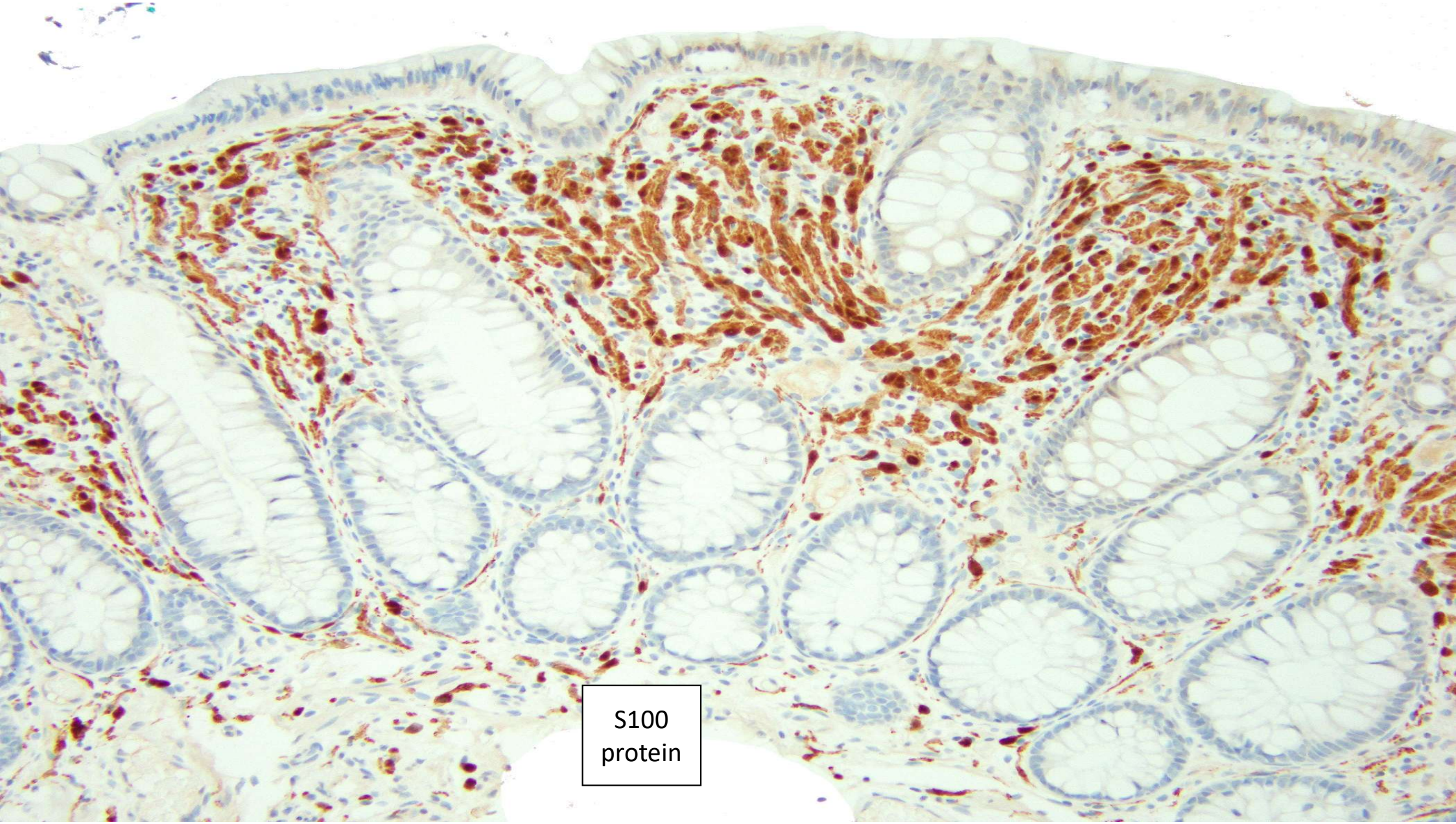
“Schwann Cell Hamartoma”

Gibson JA, Hornick JL. Mucosal Schwann cell "hamartoma": clinicopathologic study of 26 neural colorectal polyps distinct from neurofibromas and mucosal neuromas. Am J Surg Pathol. 2009 May;33(5):781-7.








S100
protein

Cowden/PTEN Hamartoma Syndrome

World Health Organization criteria for Cowden syndrome. One or more pathognomonic criteria or two or more major or minor criteria.

Pathognomonic criteria

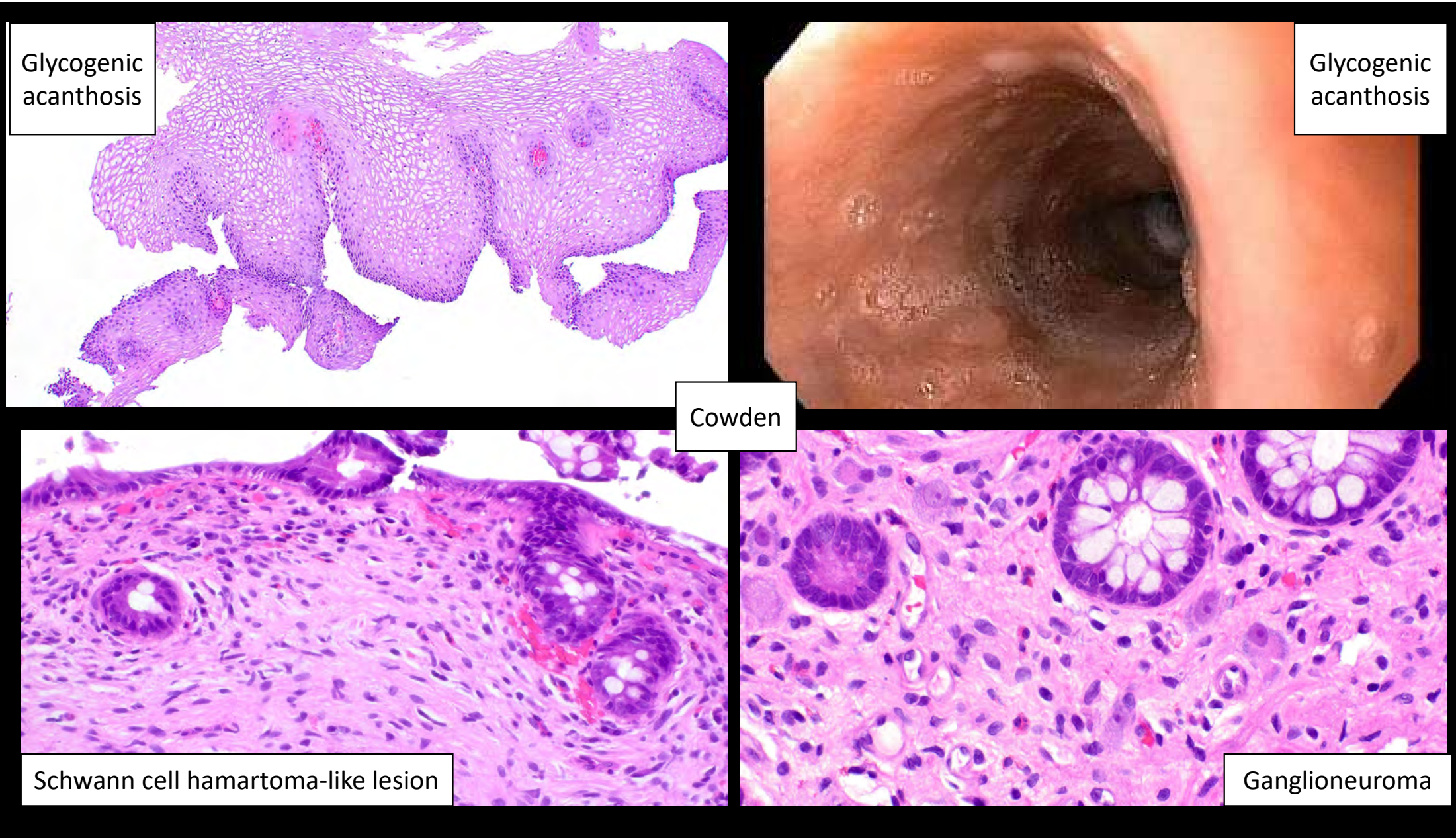
Adult L'hermitte-Duclos disease (cerebellar tumors)
Mucocutaneous lesions (facial trichilemmomas), acral keratoses, papillomatous papules)
Mucosal lesions
Autism spectrum disorder

Major criteria

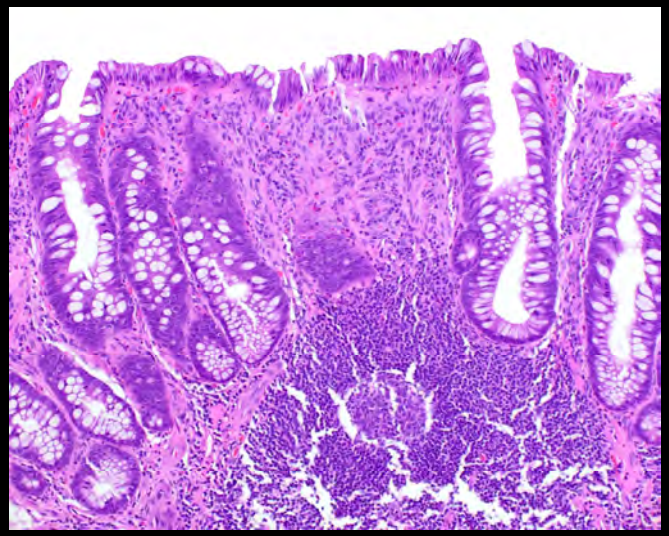
Breast cancer
Non-medullary thyroid cancer
Megalocephaly
Endometrial carcinoma
Mucocutaneous lesions (trichilemmoma- at least one biopsy proven, multiple palmoplantar keratoses, multifocal cutaneous facial papules, macular pigmentation of glans penis
Multiple gastrointestinal hamartomas or ganglioneuromas

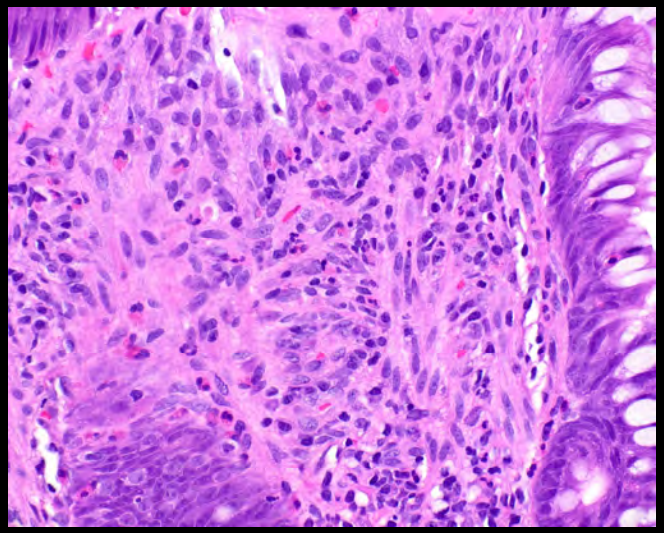
Minor criteria

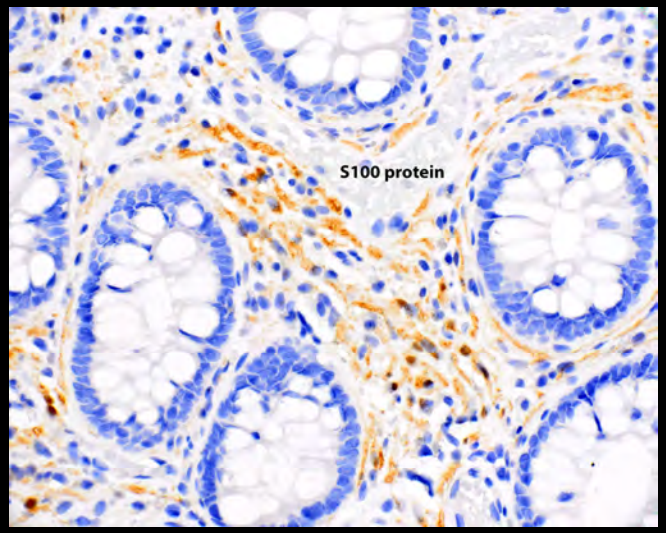
Other thyroid lesions (follicular adenoma, multinodular goiter)
Single gastrointestinal hamartoma or ganglioneuroma
Fibrocystic breast disease
Lipomas
Fibromas
Genitourinary tumors – especially renal cell carcinoma
Genitourinary malformation
Uterine leiomyomas
Autism spectrum disorder


Glycogenic acanthosis
Glycogenic acanthosis
Cowden
Schwann cell hamartoma-like lesion
Ganglioneuroma

Cowden-Associated Neural Lesion

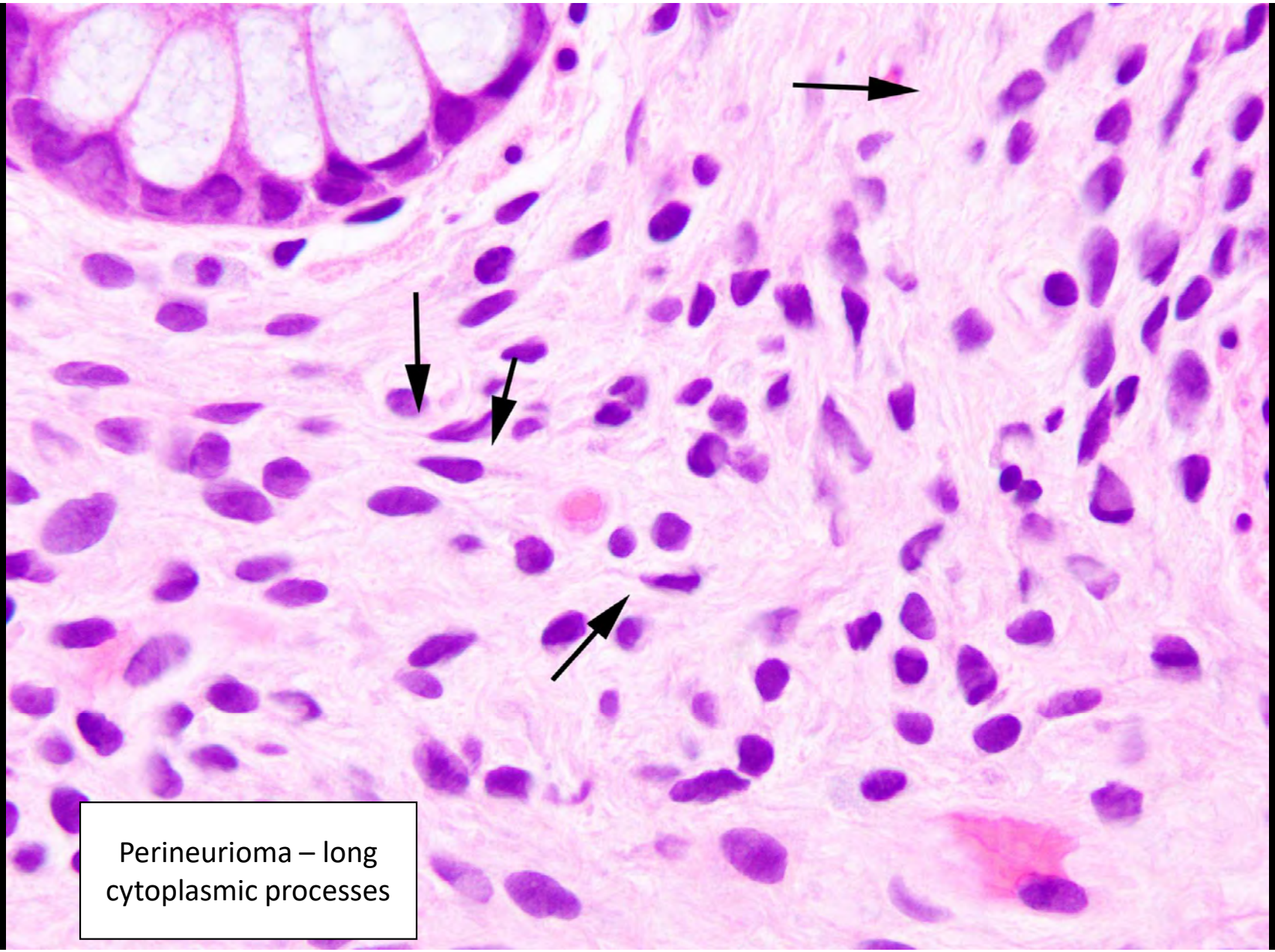


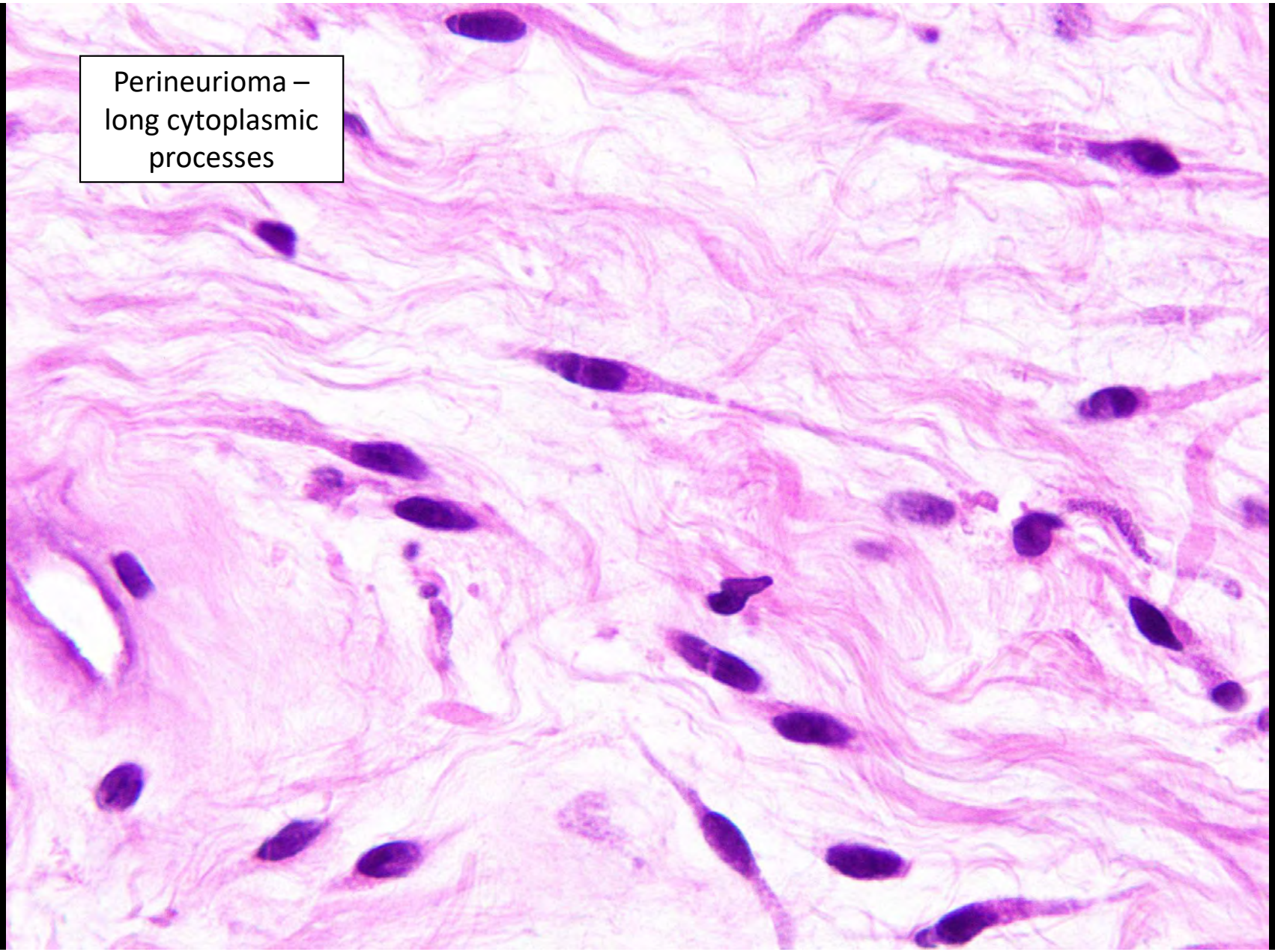


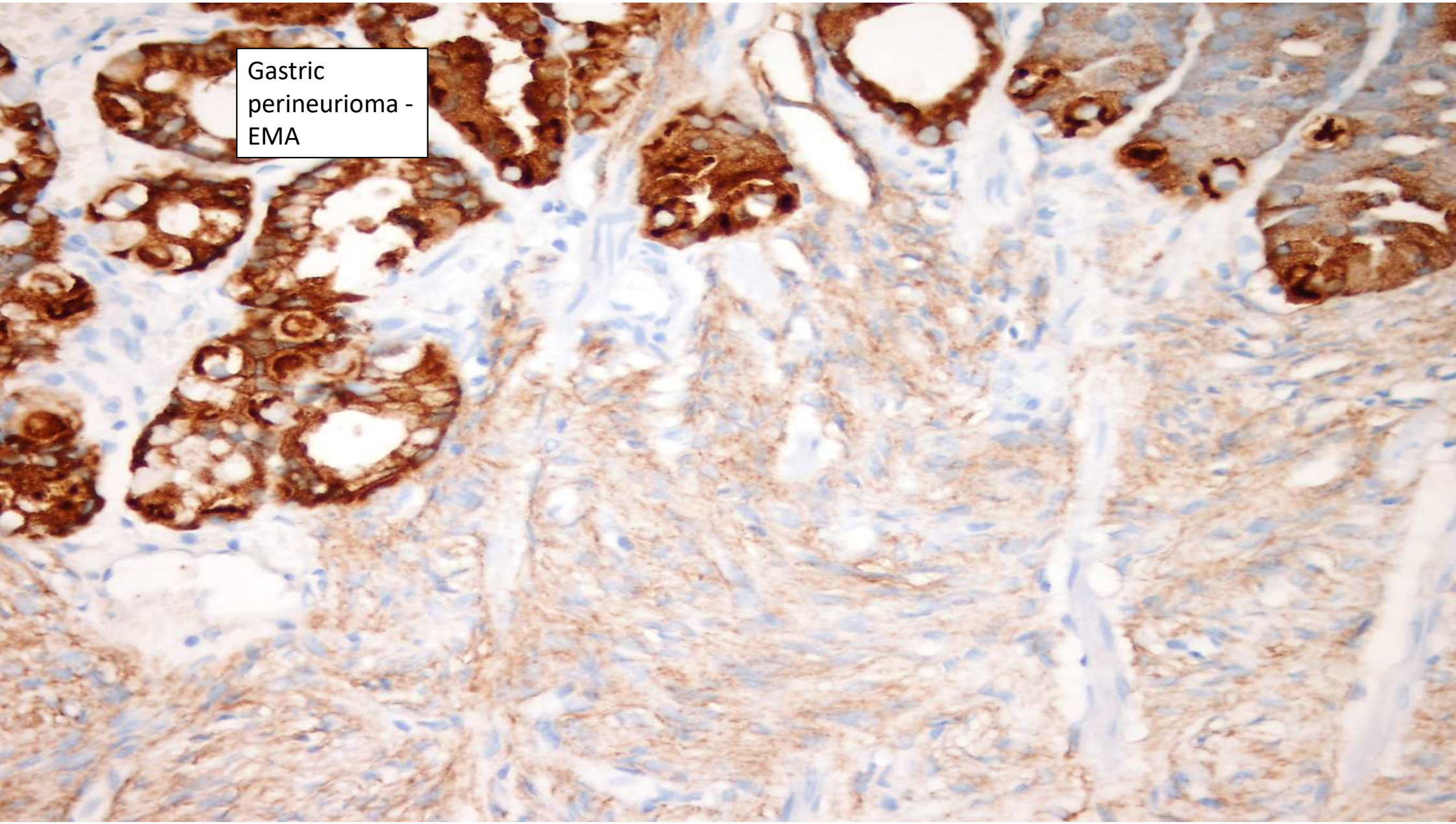


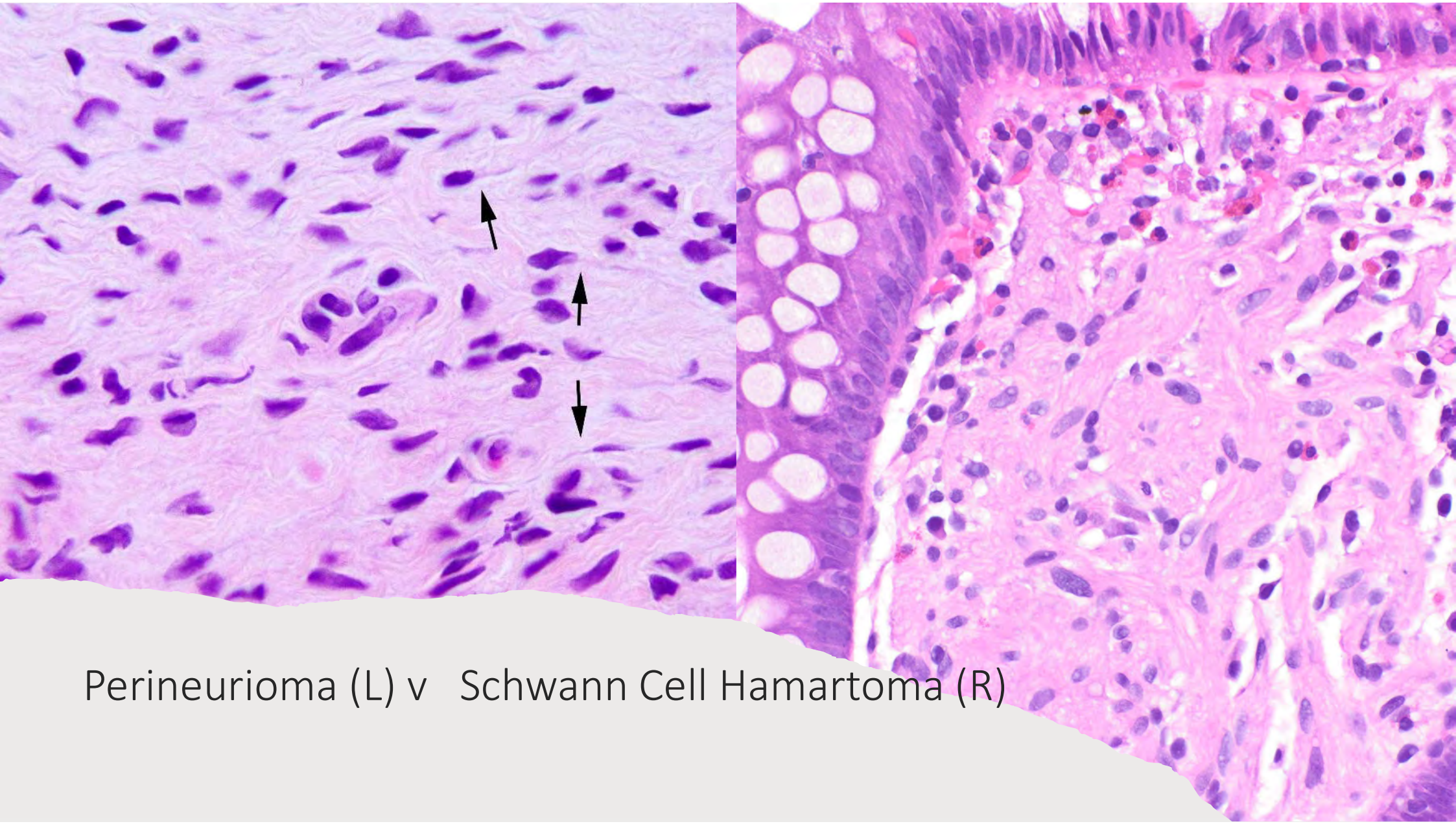
Benign fibroblastic polyps of the colon/perineurioma

- Incidental -detected in adult patients undergoing screening colonoscopy.
- Lamina propria - Some intimately admixed with serrated polyps.
- Lack CD31, S-100, CD117/c-kit, Bcl-2, and desmin.
- A few have focal SMA and CD34.
- **Same lesions with EMA/ glut1/ claudin 1 can be regarded as "perineurioma"**


Perineurioma – long cytoplasmic processes


Perineurioma –
long cytoplasmic
processes

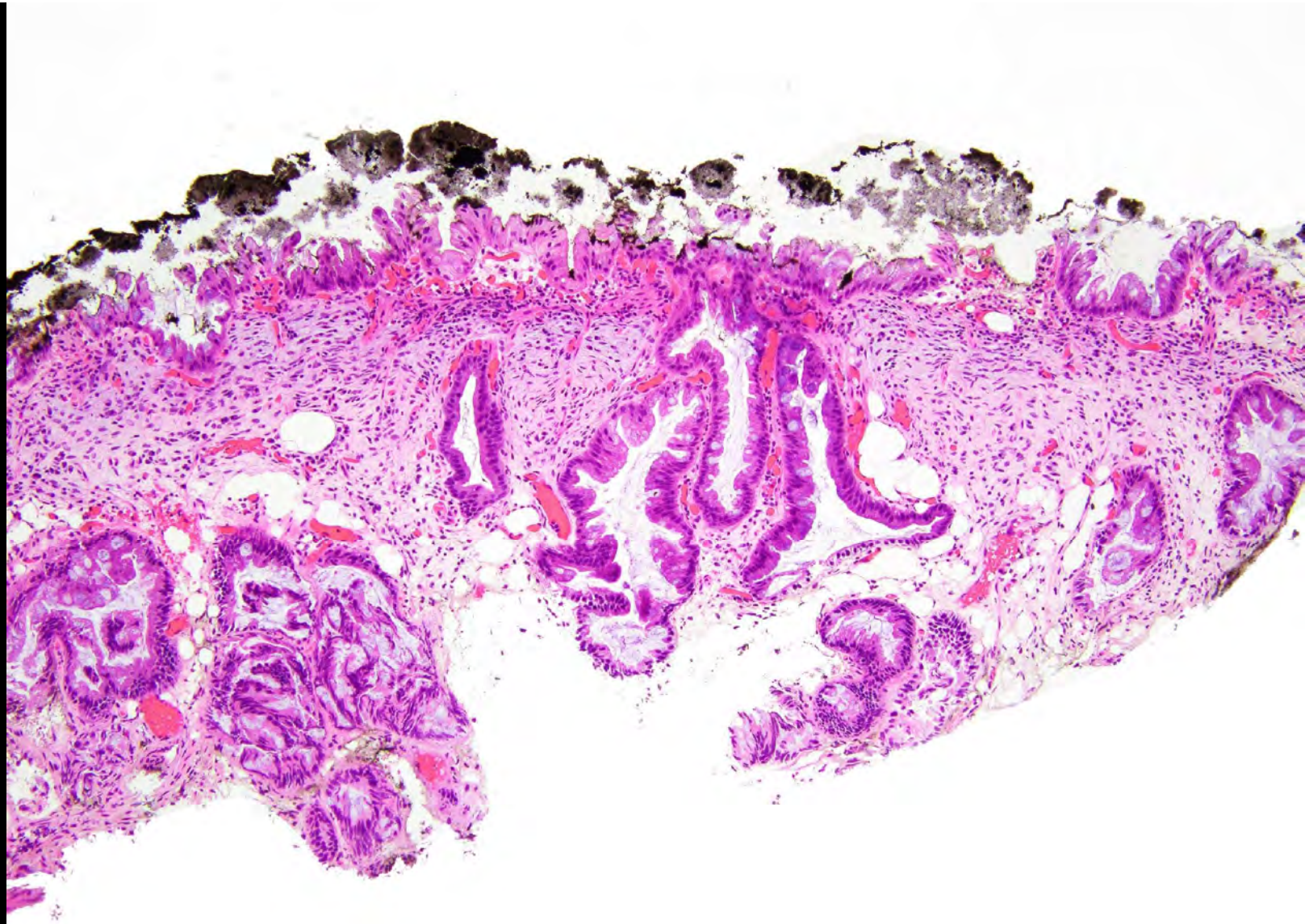

Gastric perineurioma - EMA

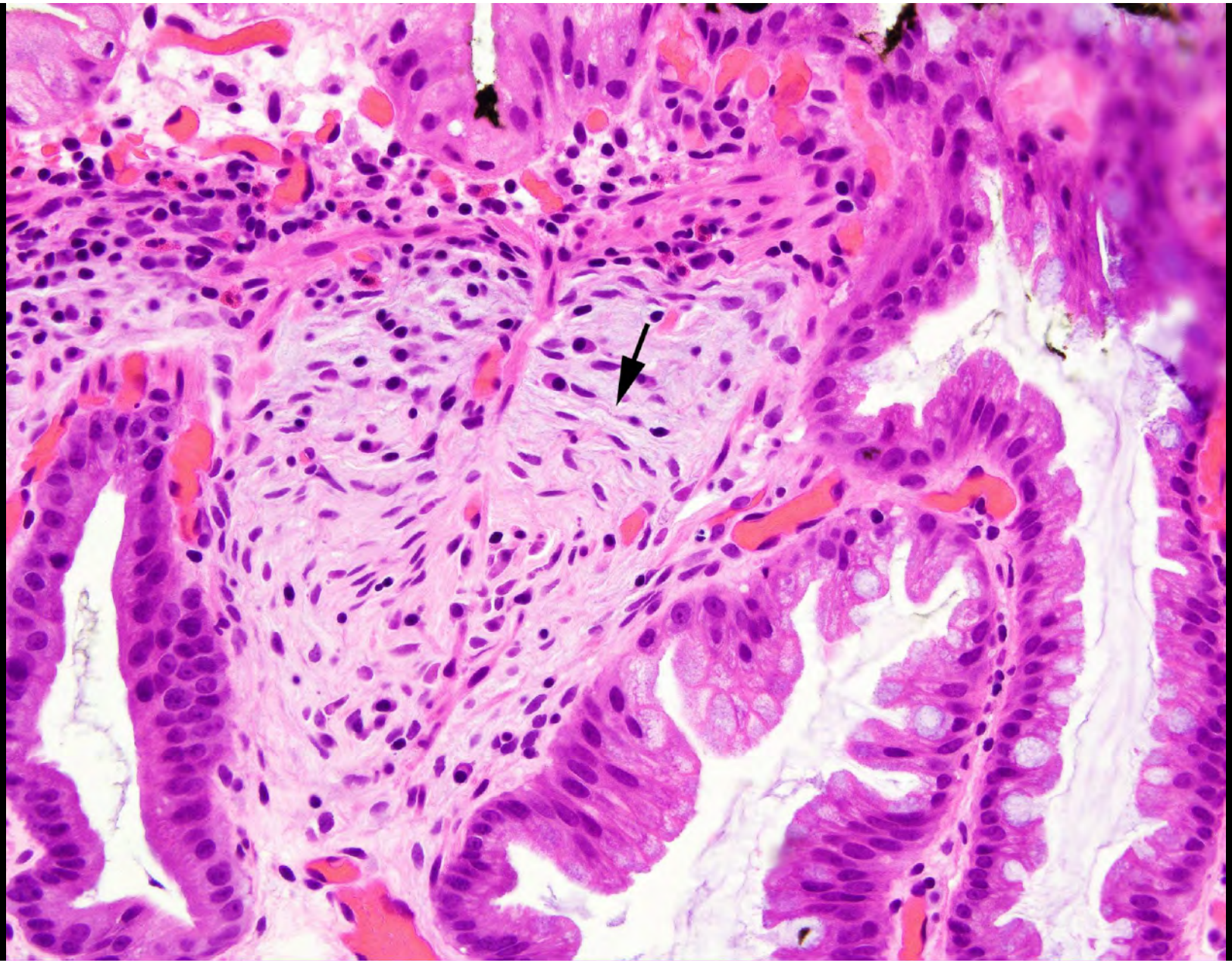


Perineurioma (L) v Schwann Cell Hamartoma (R)

These proliferations can be associated with serrated polyps. Some observers question whether they are simply expanded crypt sheath cells

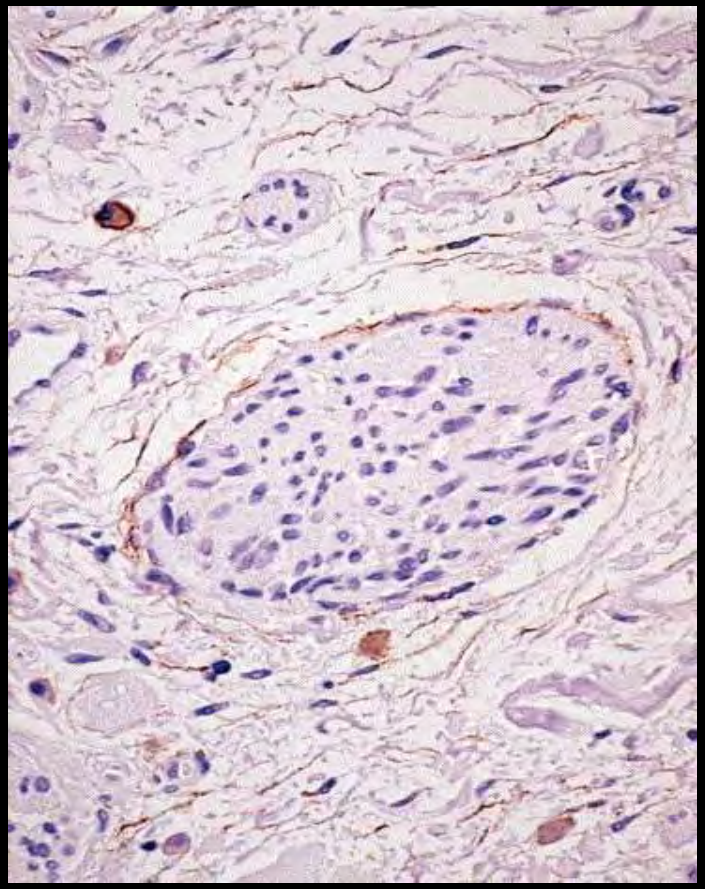
Hissong E, Yantiss RK. Epithelial-Stromal Polyps of the Colon Are Not Perineuriomas. Am J Clin Pathol. 2021 Jun 17;156(1):109-116. PMID: 33313671.

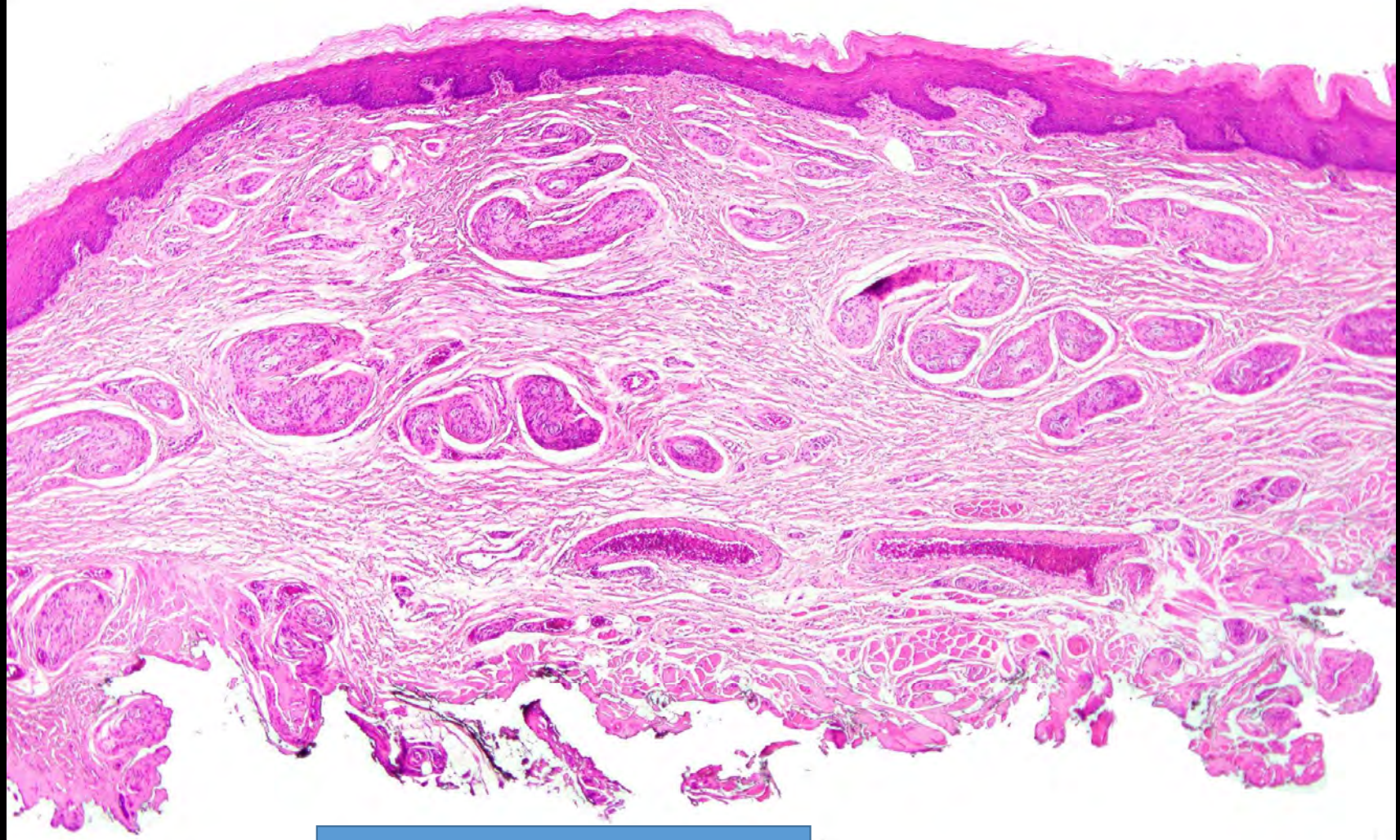




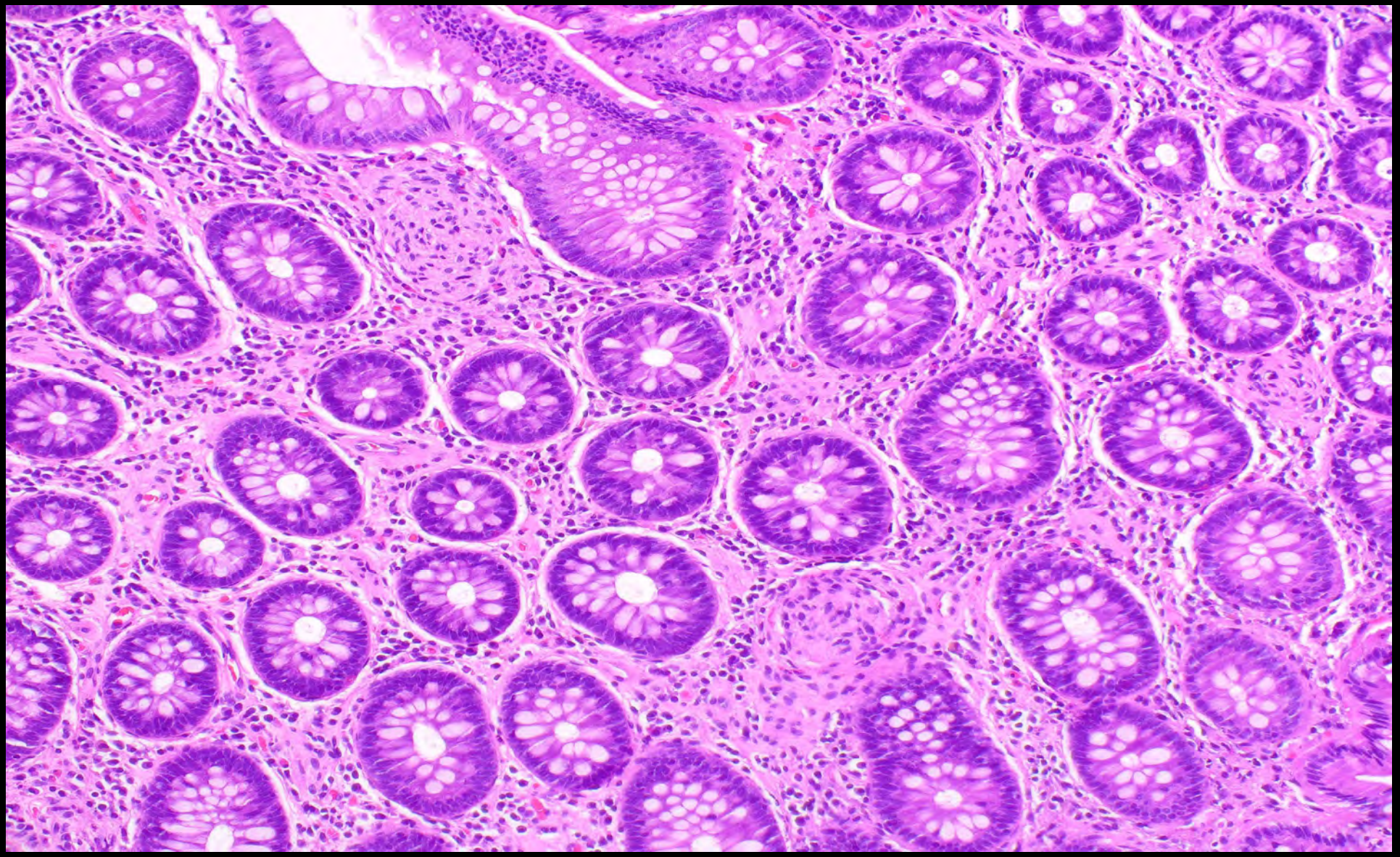
Mucosal Nerve Sheath Lesions

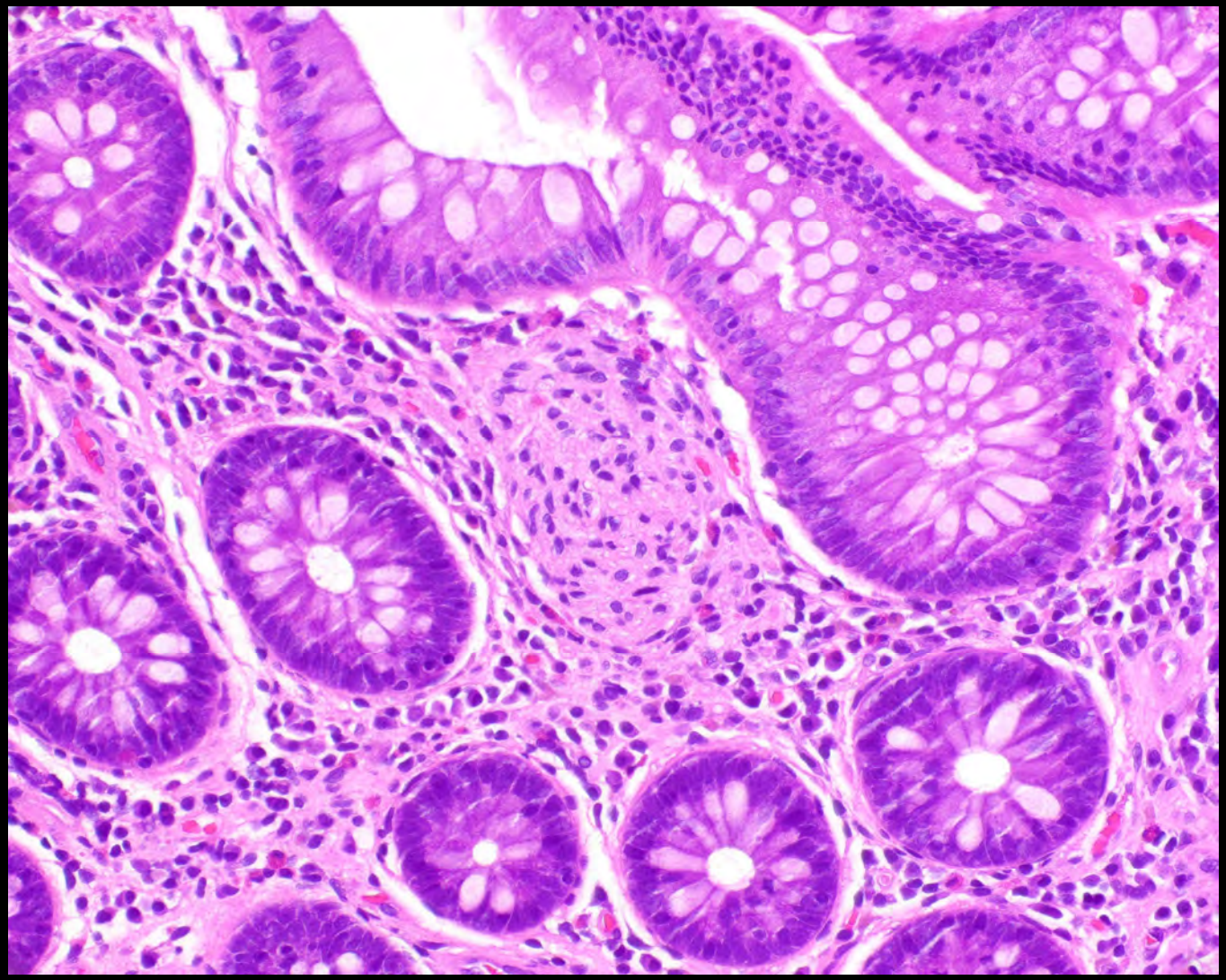
- Benign
- No need to worry about GIST – if is extension from a GIST it will look ugly
- Differ from “Mucosal neuromas” of MEN2B – medullary thyroid carcinoma, pheochromocytoma, neuromas/ganglioneuromas

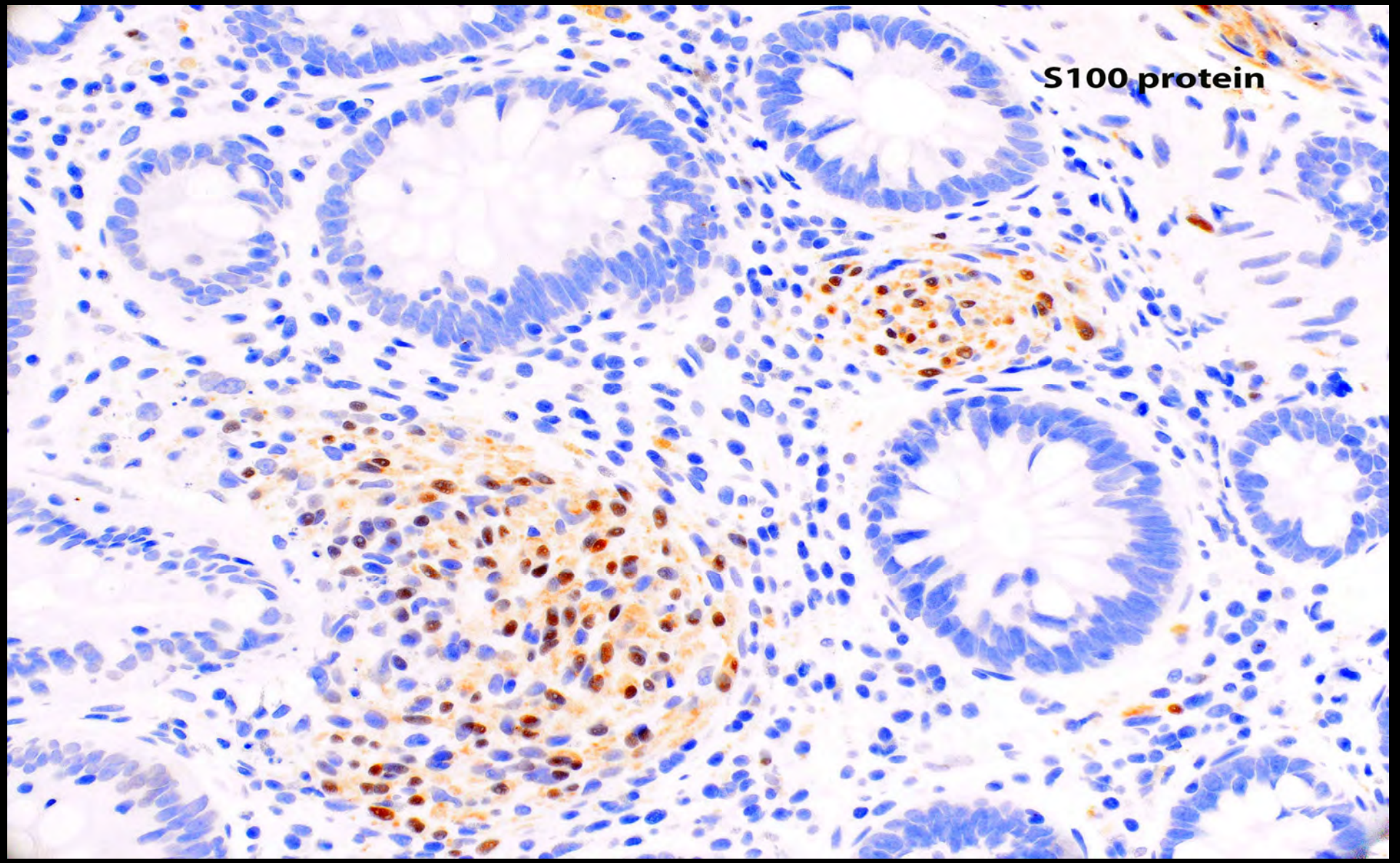


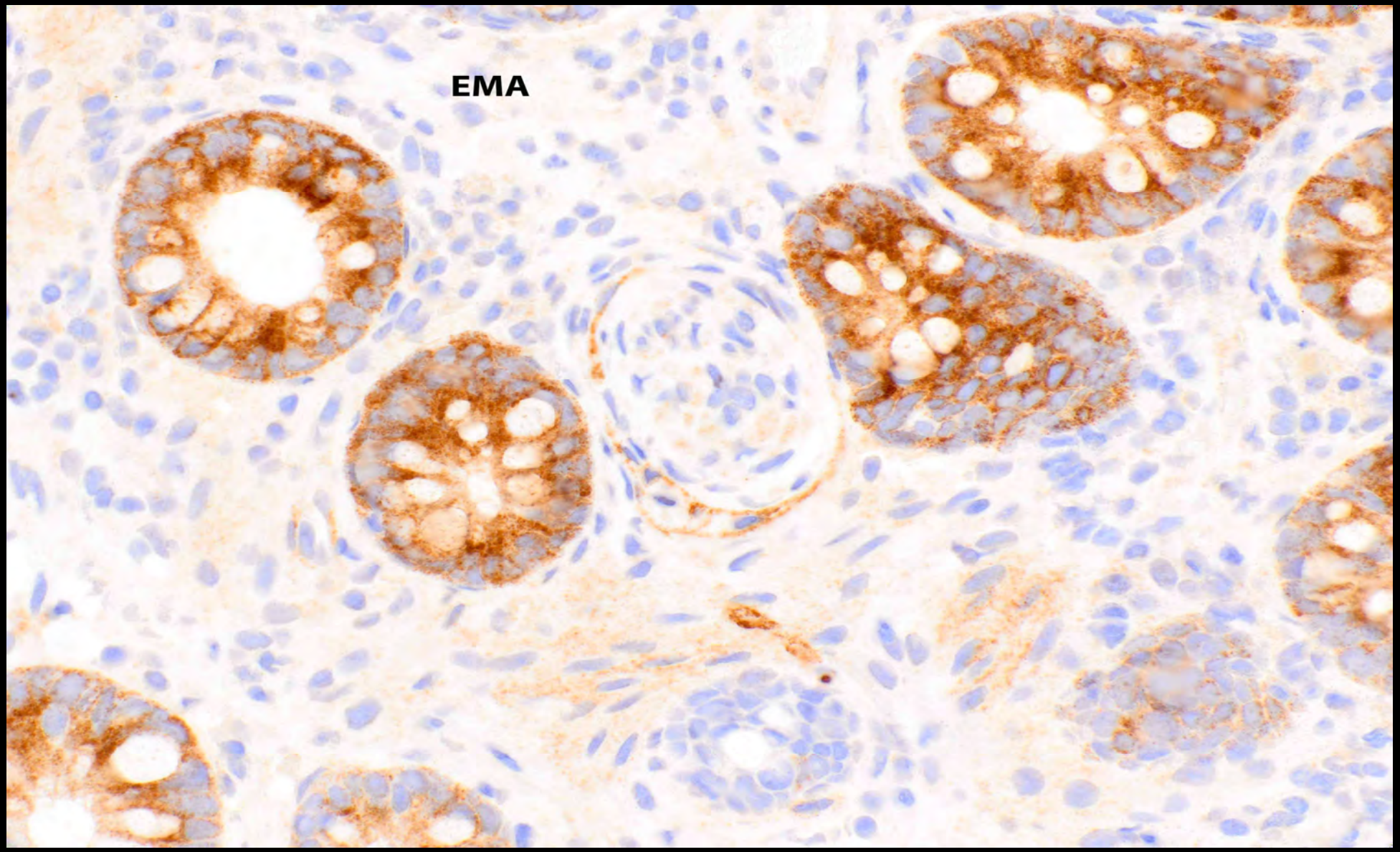


Mucosal neuroma



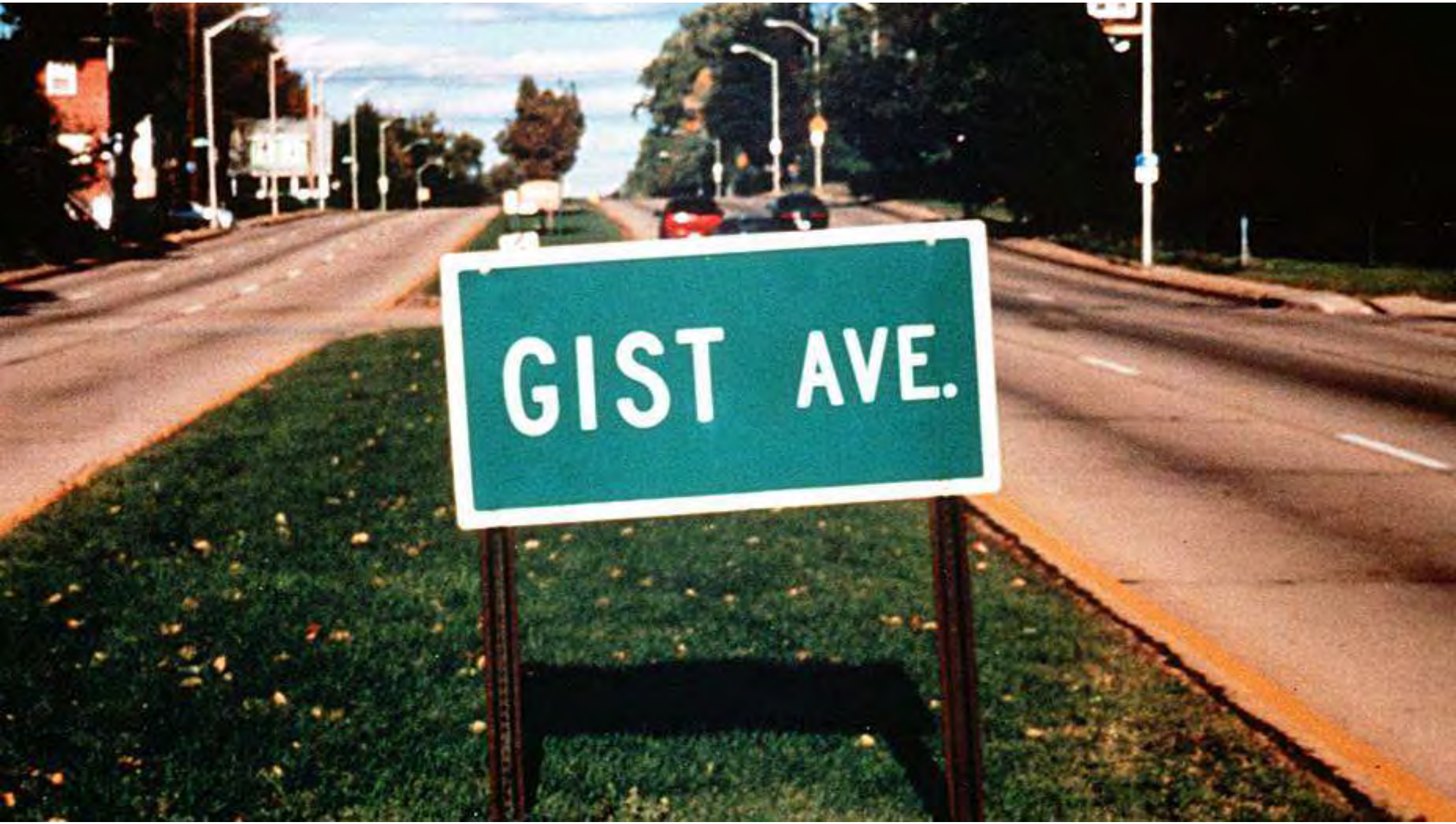



S100 protein


EMA

GI Mesenchymal Tumors

- We have covered a lot
- Remember the importance of the layers in diagnosing GI mesenchymal neoplasms
- Most are “H&E diagnoses”
- Sometimes a little immunohistochemical staining can reassure us!


GIST AVE.

VÅRMÖTE I PATOLOGI

NPM 2025

19–21 MAY

NORDIC PATHOLOGY MEETING