



<https://www.youtube.com/c/vikramdeshpandePathology>

@Vik_Deshpande



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

GISTs and All Thing Mesenchymal in the Gastrointestinal Tract

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Professor of Pathology

Harvard Medical School

Pathologist

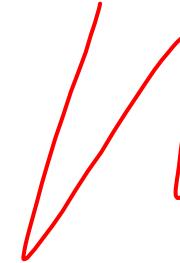
Director of GI pathology

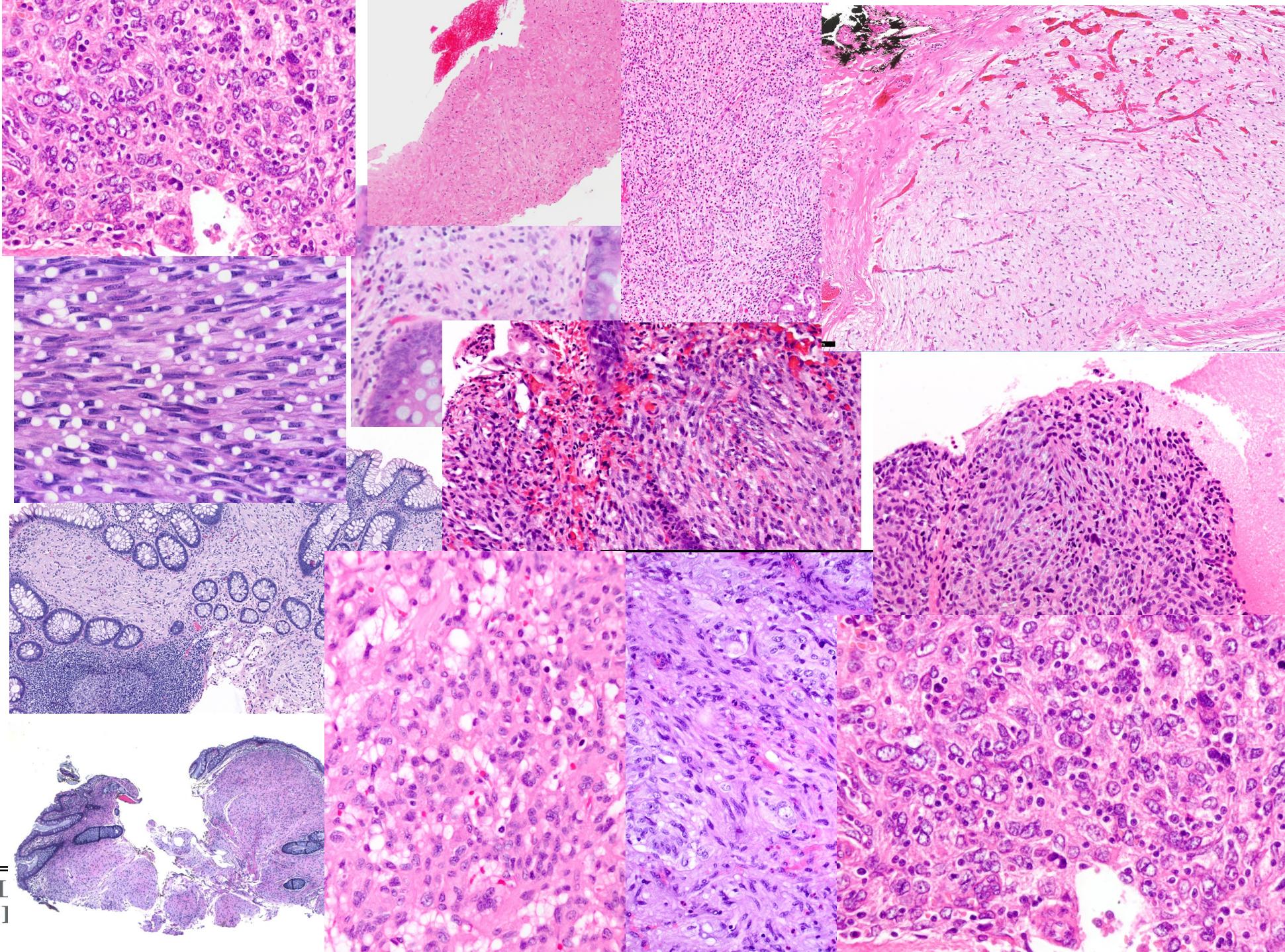
Beth Israel Deaconess Medical Center

Editor-in-Chief

Journal of Clinical Pathology

vikramdirdeshpande@gmail.com





MGH

SCHOOL

Location

Location

Location



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Esophagus

Mucosa

Granular cell tumor
Melanoma

Submucosa

Leiomyoma

Muscularis

Leiomyoma
GIST

Serosa

Stomach

Mucosa

Melanoma

Submucosa

Inflammatory fibroid polyp

Muscularis

GIST, Glomus, plexiform fibromyxoma, Schwannoma, astroblastoma
Gastrointestinal clear cell sarcoma / malignant gastrointestinal
neuroectodermal tumor

Serosa

Small Bowel

Mucosa

Melanoma

Submucosa

Gangliocytic paraganglioma (CoGNET)

Inflammatory fibroid polyp

Muscularis

GIST

Gastrointestinal clear cell sarcoma / malignant gastrointestinal neuroectodermal tumor

Serosa

Fibromatosis, sclerosing mesenteritis, IgG4-related disease, inflammatory myofibroblastic tumor

Colon

Mucosa

Schwann cell hamartoma, Perineurioma, Ganglioneuroma, melanoma

Leiomyoma

Submucosa

Inflammatory fibroid polyp

Muscularis

GIST
Gastrointestinal clear cell sarcoma / malignant gastrointestinal neuroectodermal tumor

Serosa

Fibromatosis, sclerosing mesenteritis, IgG4-related disease, inflammatory myofibroblastic tumor

Serosal-based

With or without involvement of the muscularis propria

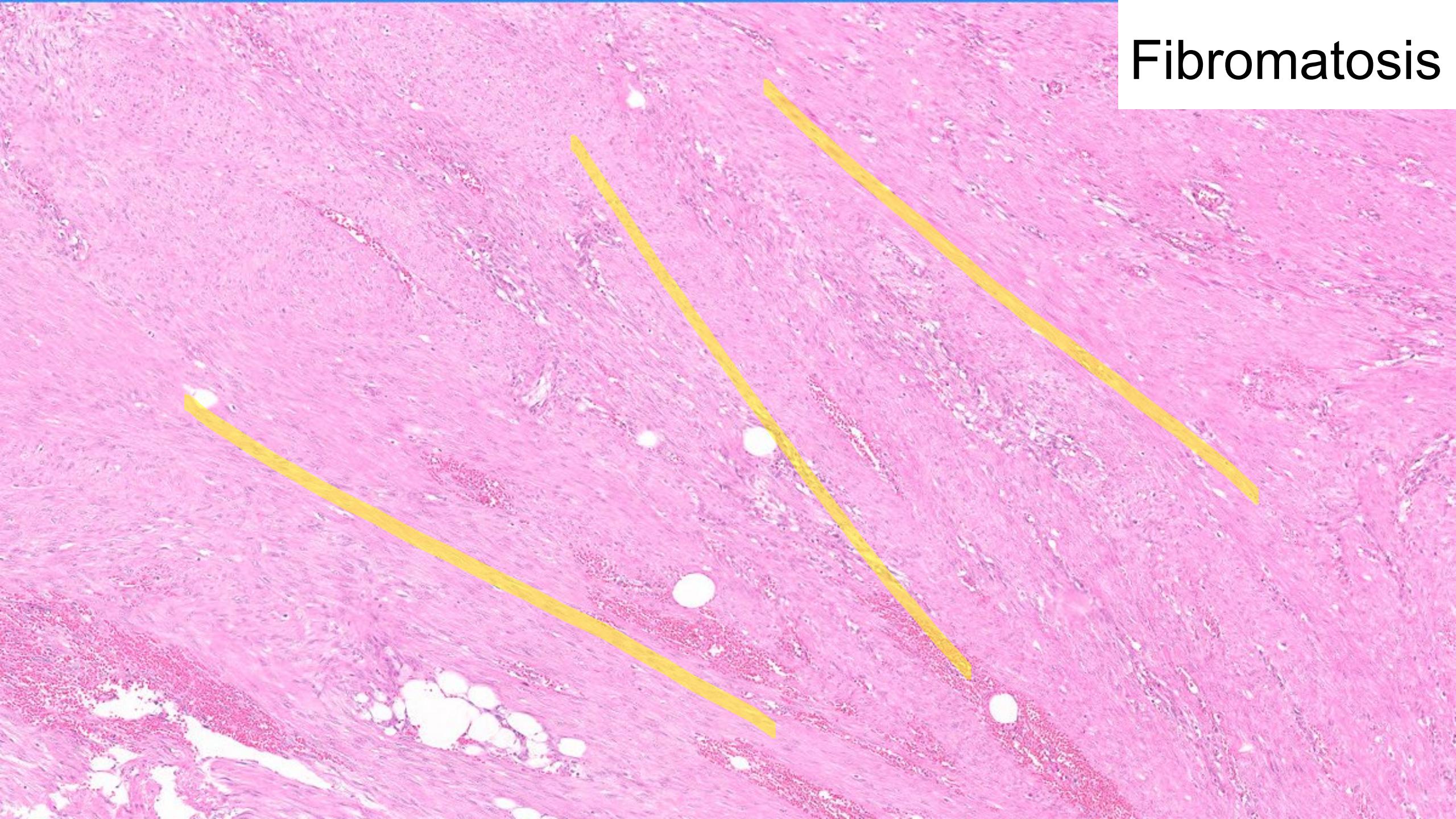


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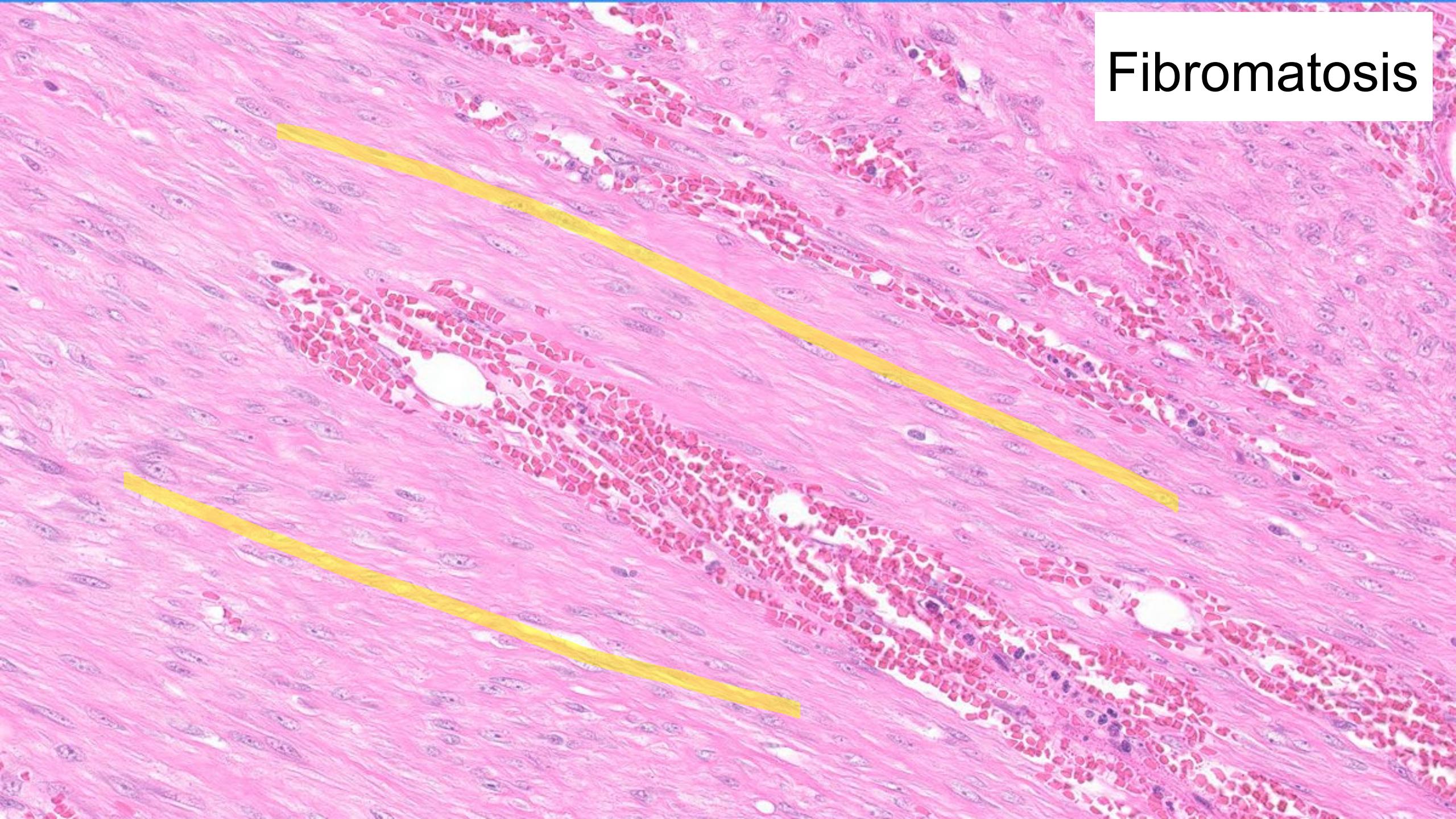
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MEDICAL SCHOOL





Fibromatosis

Fibromatosis





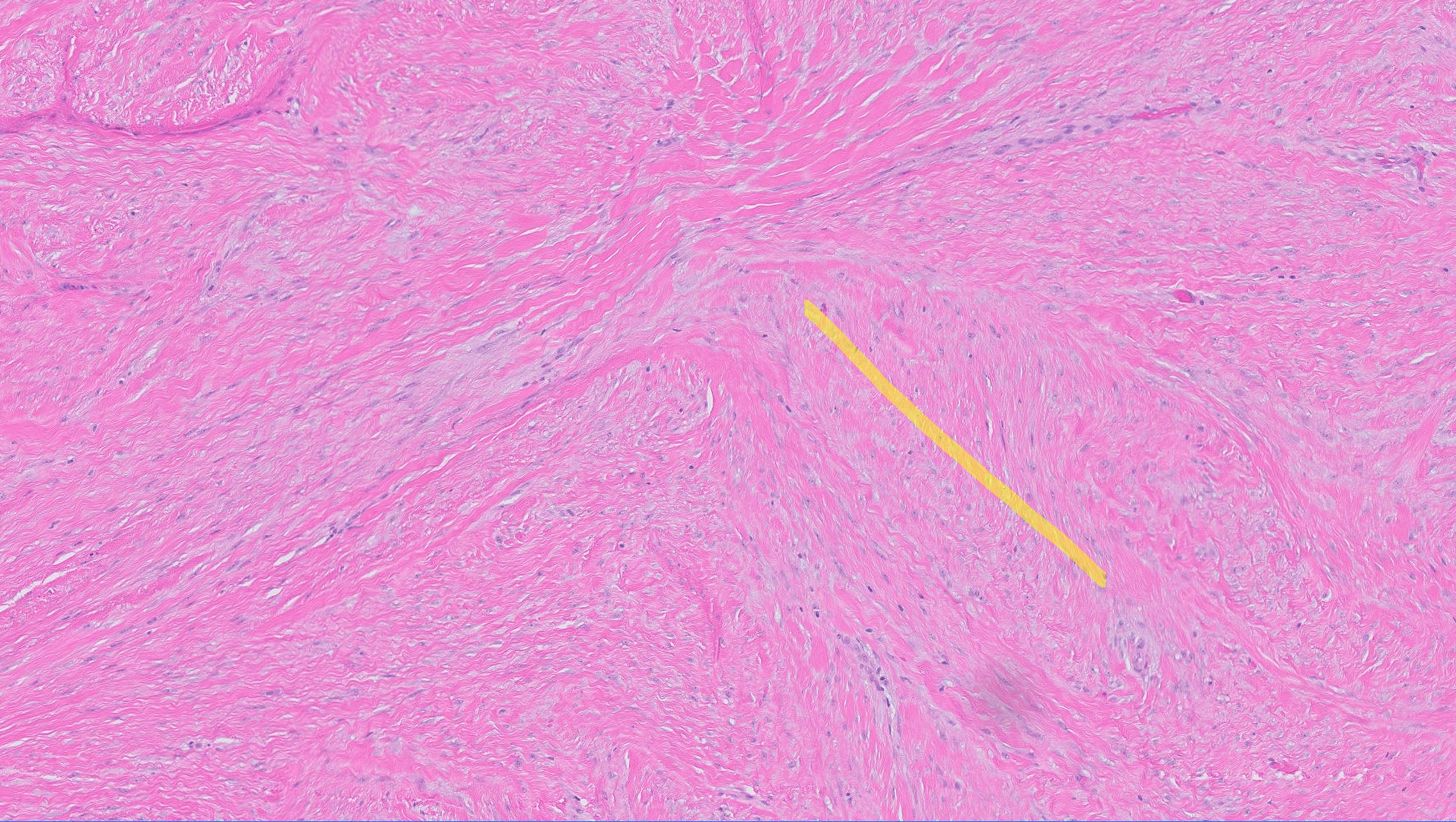


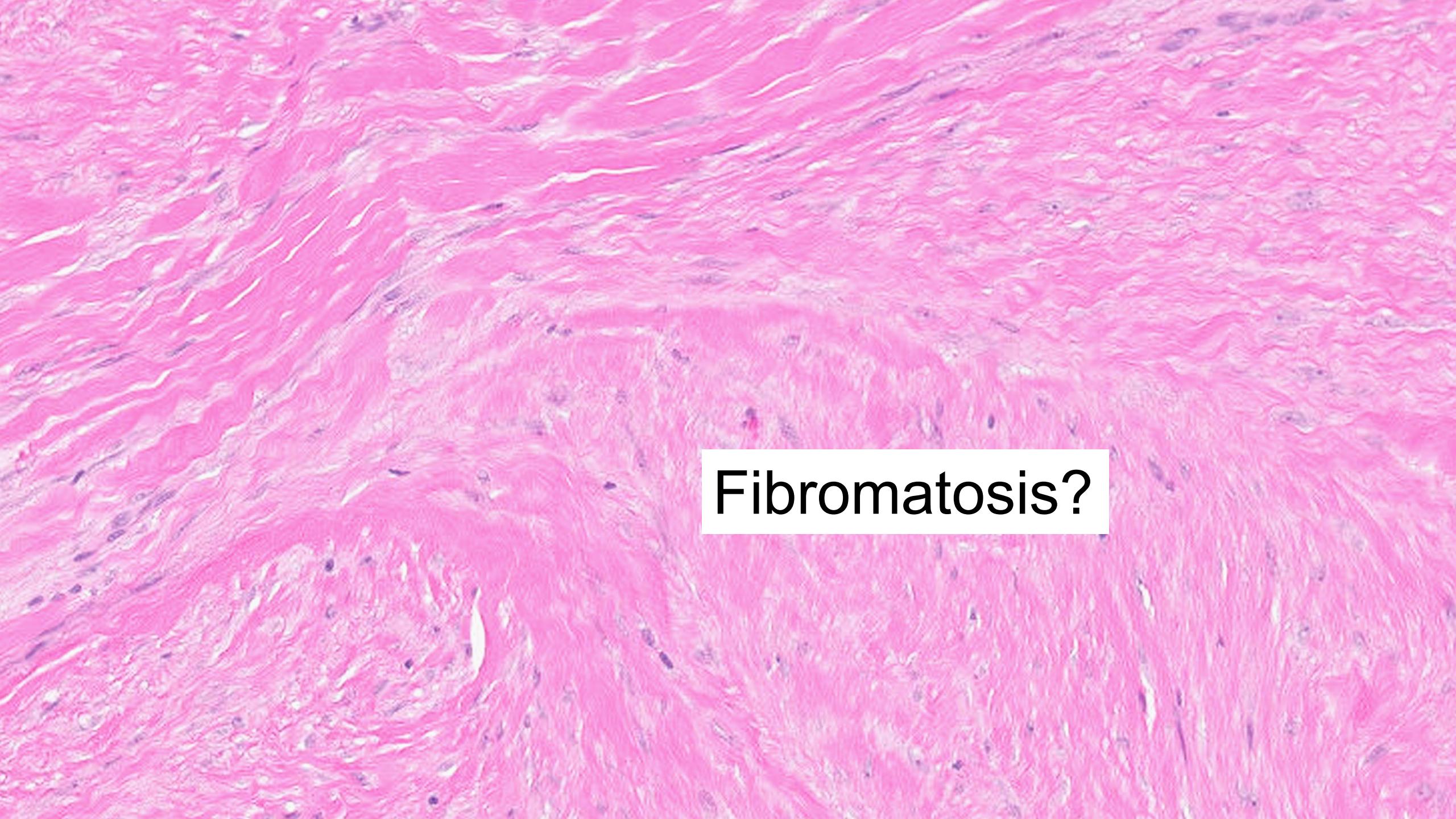
Beta-catenin



A histological slide showing a dense, interwoven arrangement of collagen fibers, characteristic of fibromatosis. The fibers are pinkish-purple and form a dense, somewhat whorled pattern. There are also some darker, more cellular areas. A white rectangular box is overlaid on the top left corner of the image.

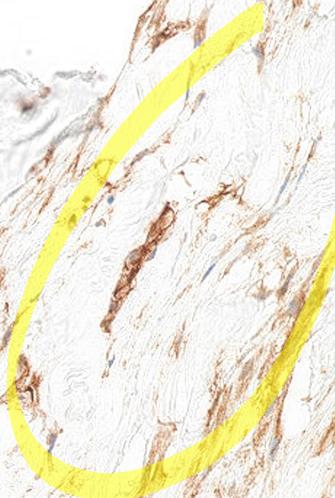
Fibromatosis?

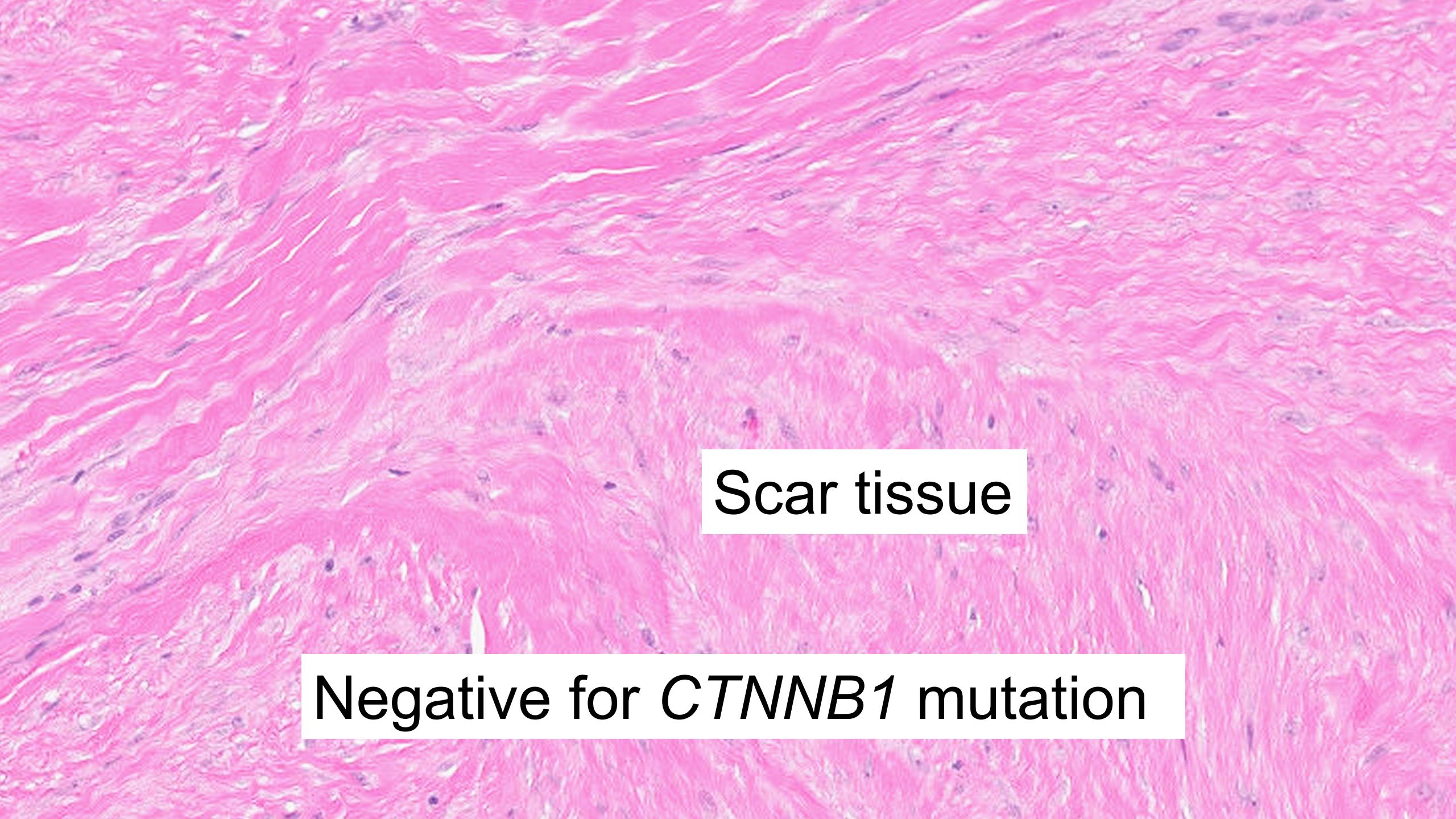


A histological slide showing a dense, pink-stained connective tissue stroma. Within the stroma, there are several small, dark, oval-shaped nuclei, likely belonging to fibroblasts. The overall texture is somewhat wavy and lacks the organized arrangement typical of a tumor. A white rectangular box is overlaid on the image, containing the text "Fibromatosis?".

Fibromatosis?

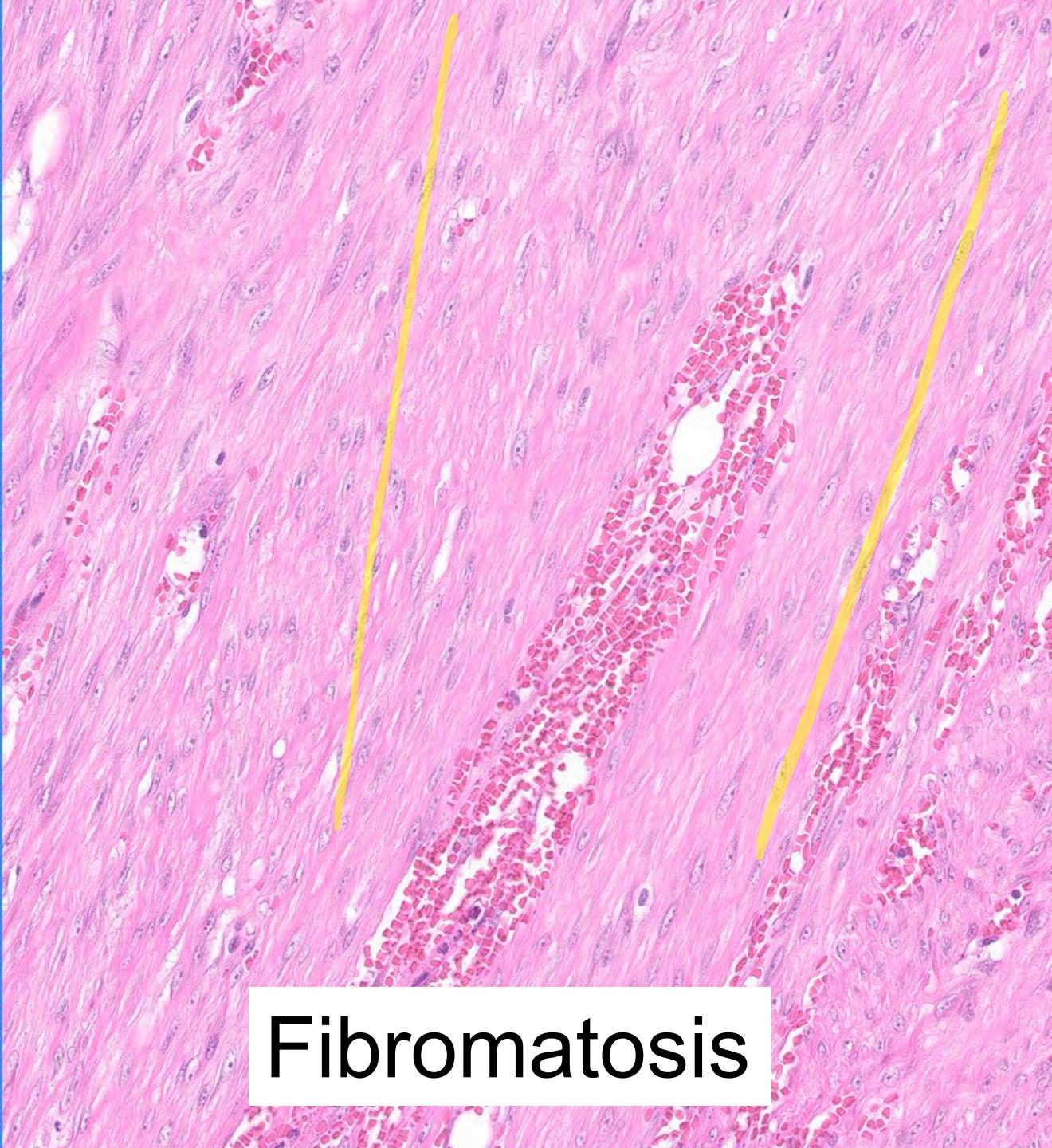
Beta-catenin



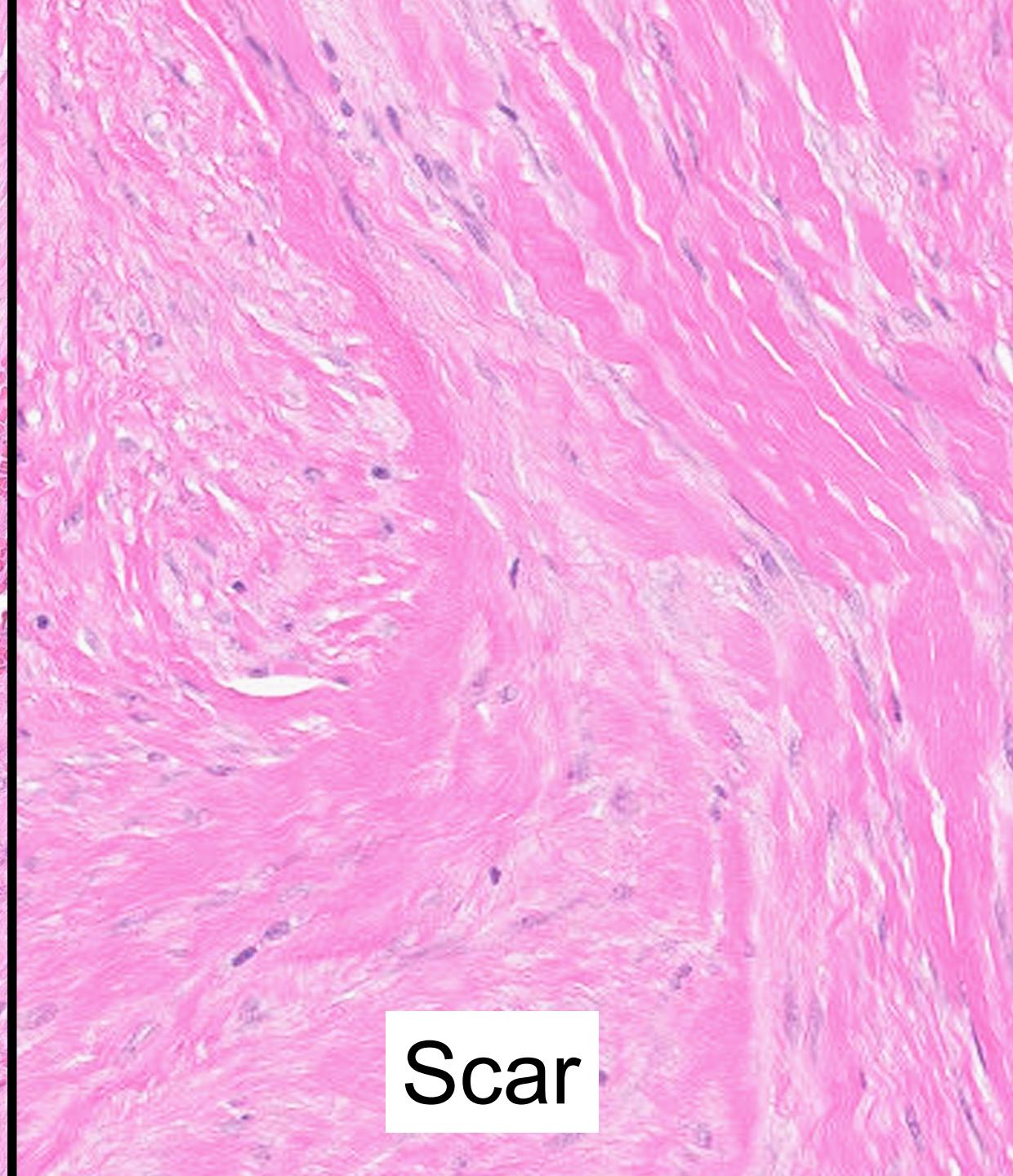
A high-magnification H&E stained histological section. The image is dominated by a dense, wavy pattern of pink-stained fibers, characteristic of collagenous scar tissue. Interspersed among these fibers are small, dark-staining nuclei of fibroblasts. A few larger, more rounded nuclei, possibly of epithelial origin, are also visible. The overall texture is somewhat irregular and lacks the organized structure of normal tissue.

Scar tissue

Negative for *CTNNB1* mutation



Fibromatosis



Scar

Serosal surface

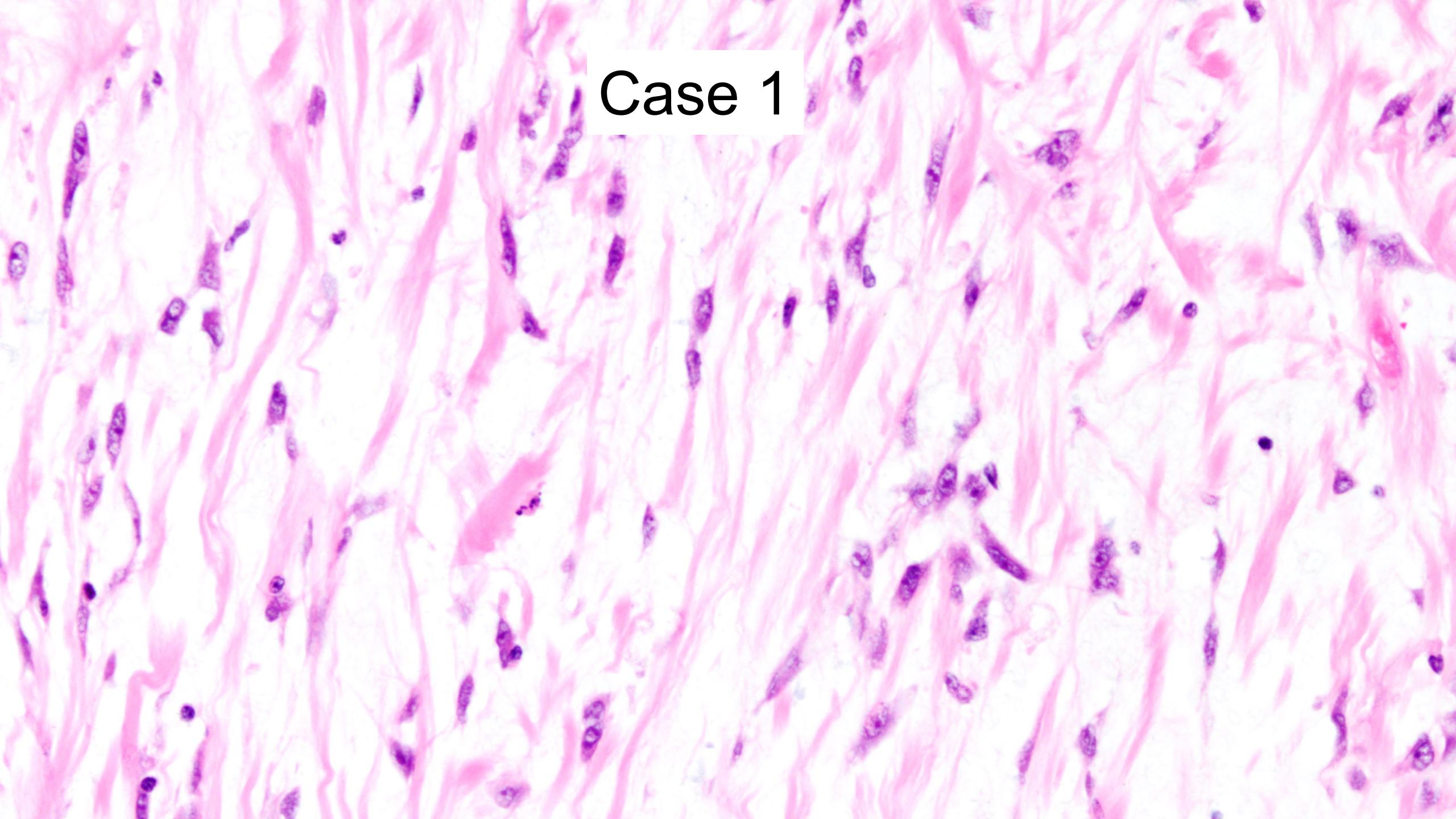


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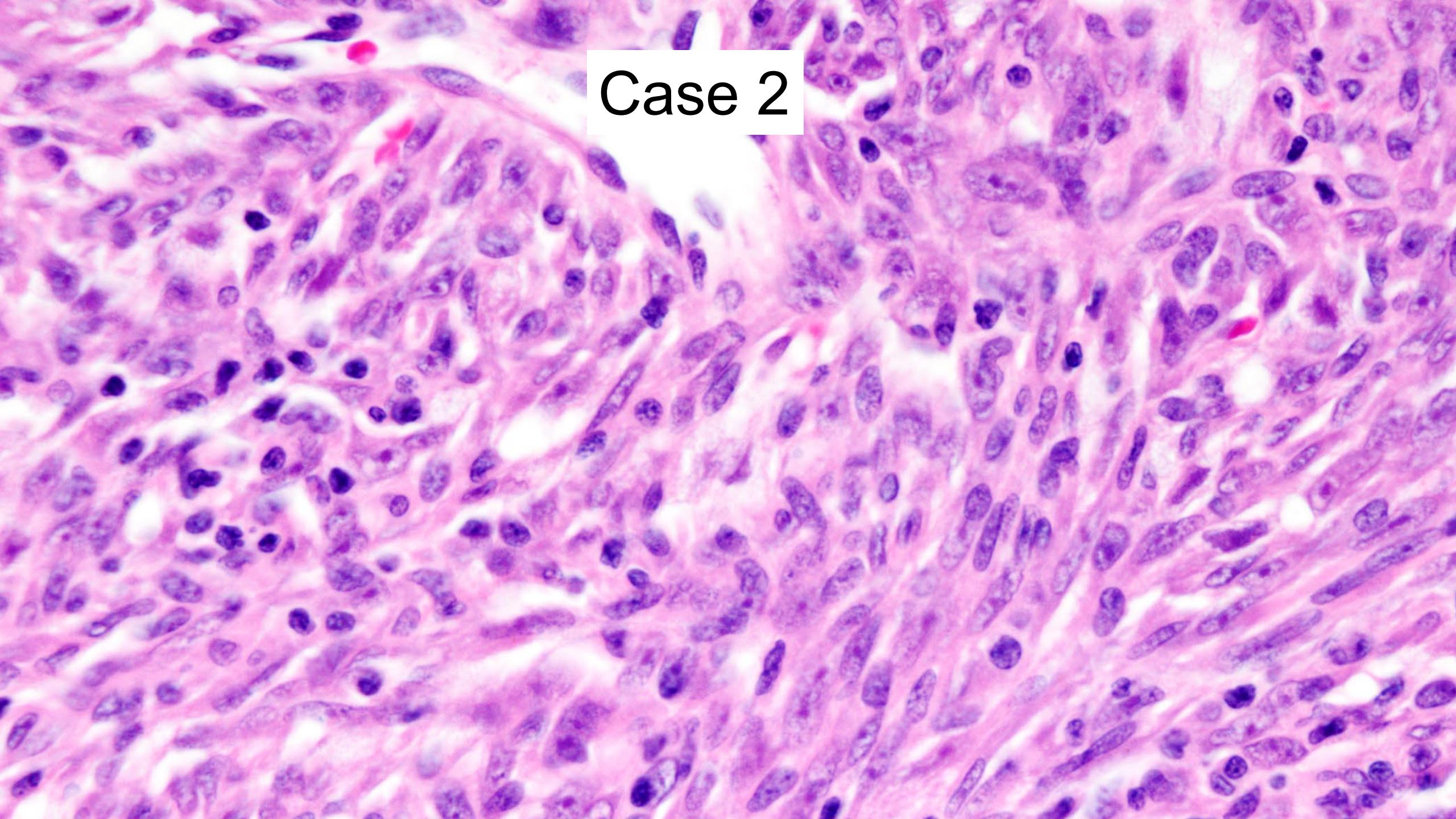


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MEDICAL SCHOOL

Case 1

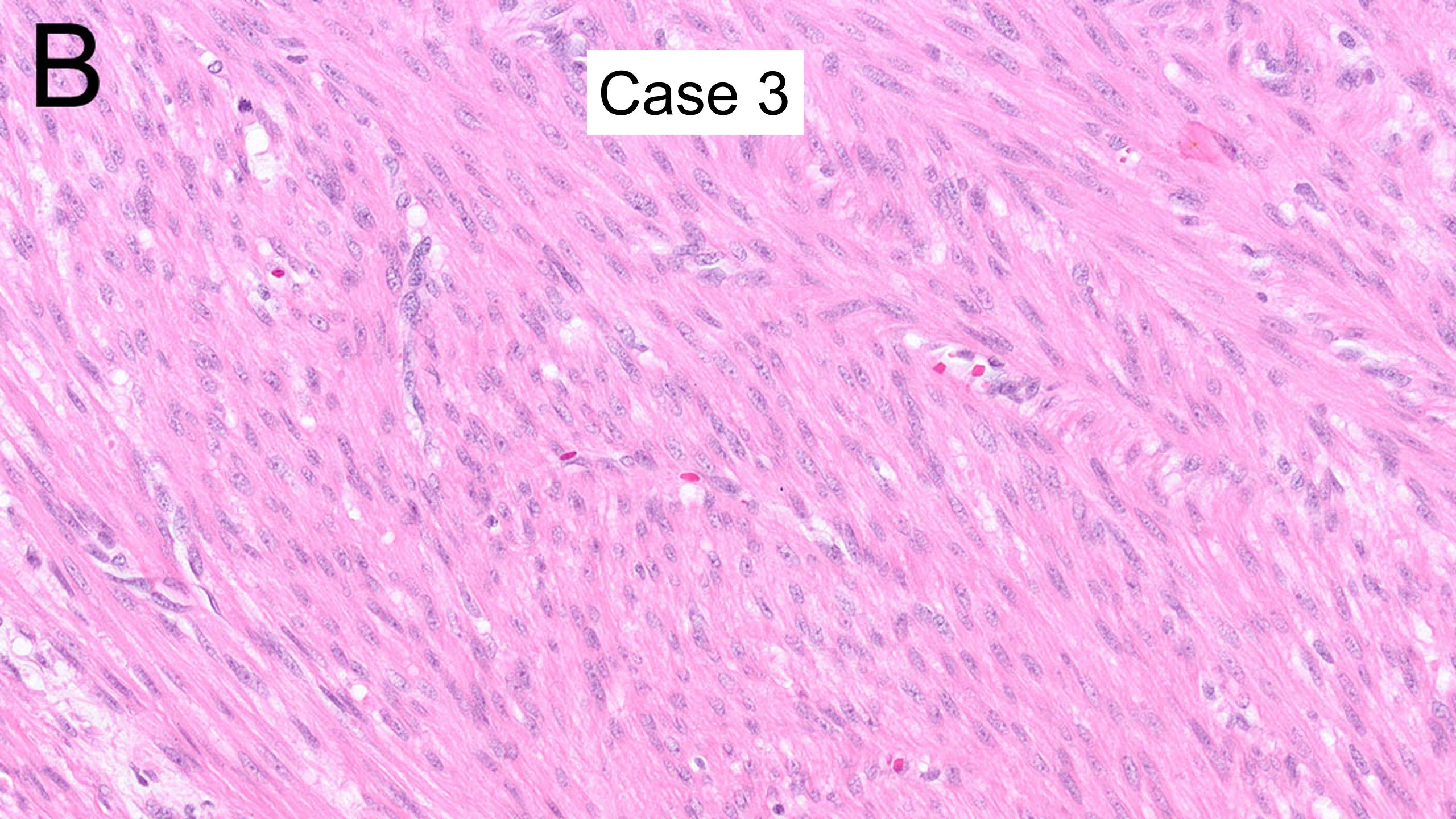


Case 2

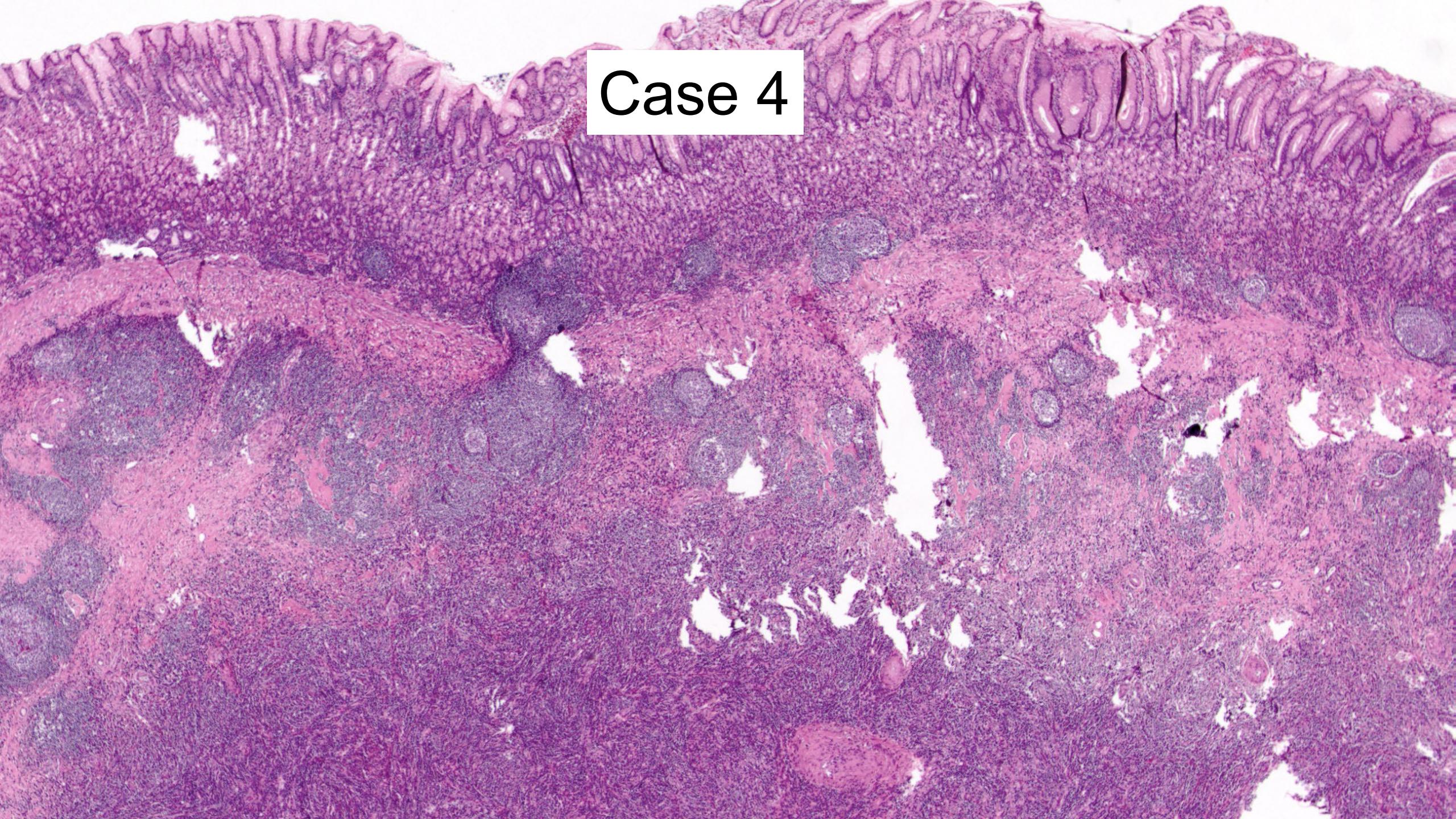


B

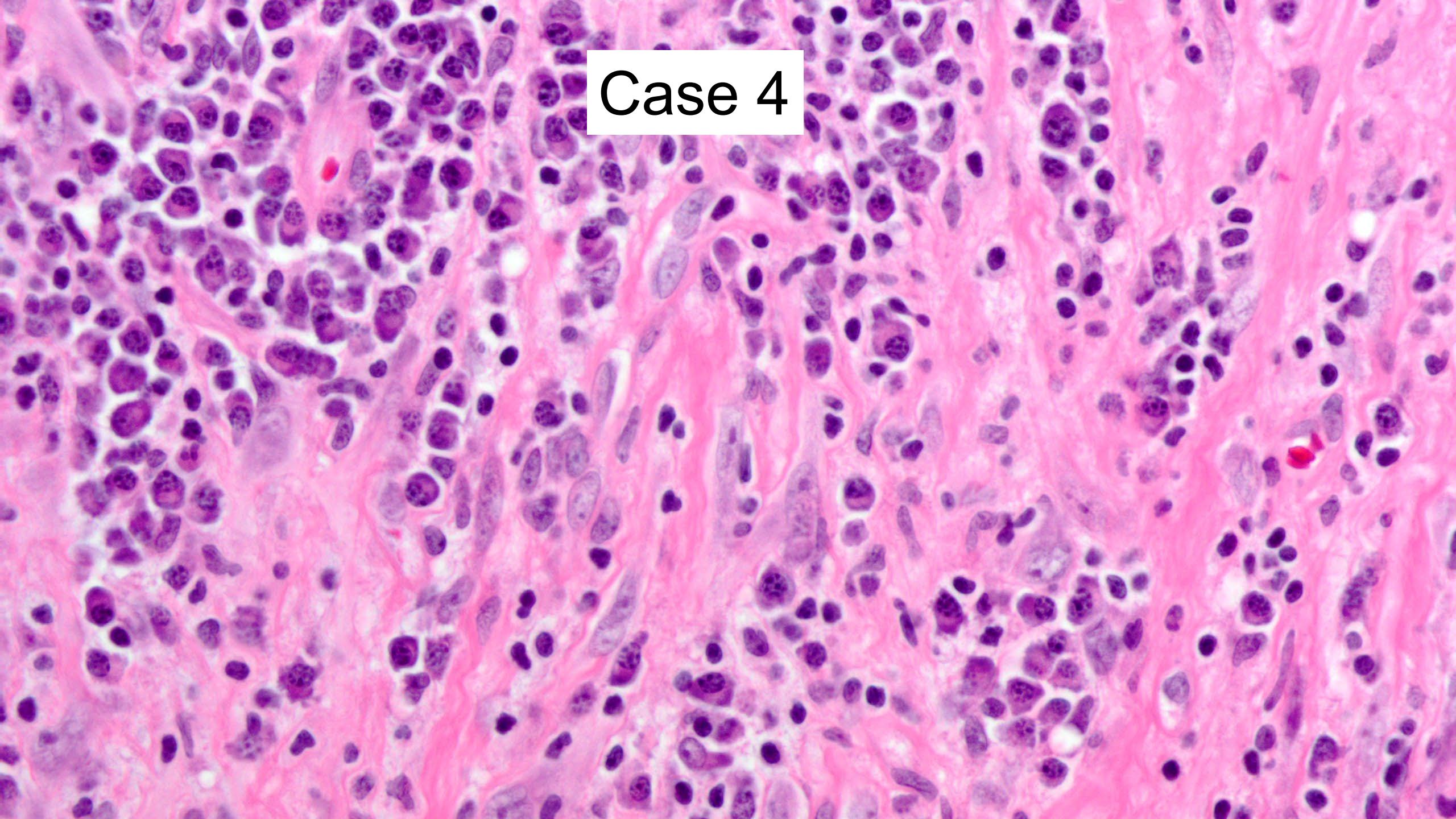
Case 3



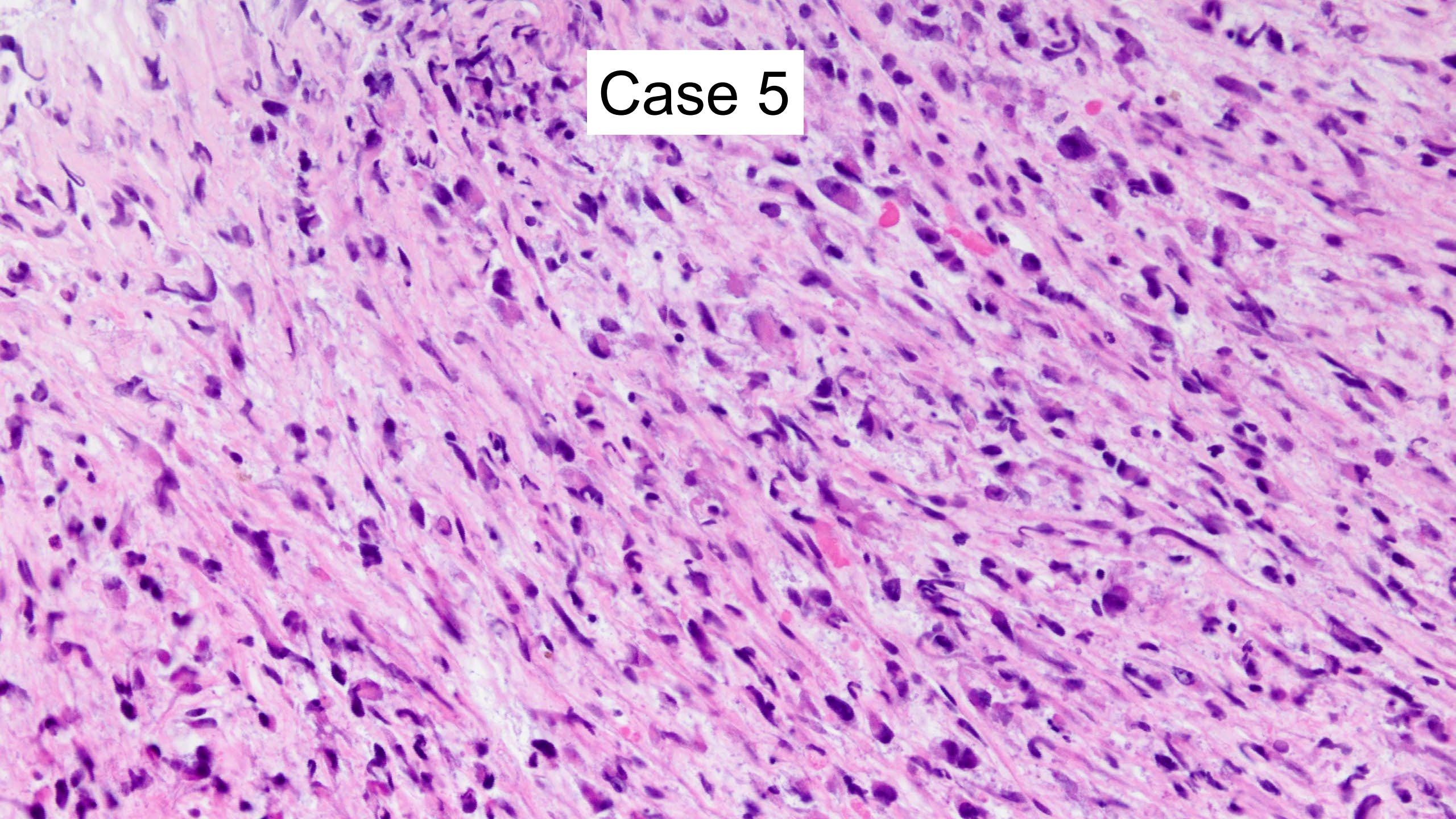
Case 4



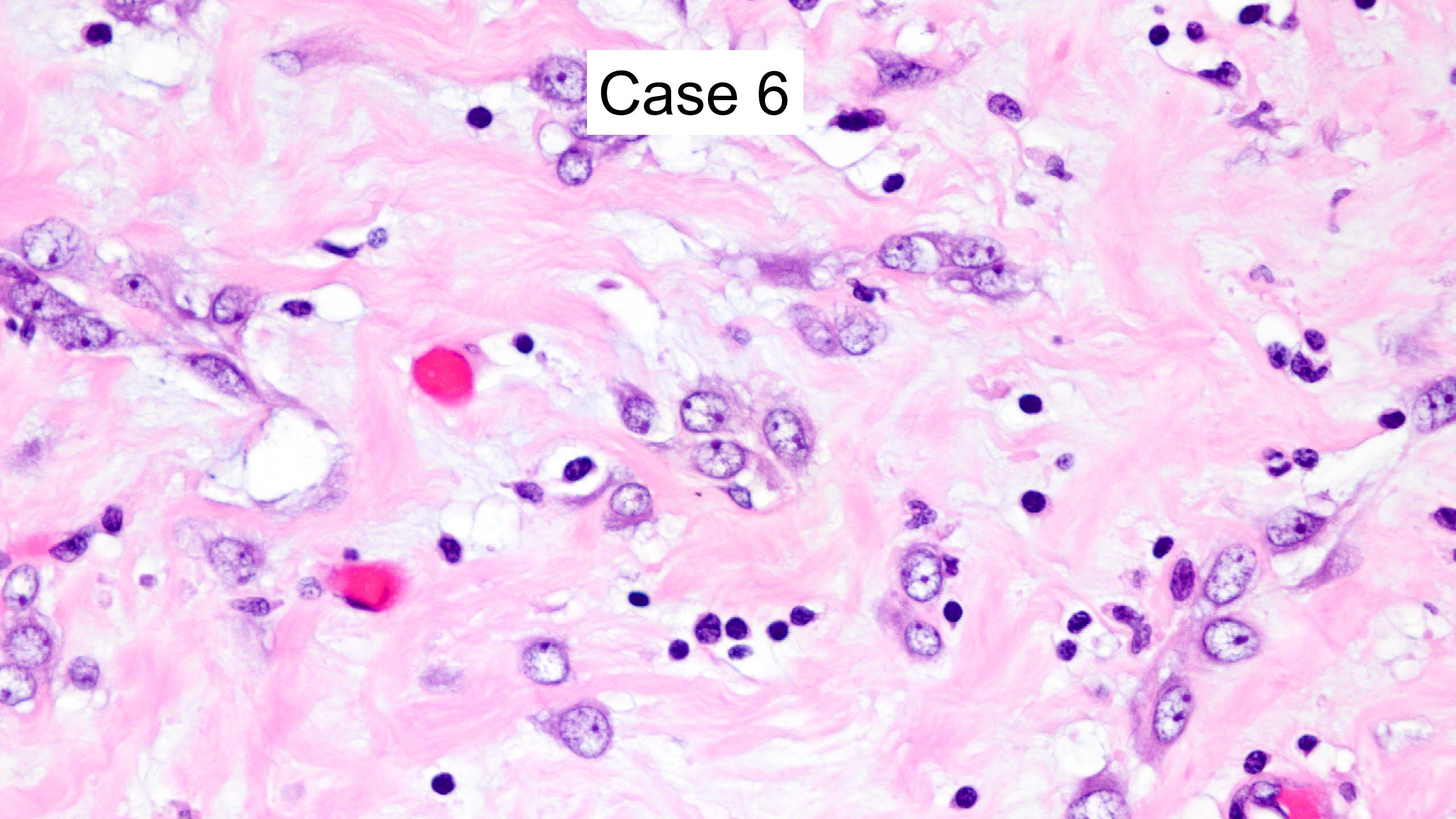
Case 4



Case 5



Case 6



Diagnosis



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Inflammatory Myofibroblastic Tumor

Serosal-based tumor

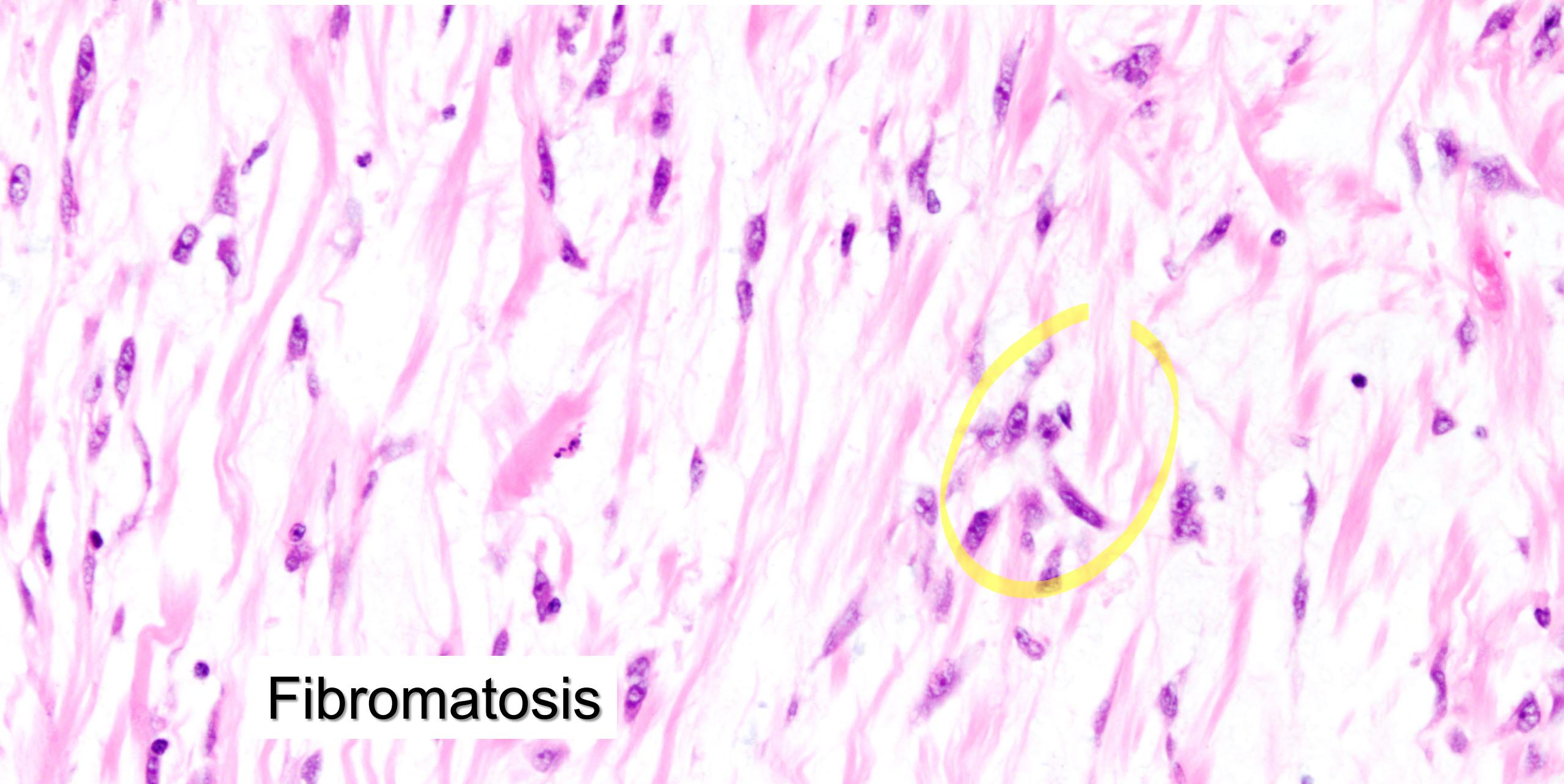


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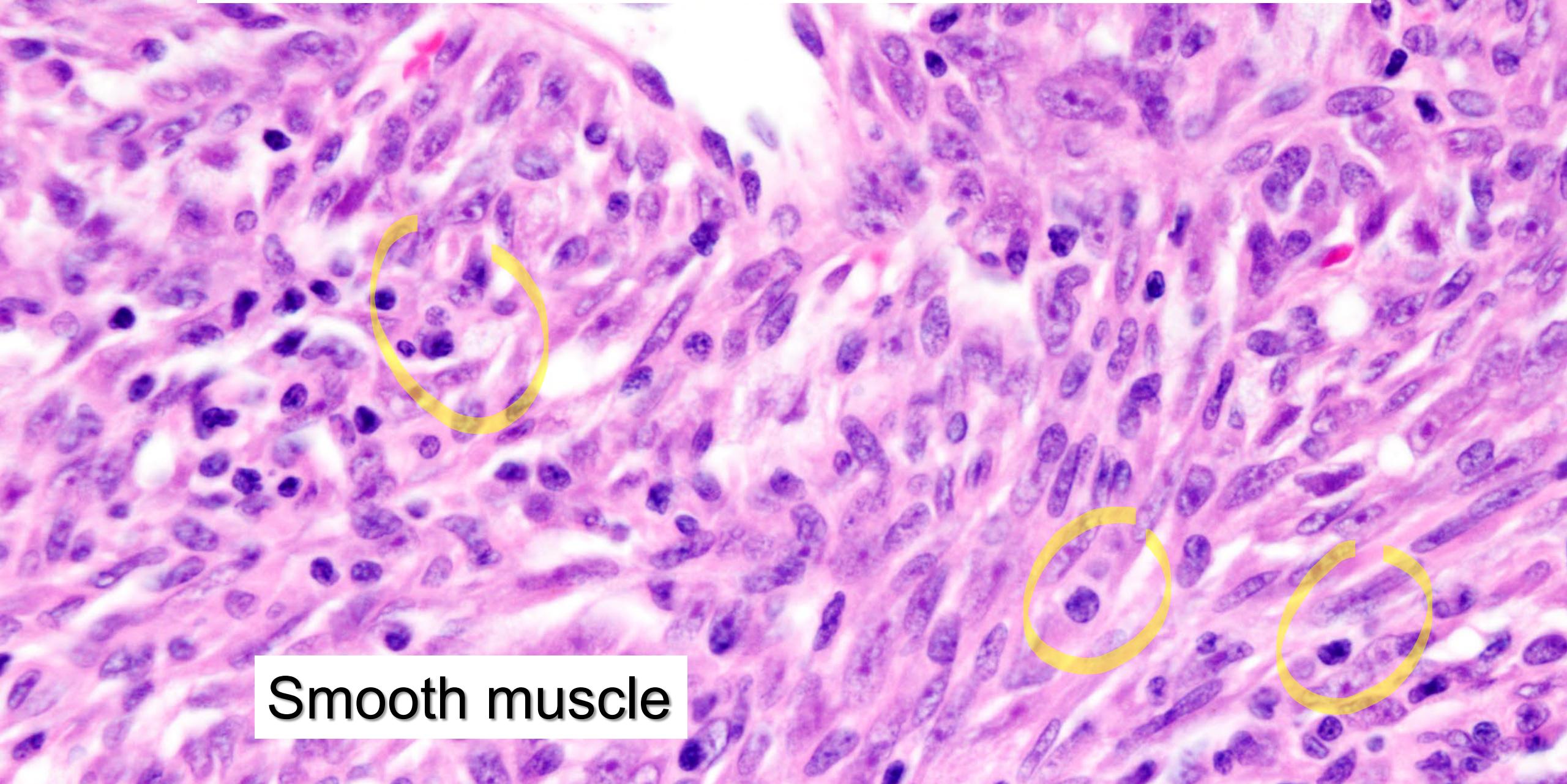
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Inflammatory myofibroblastic tumor



Fibromatosis

Inflammatory myofibroblastic tumor



Leiomyoma

- Devins KM, Samore W, Nielsen GP, Deshpande V, Oliva E. Leiomyoma-like Morphology in Metastatic Uterine Inflammatory Myofibroblastic Tumors. *Mod Pathol.* 2023 Feb 18;36(6):100143. doi: 10.1016/j.modpat.2023.100143. Epub ahead of print. PMID: 36806735.

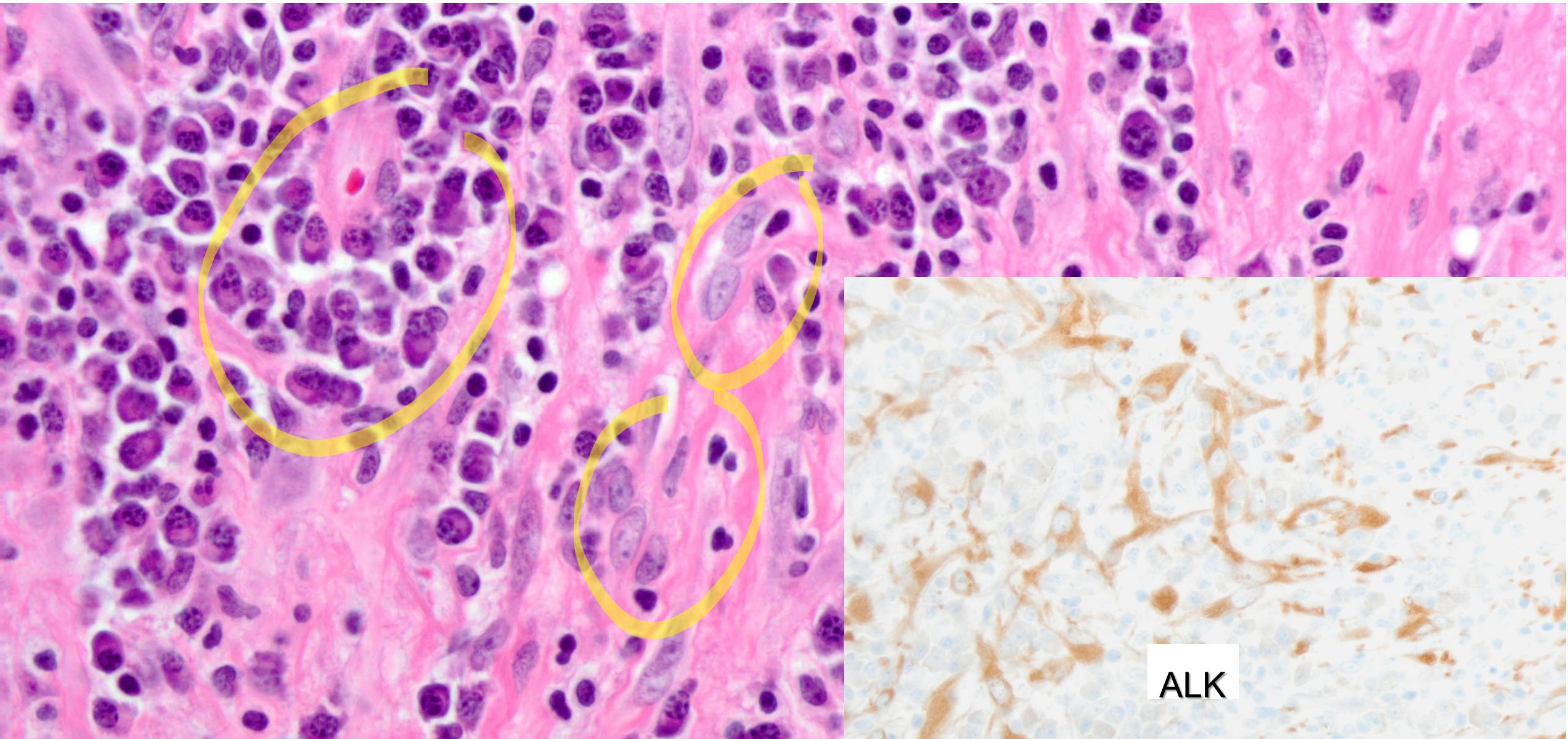


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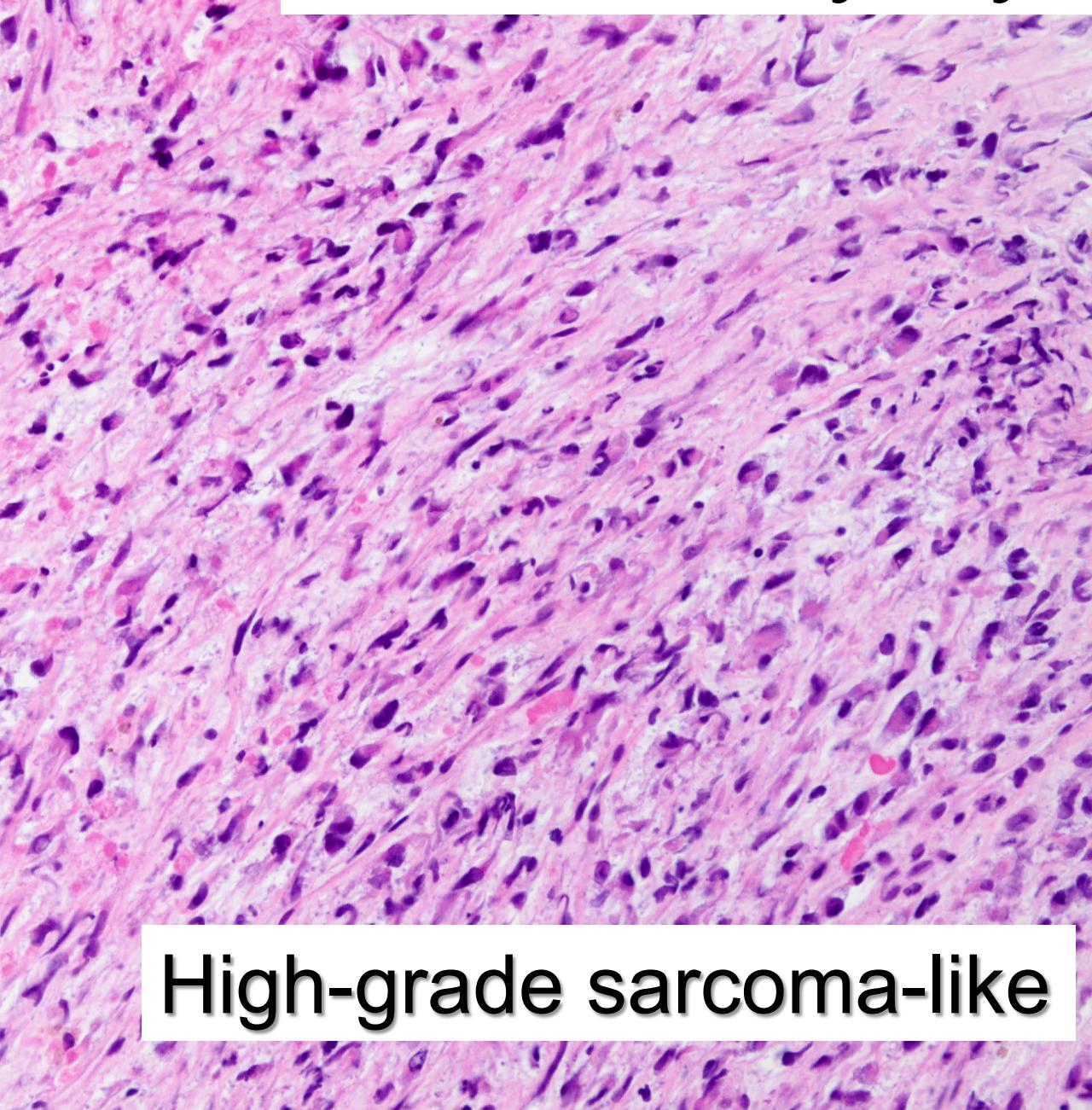
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(Super) Inflammatory myofibroblastic tumor

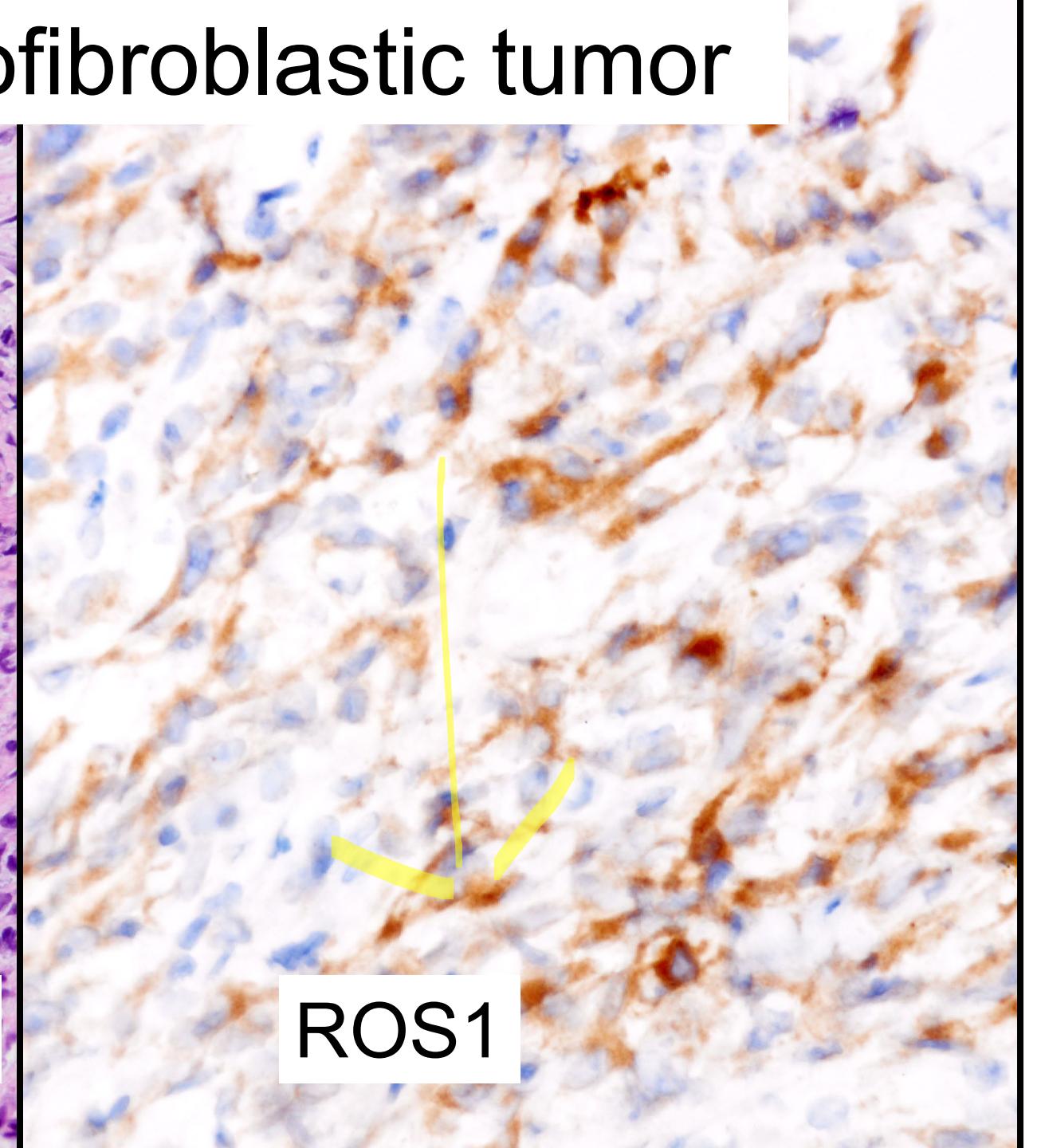


ALK

Inflammatory myofibroblastic tumor

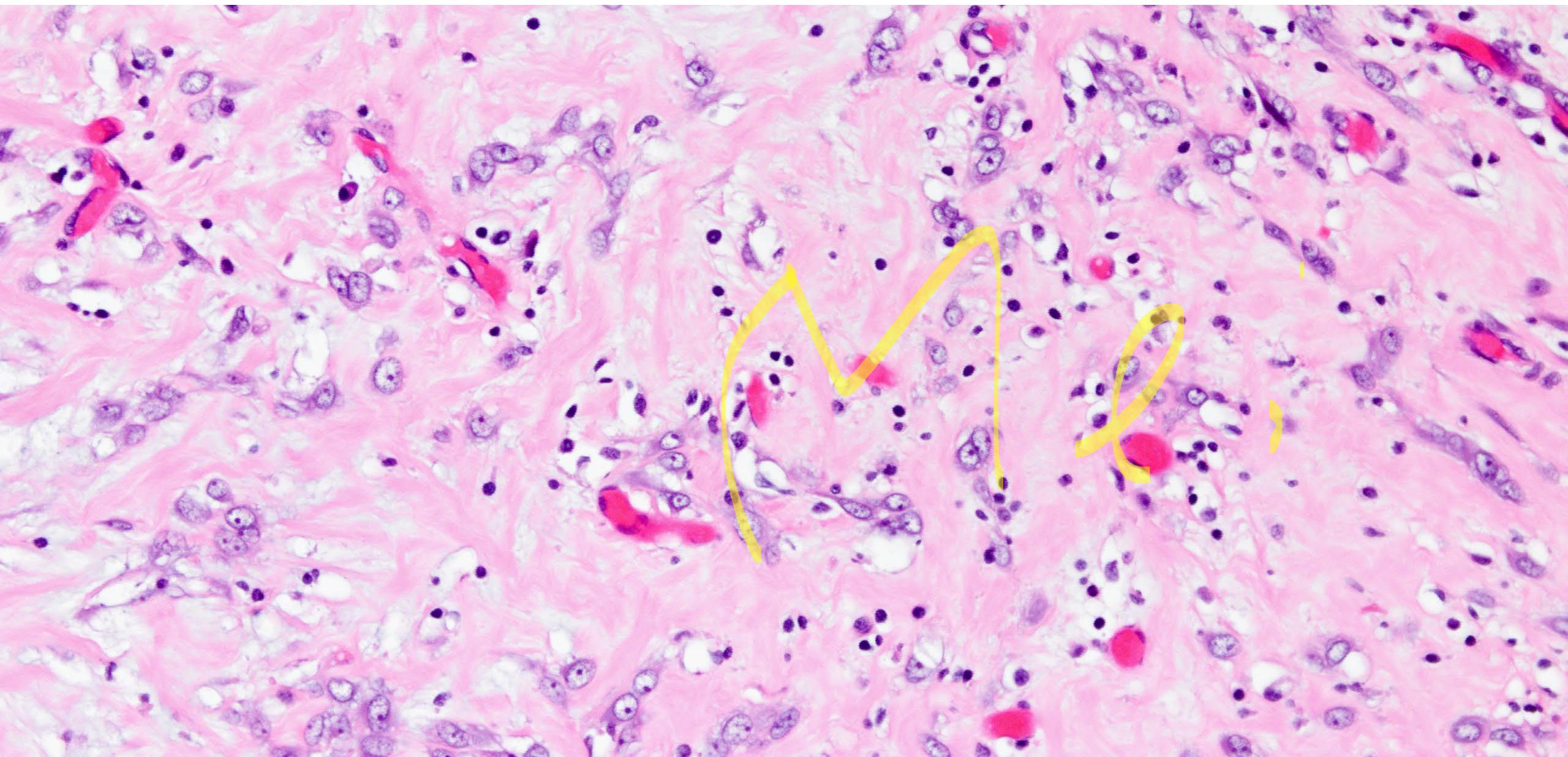


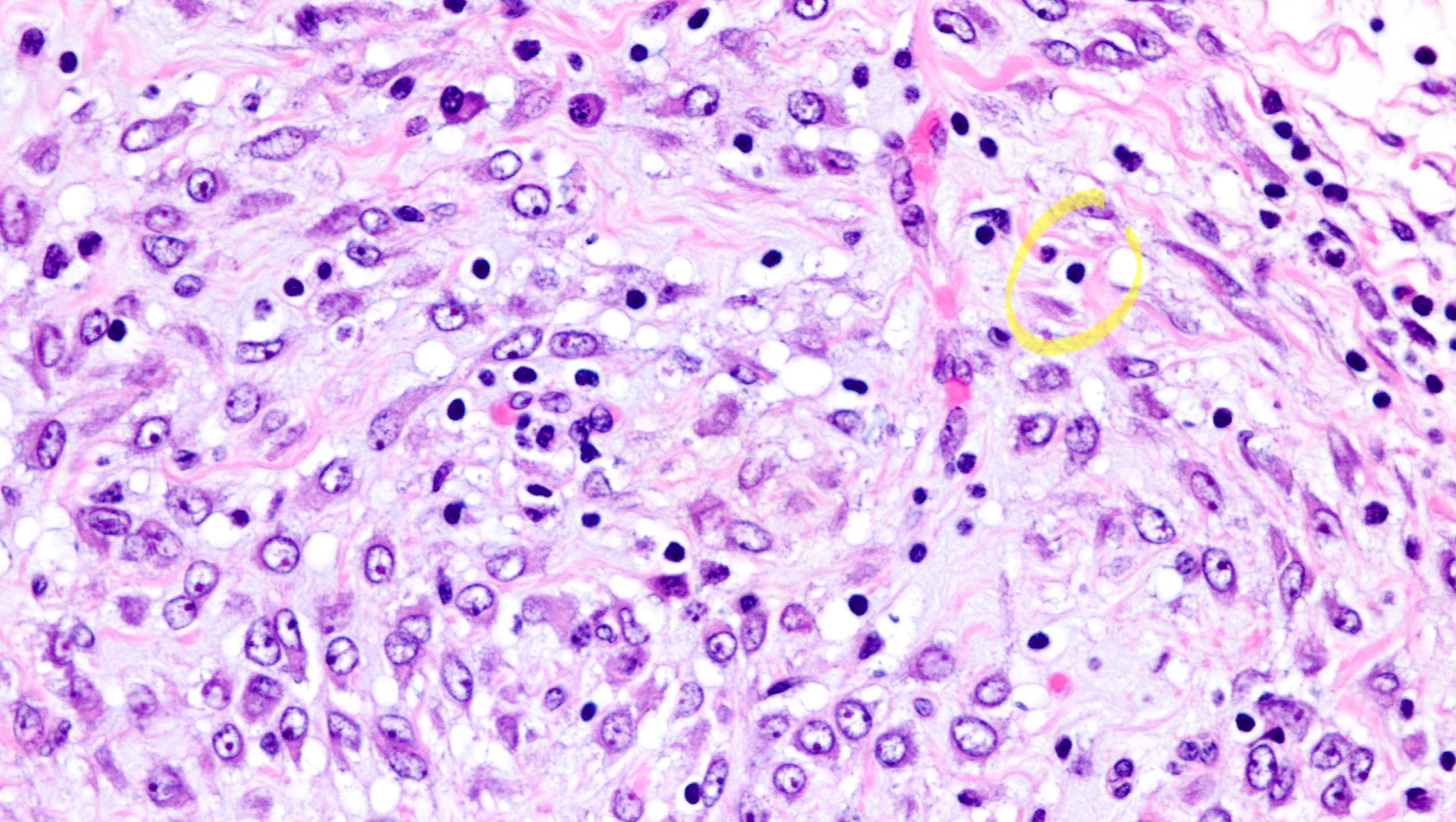
High-grade sarcoma-like

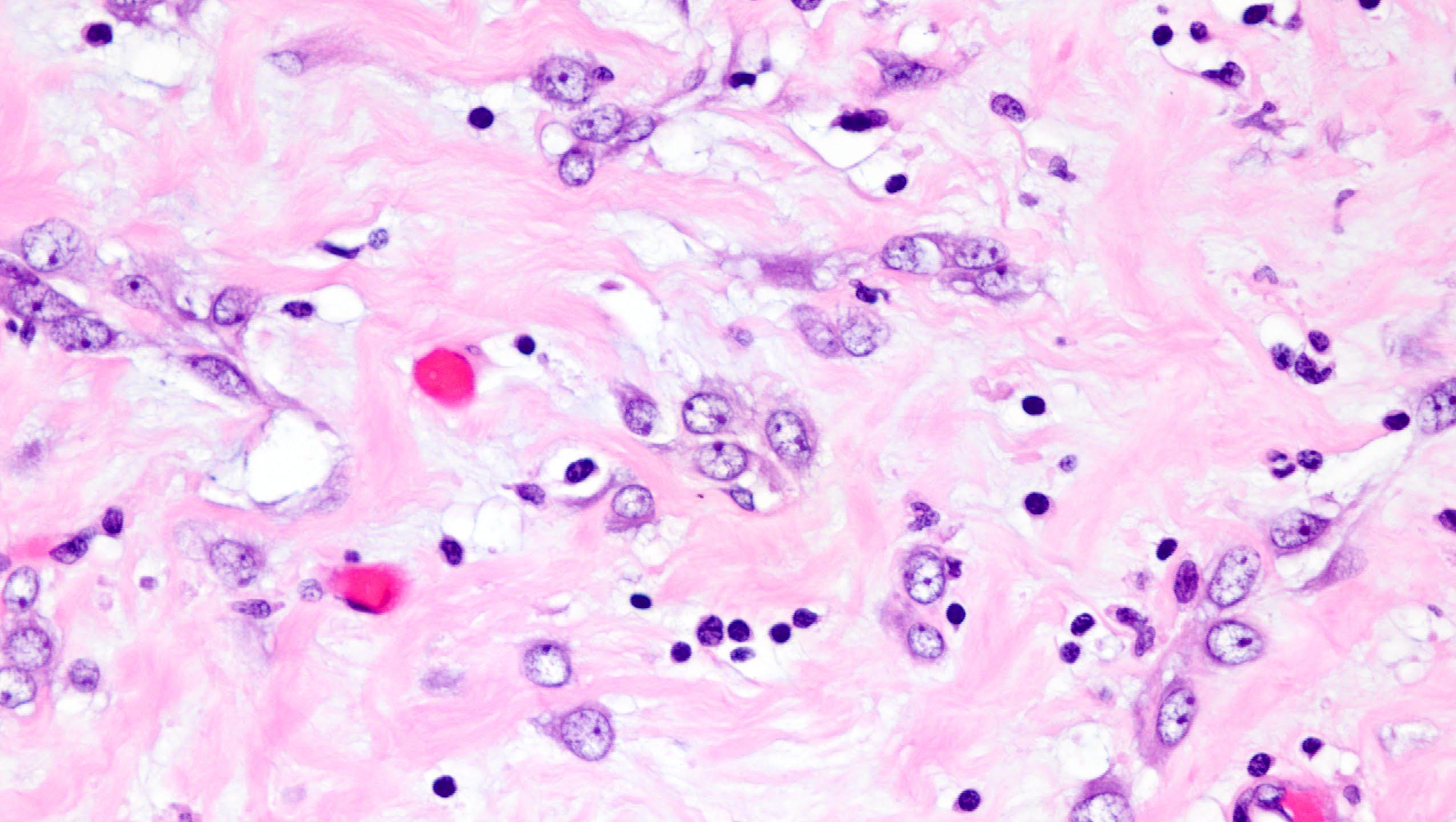


ROS1

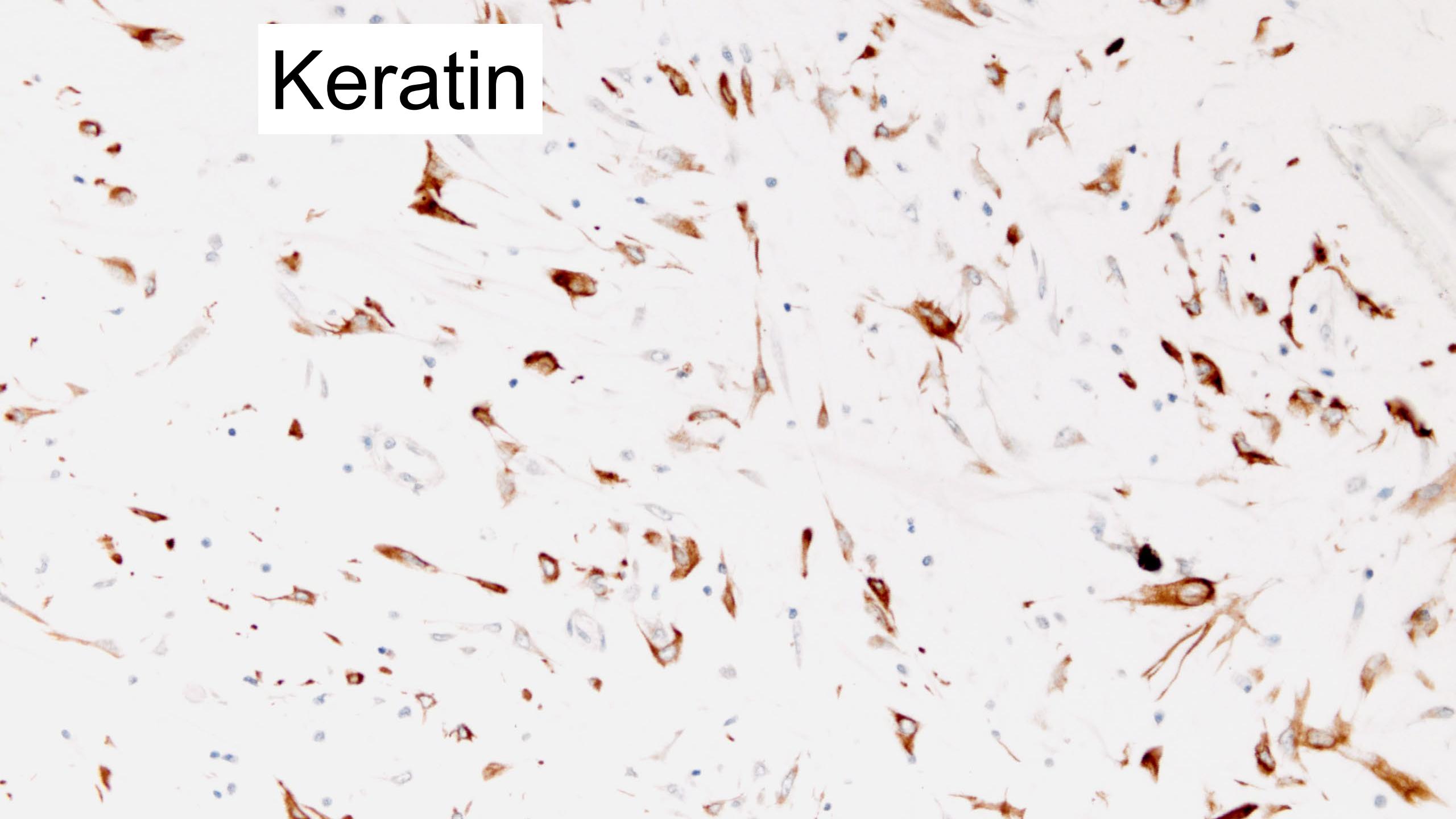
Epithelioid Inflammatory Myofibroblastic Tumor





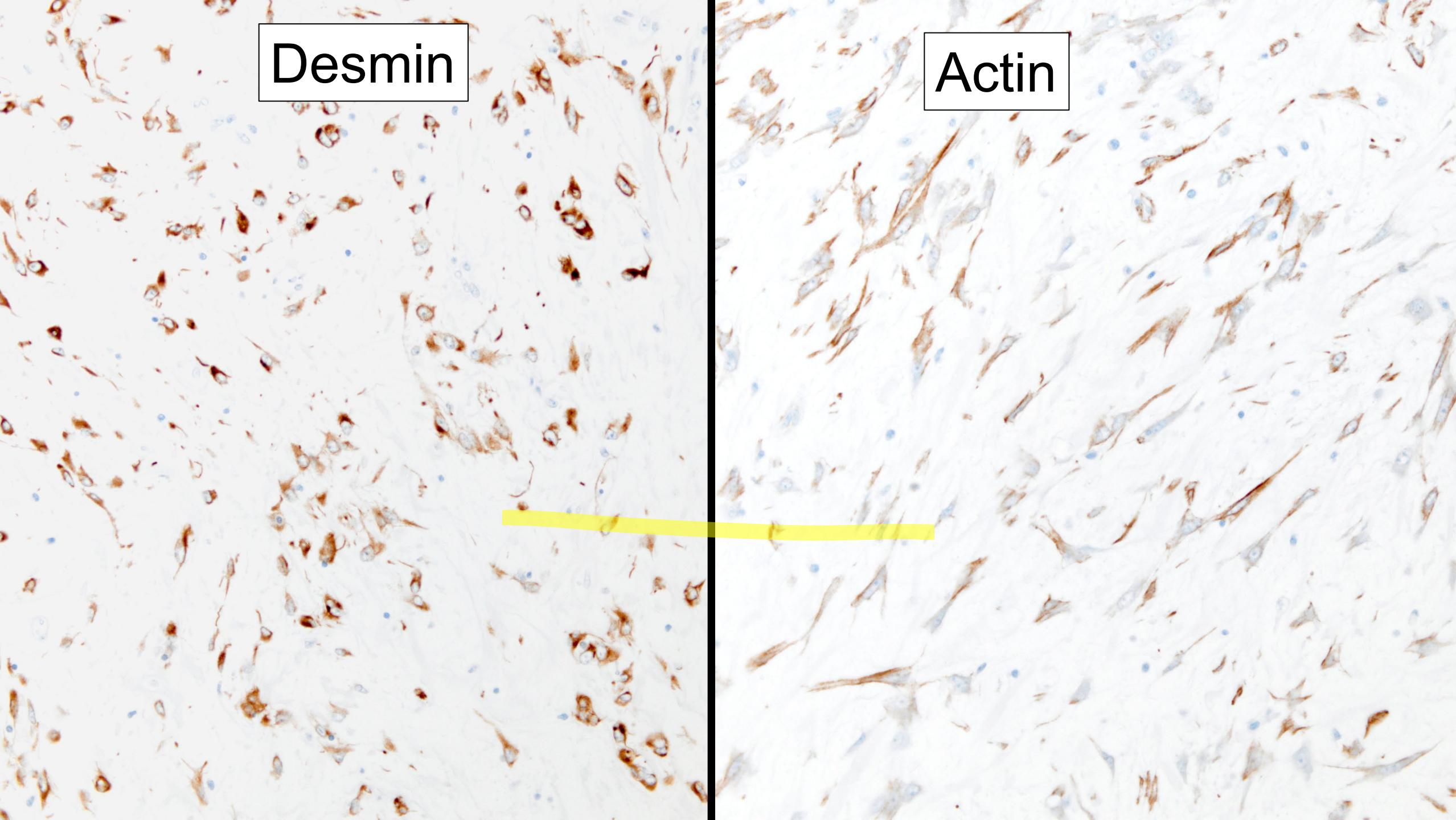


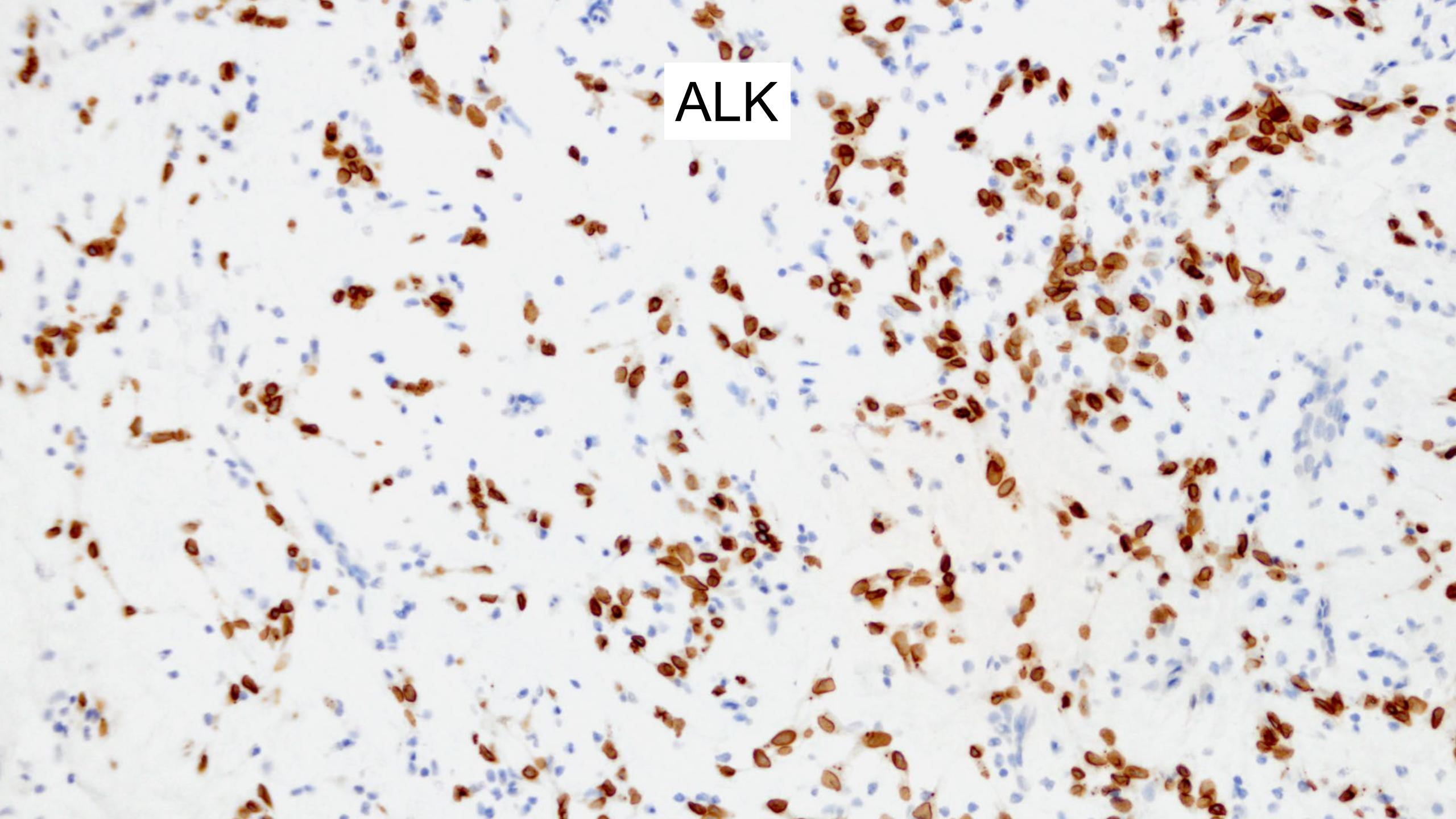
Keratin



Desmin

Actin





ALK



Epithelioid IMT

- Wide age range
- Male predominance
- Intraabdominal predominance
- Epithelioid phenotype, myxoid stroma
- Desmin positive
- ALK+ perinuclear reactivity
- *RANBP2-ALK* fusion
- Aggressive biology



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Genetic change in IMT

Therapy

ALK-1

Crizotinib

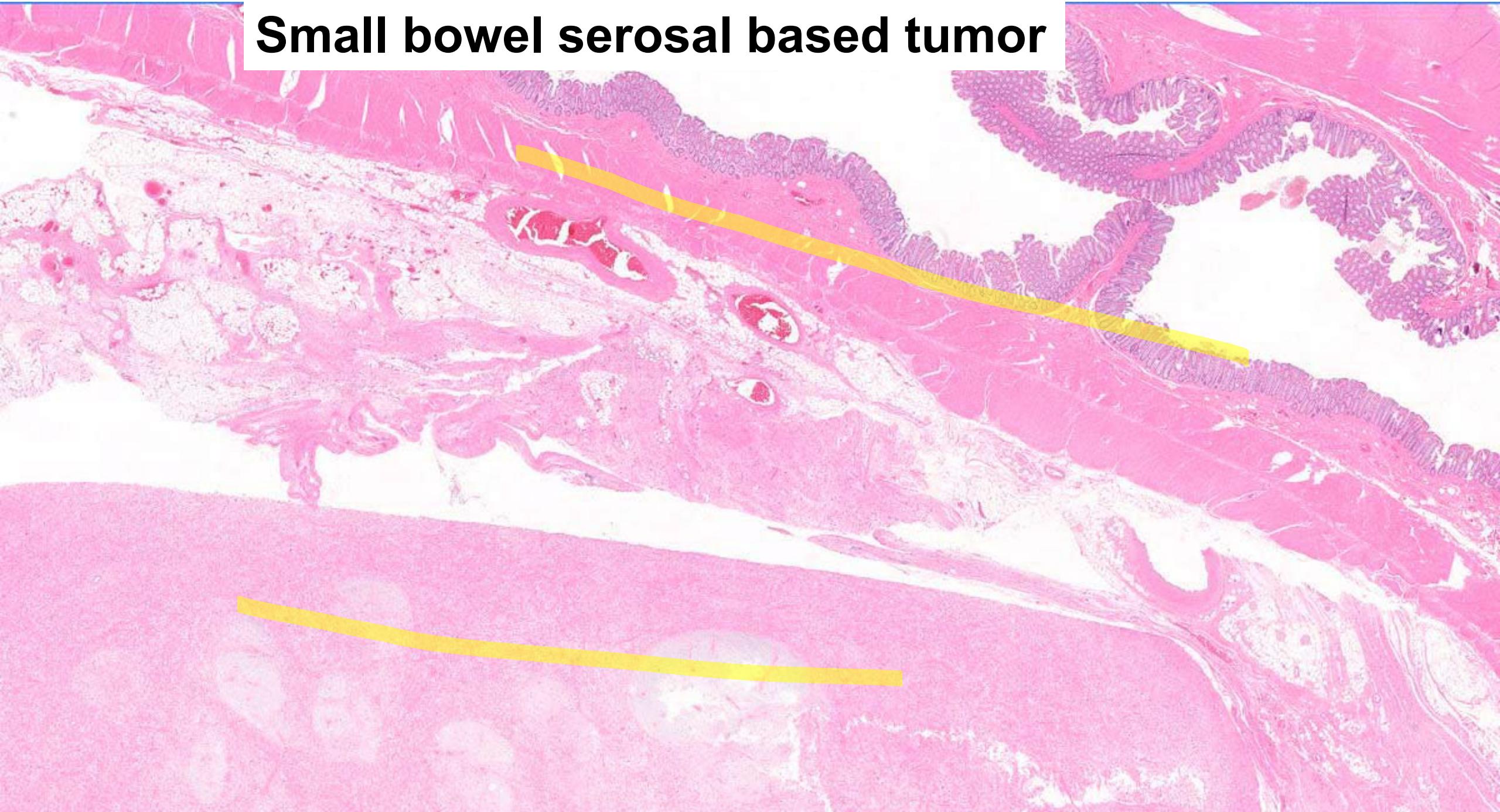
ROS1

Crizotinib

NTRK

Iarotrectinib

Small bowel serosal based tumor

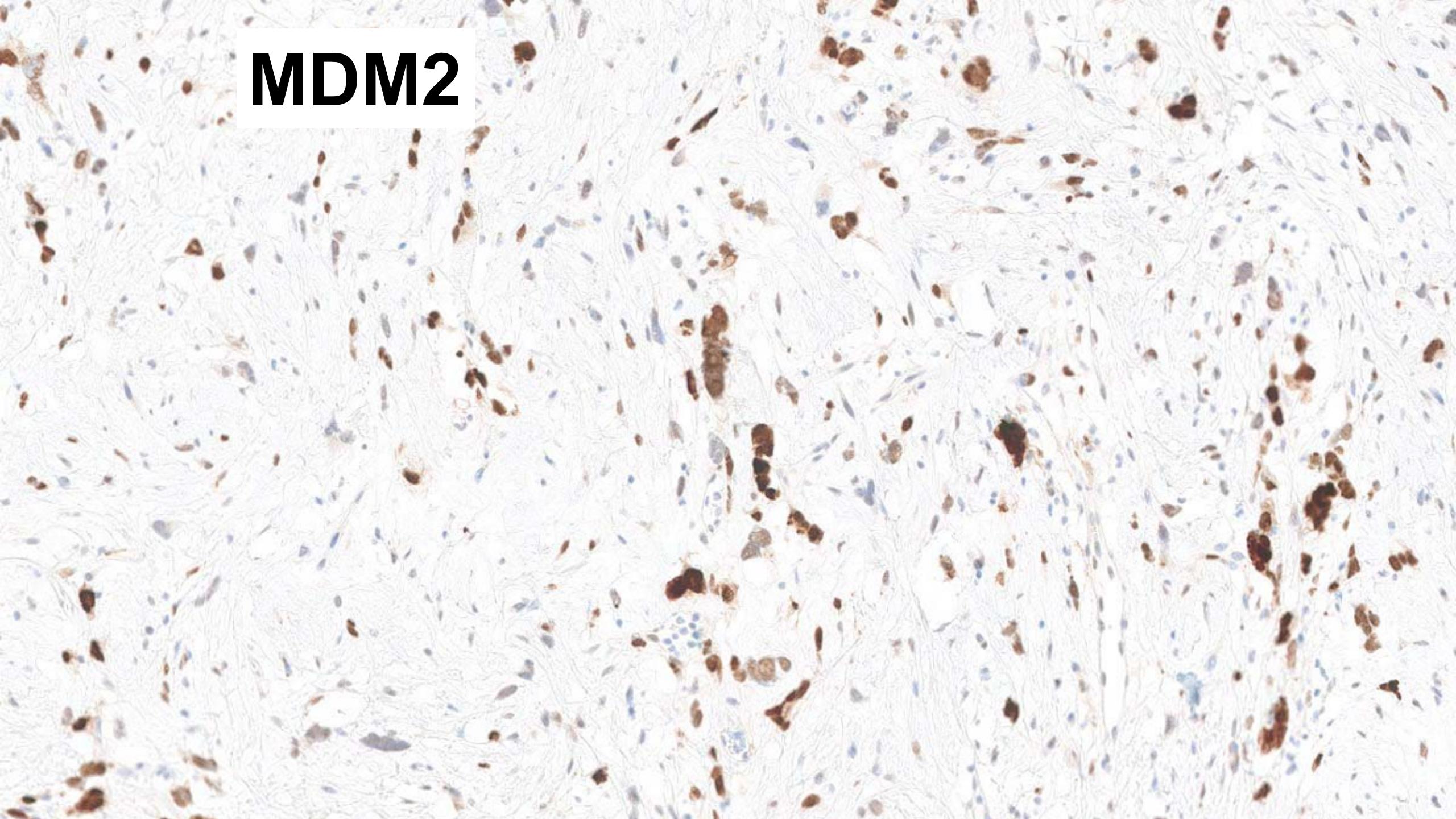


High grade sarcoma



Dedifferentiated liposarcomas

MDM2



Lesson I've learnt

All intra-abdominal high-grade
sarcomas represent
dedifferentiated liposarcomas

Until proven otherwise

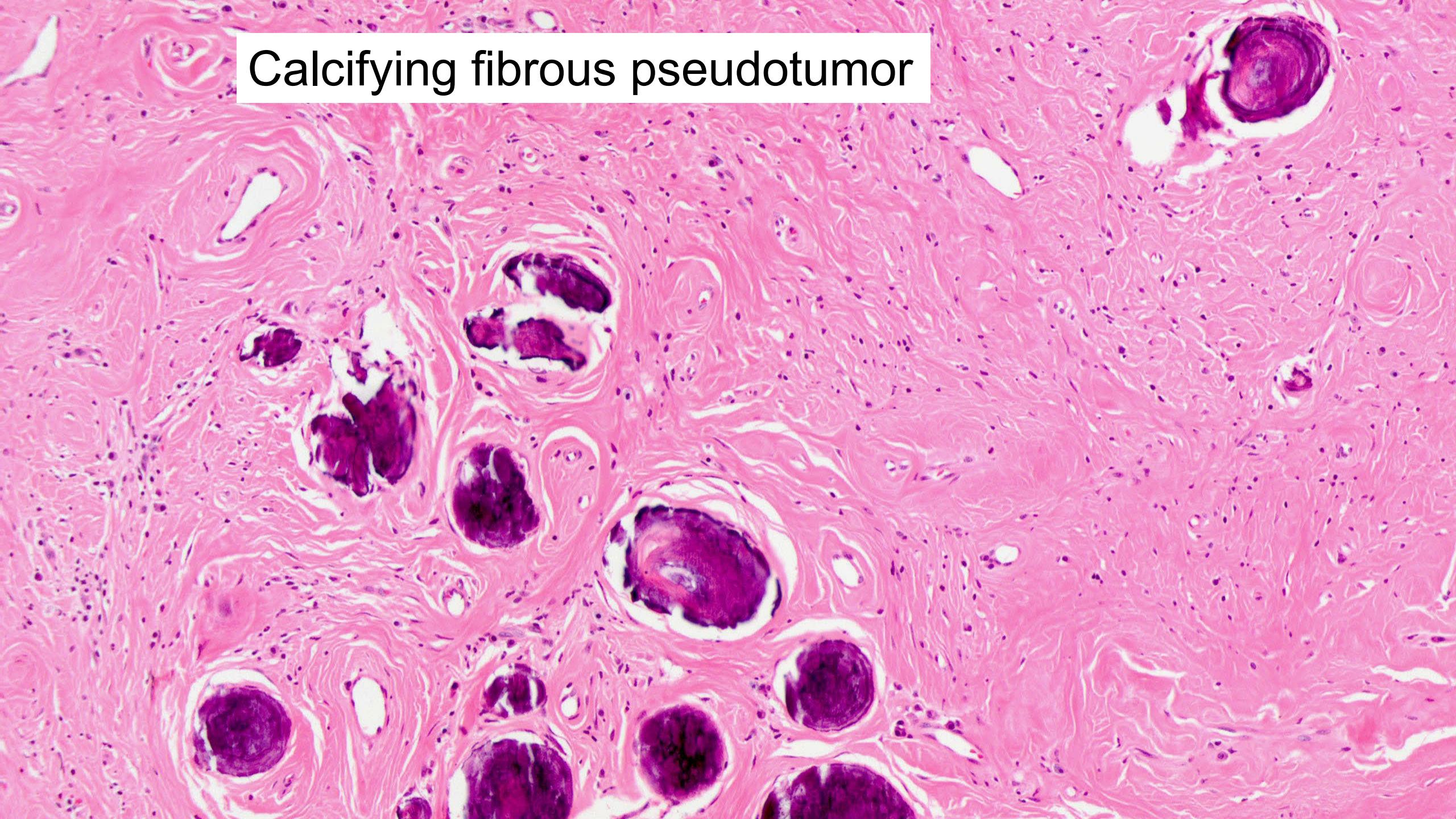


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Calcifying fibrous pseudotumor



Muscularis Propria

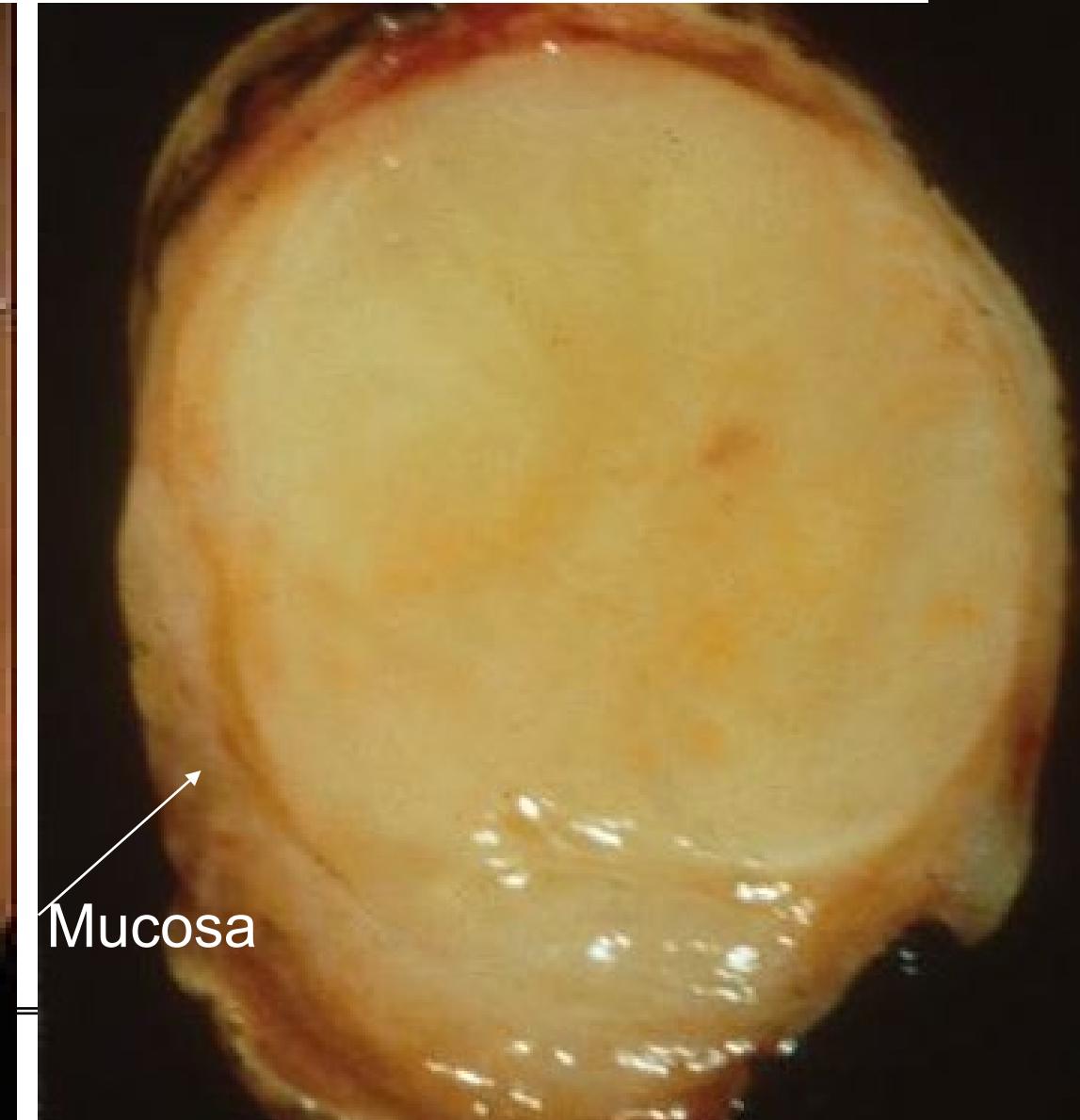


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HARVARD
MEDICAL SCHOOL

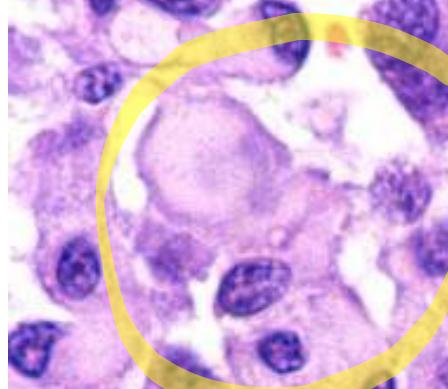
Gastrointestinal Stromal Tumor



Gastrointestinal Stromal Tumor



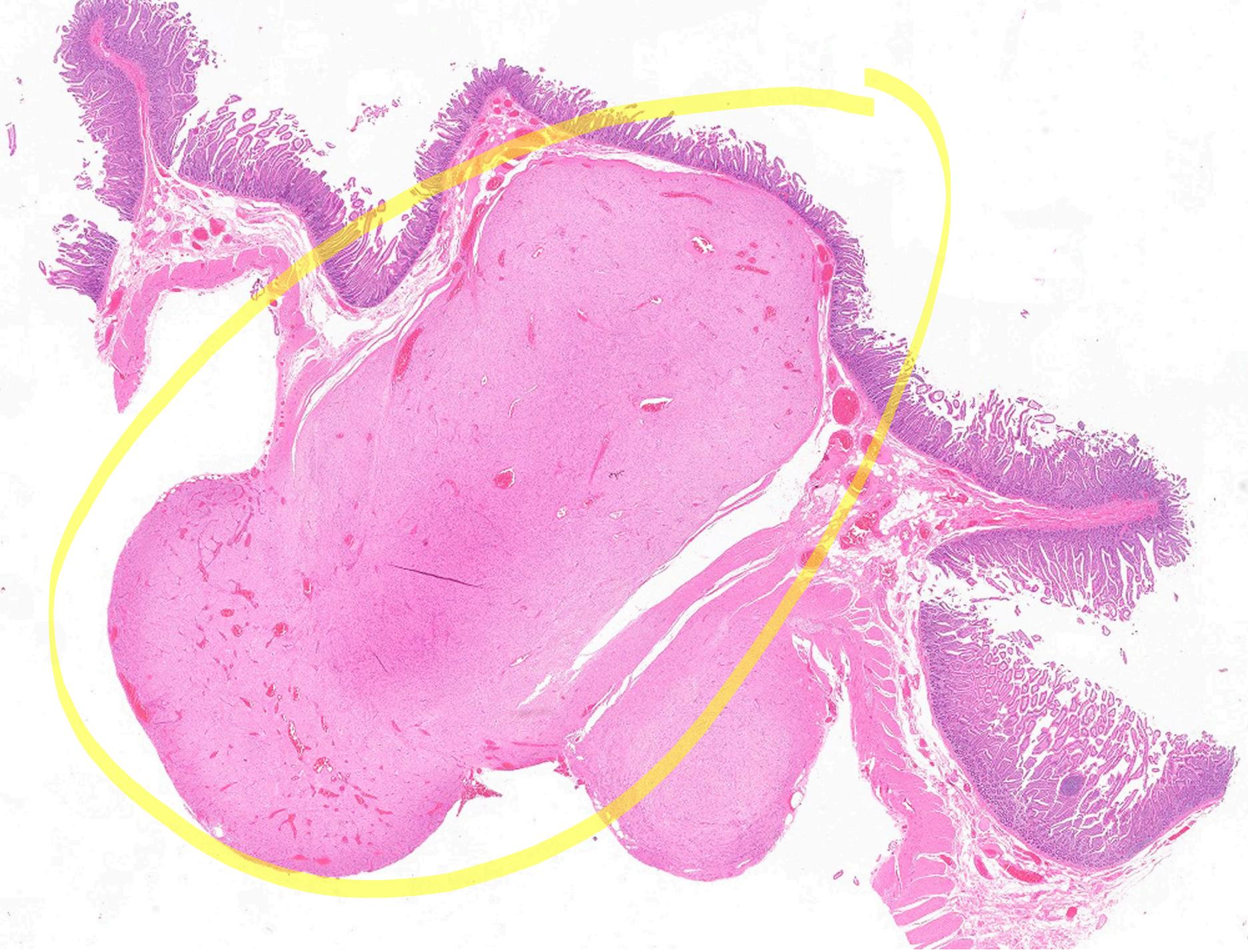
Spindle cell 70%



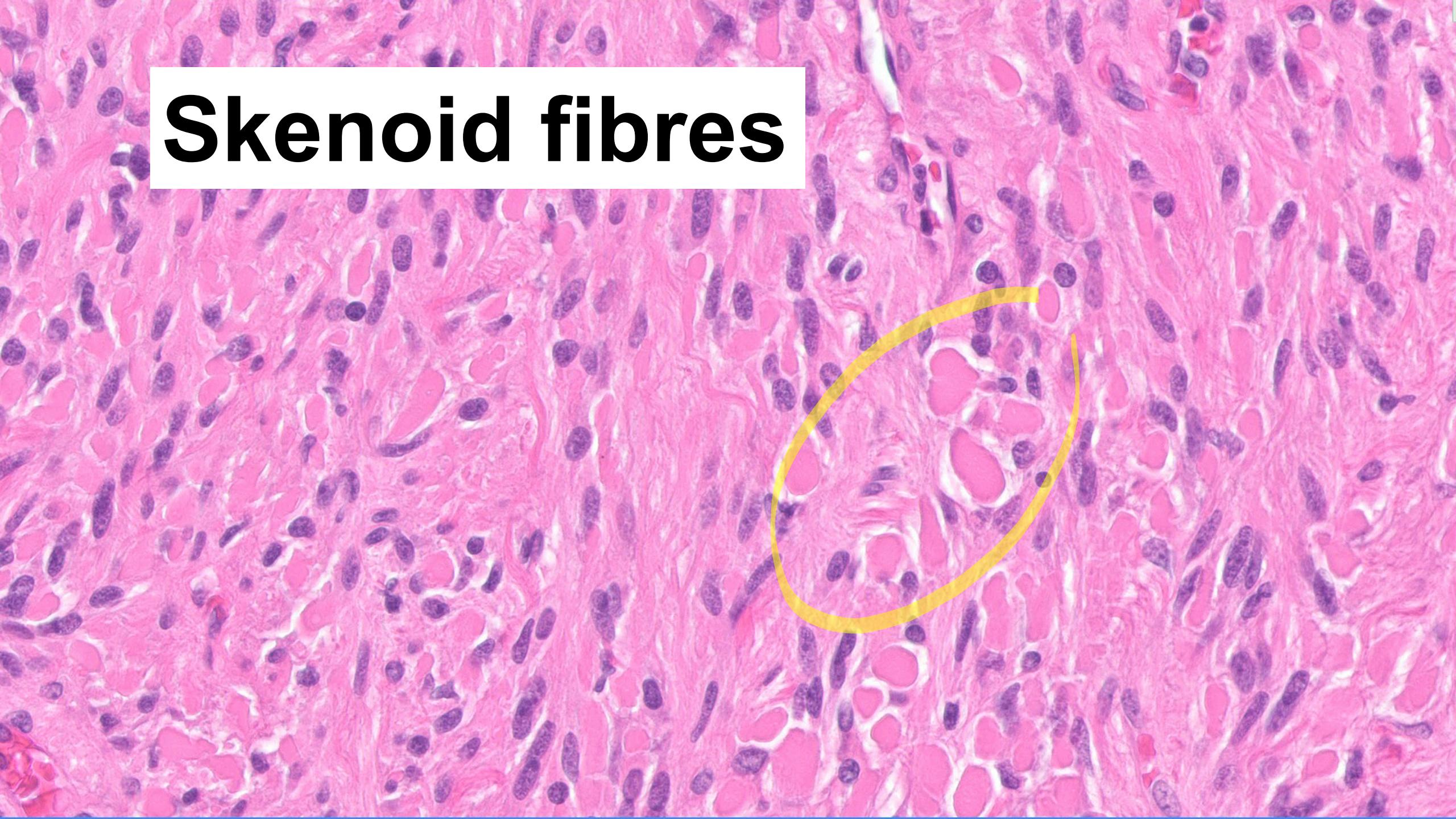
Epithelioid 20%

GIST

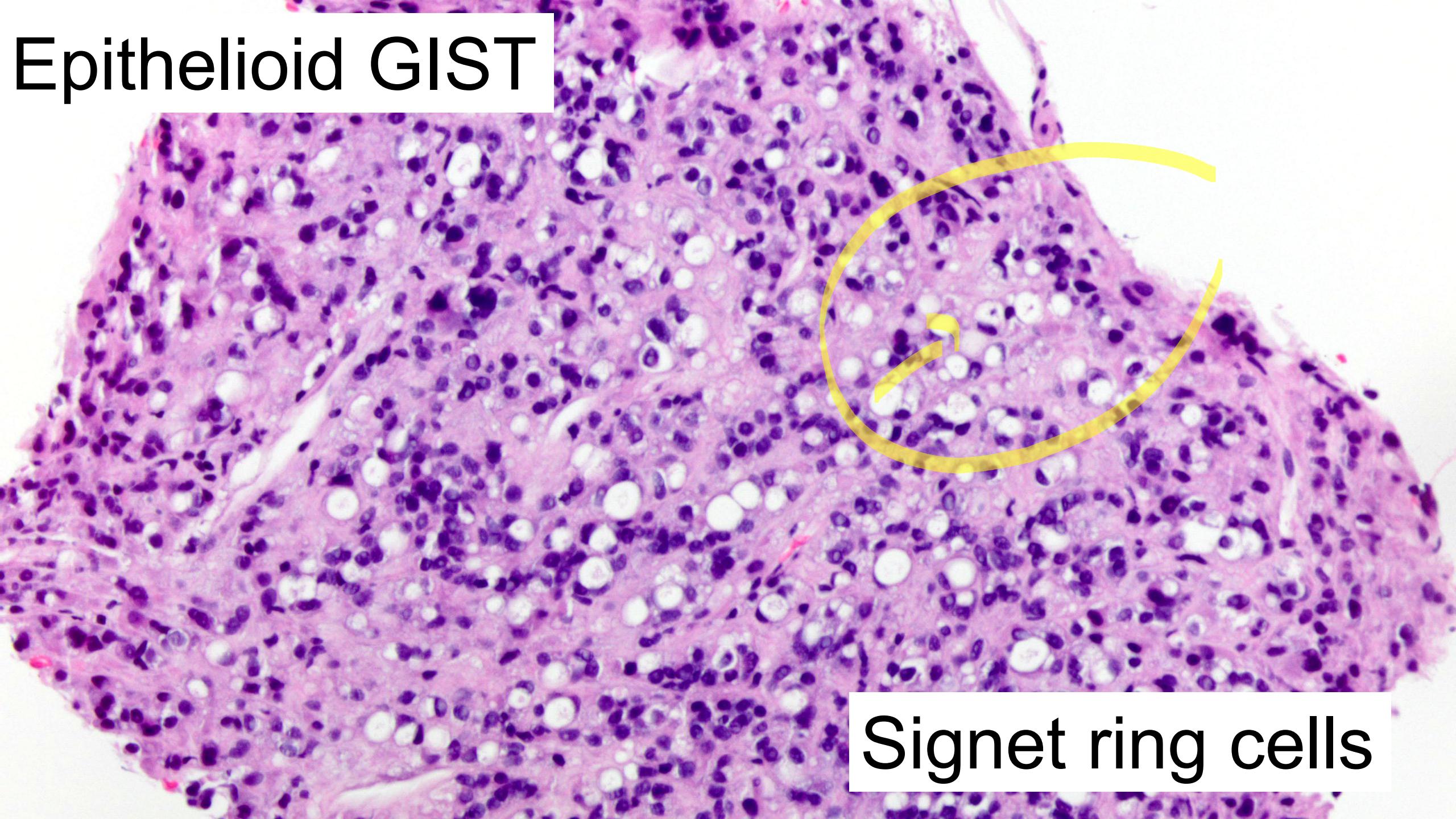




Skenoid fibres

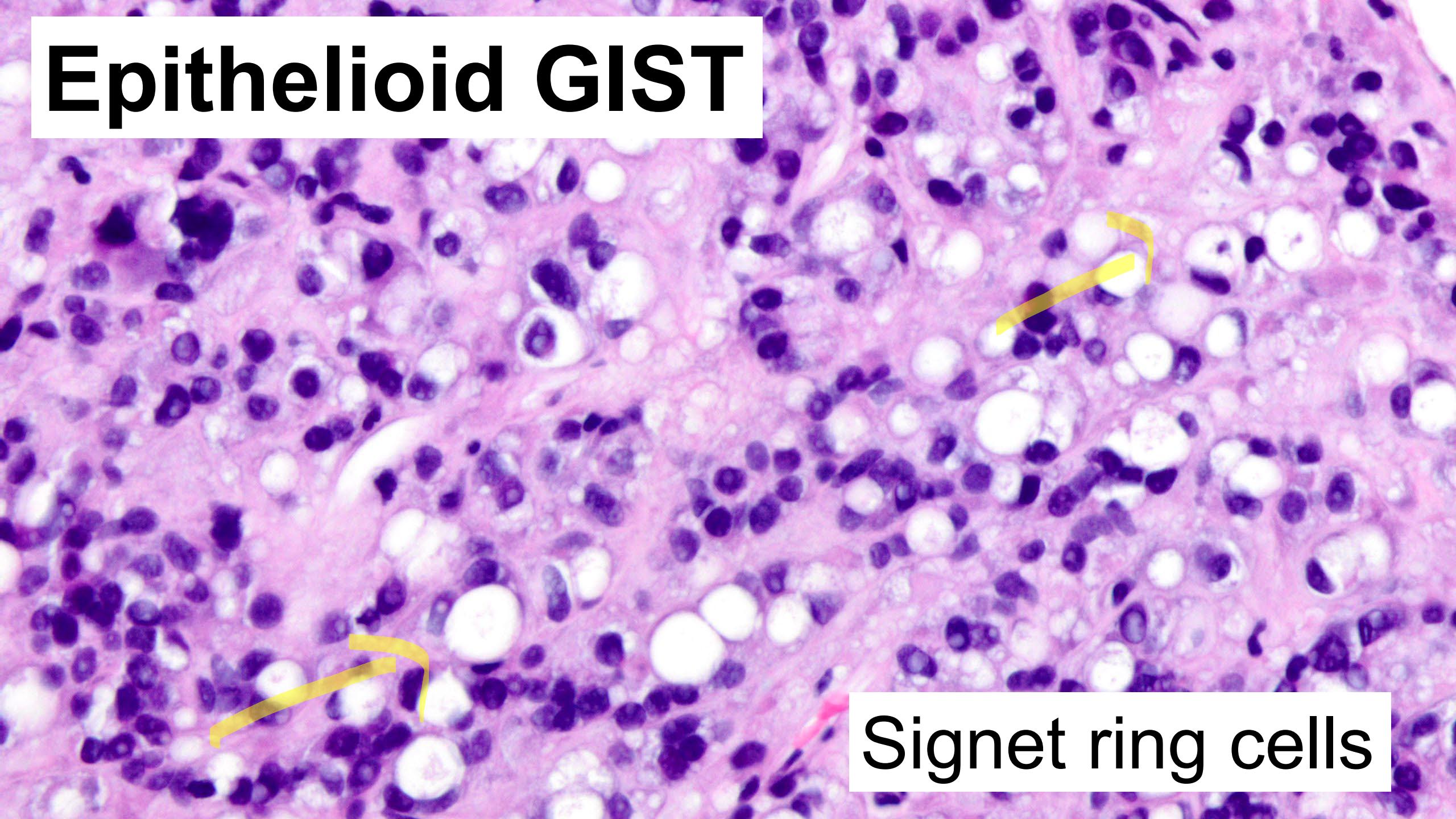


Epithelioid GIST

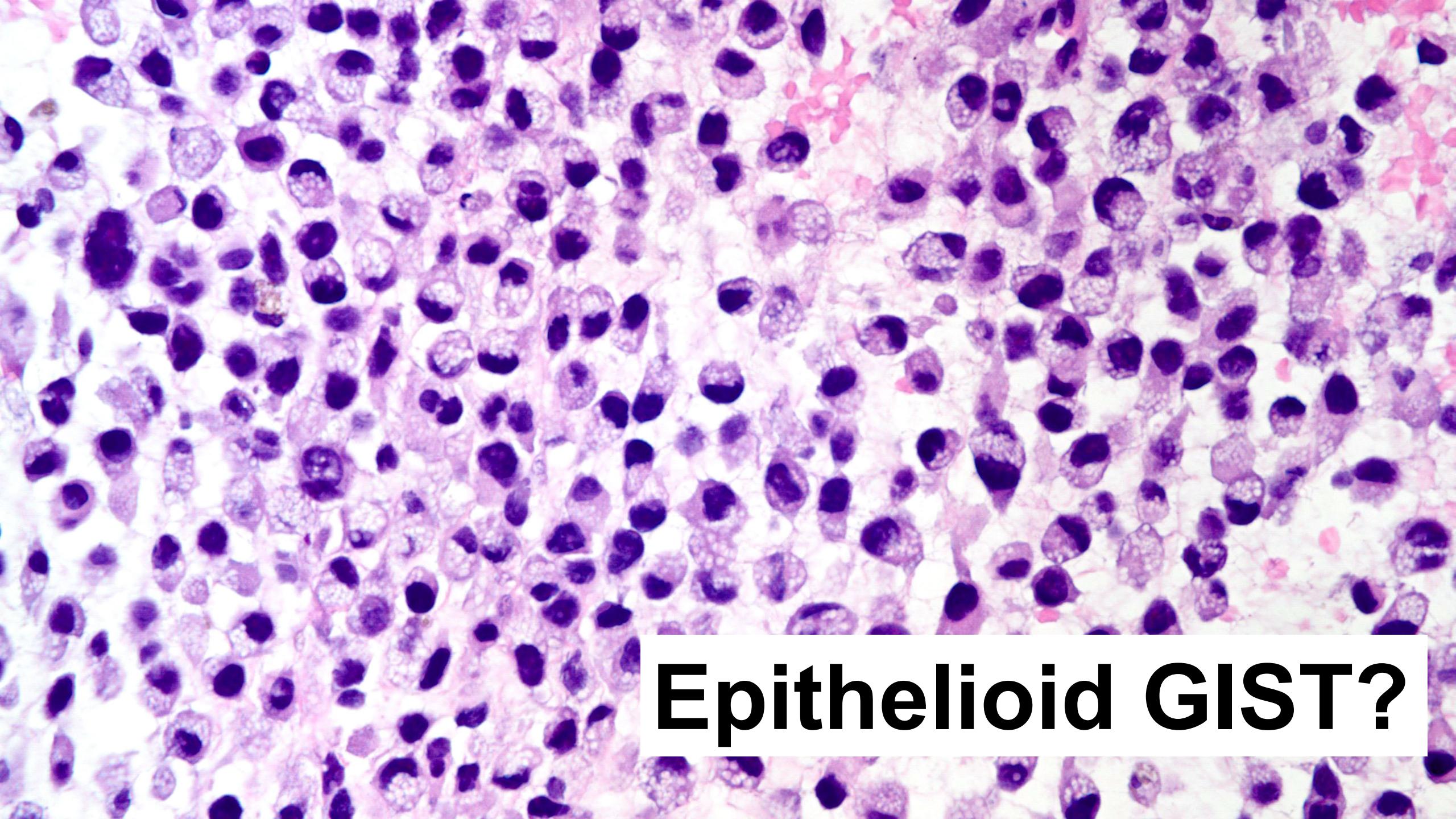


Signet ring cells

Epithelioid GIST



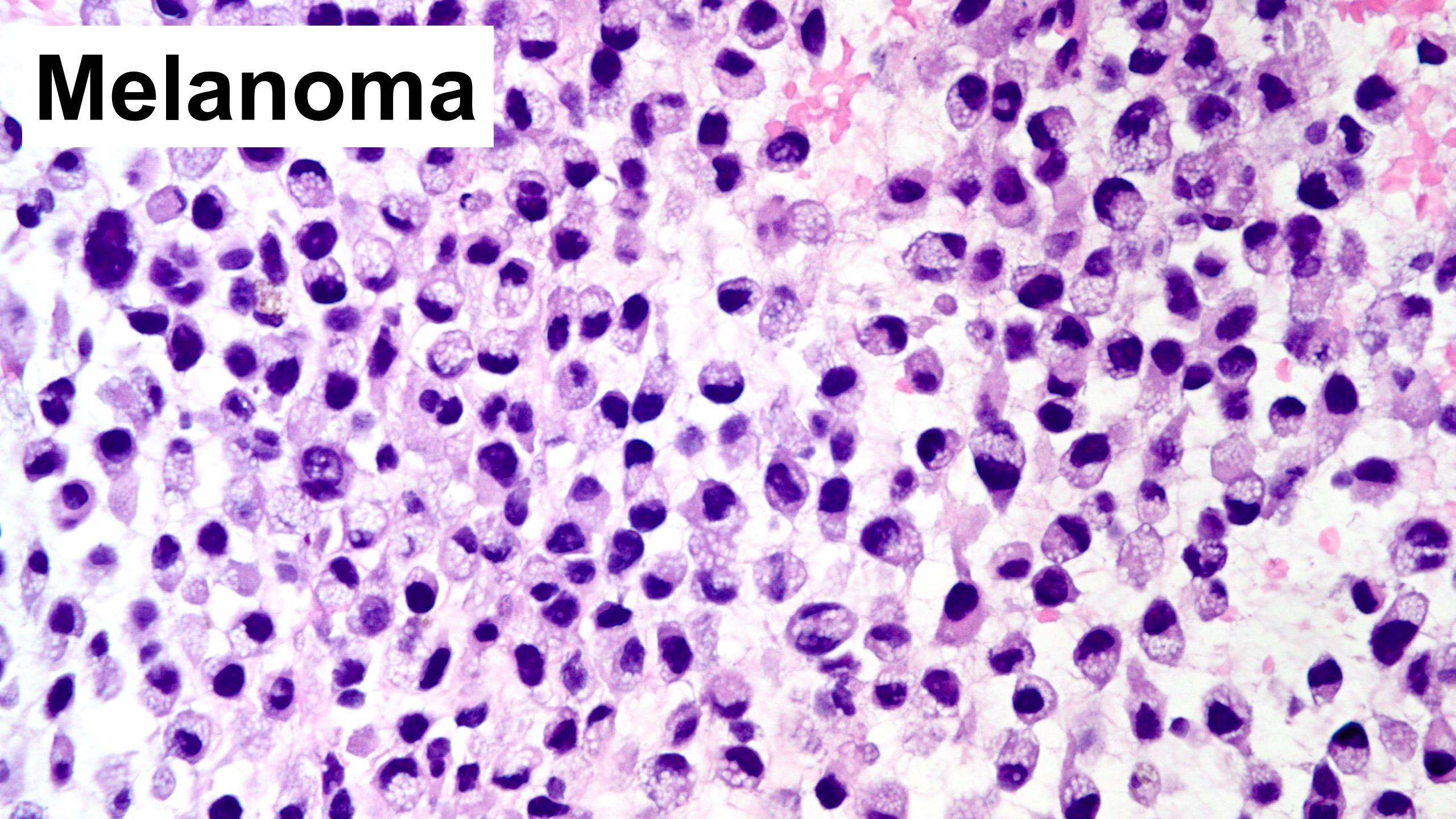
Signet ring cells



Epithelioid GIST?



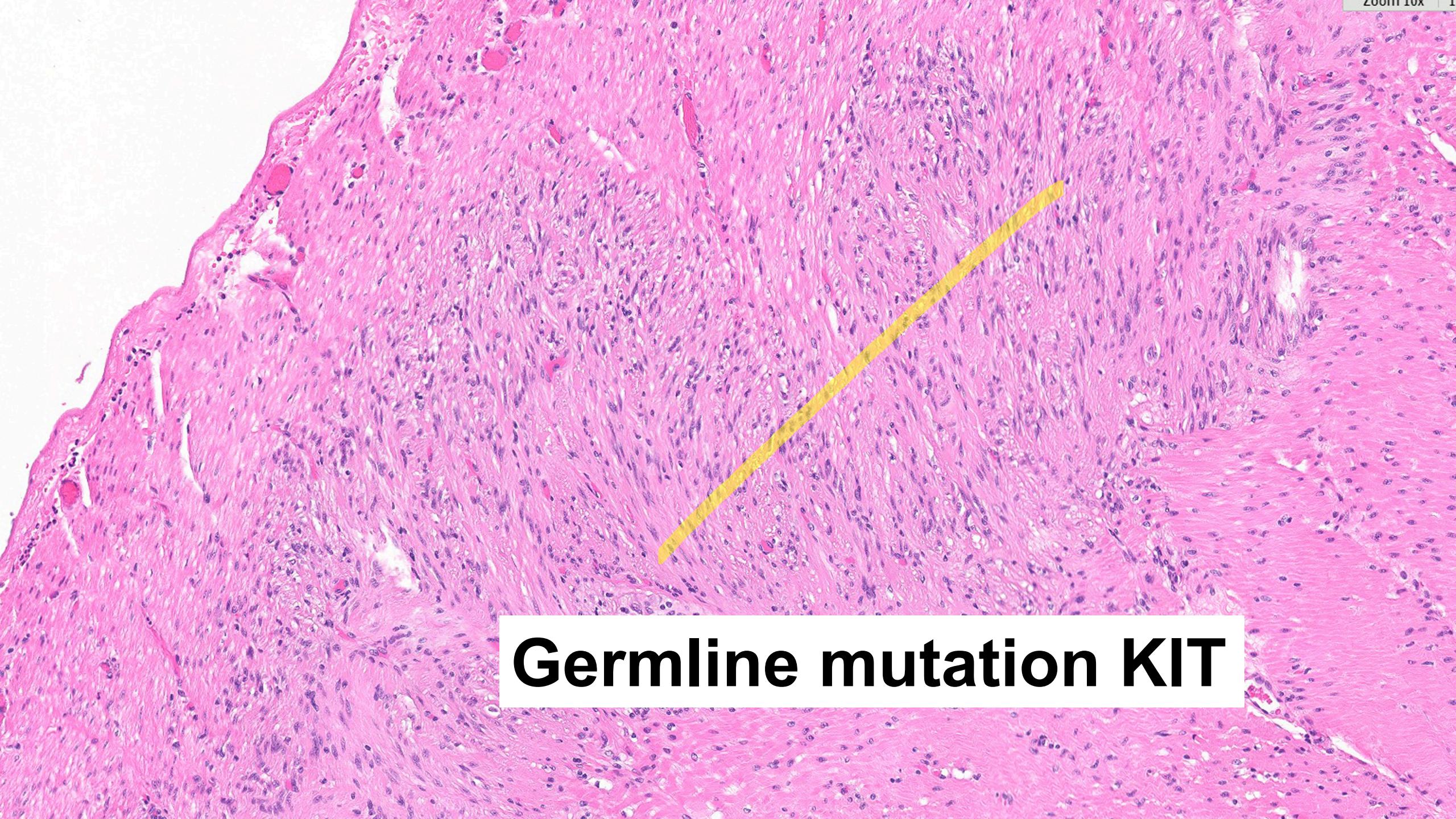
Melanoma



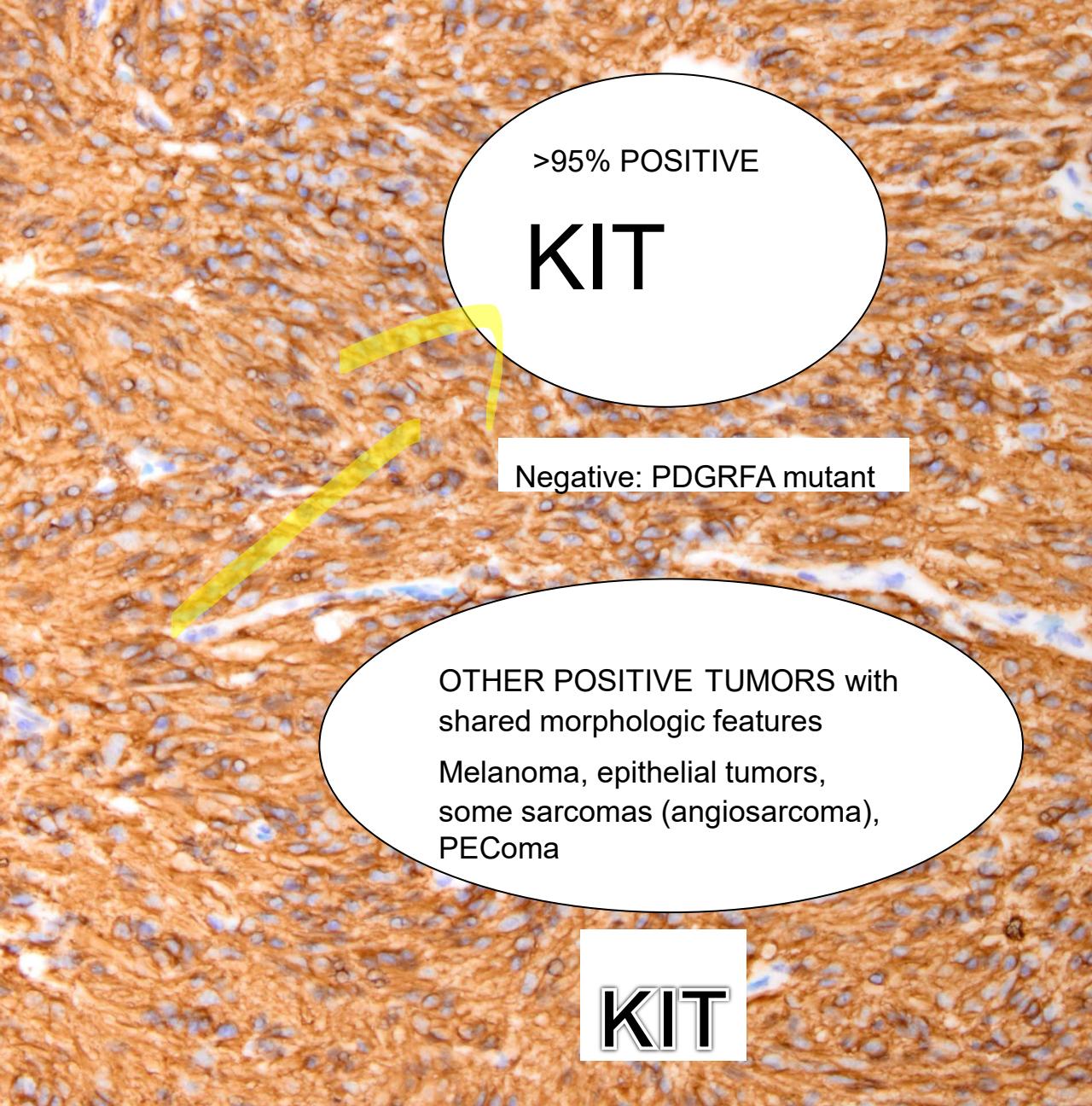
Young person





A histological slide showing a tissue sample with a yellow arrow pointing to a specific area. The tissue is stained pink and purple, and the arrow points to a cluster of cells.

Germline mutation KIT



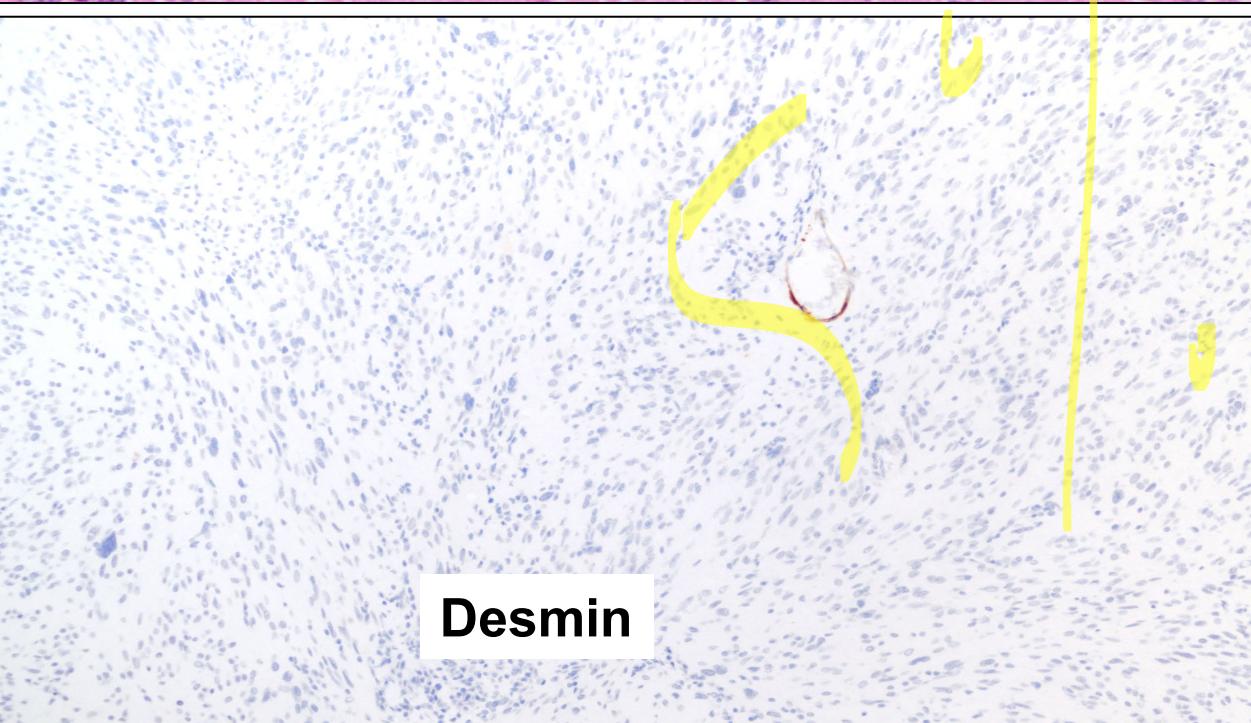
GIST



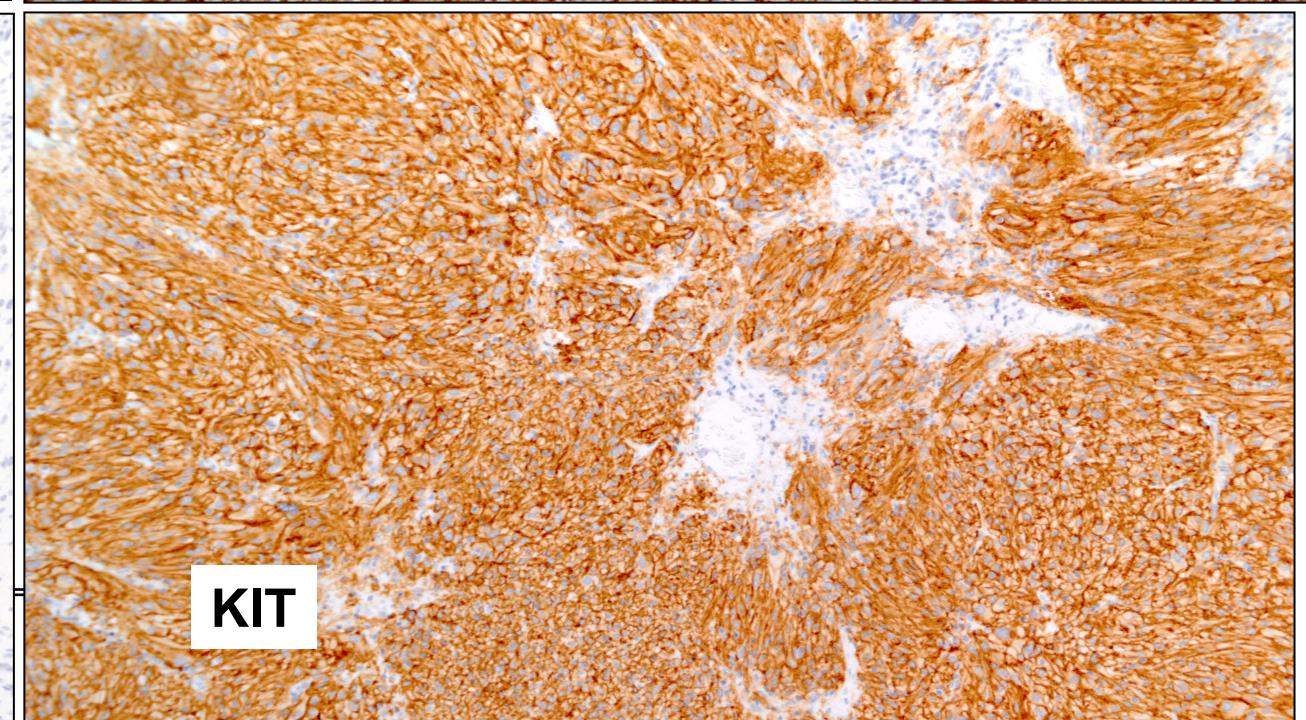
Smooth Muscle Actin

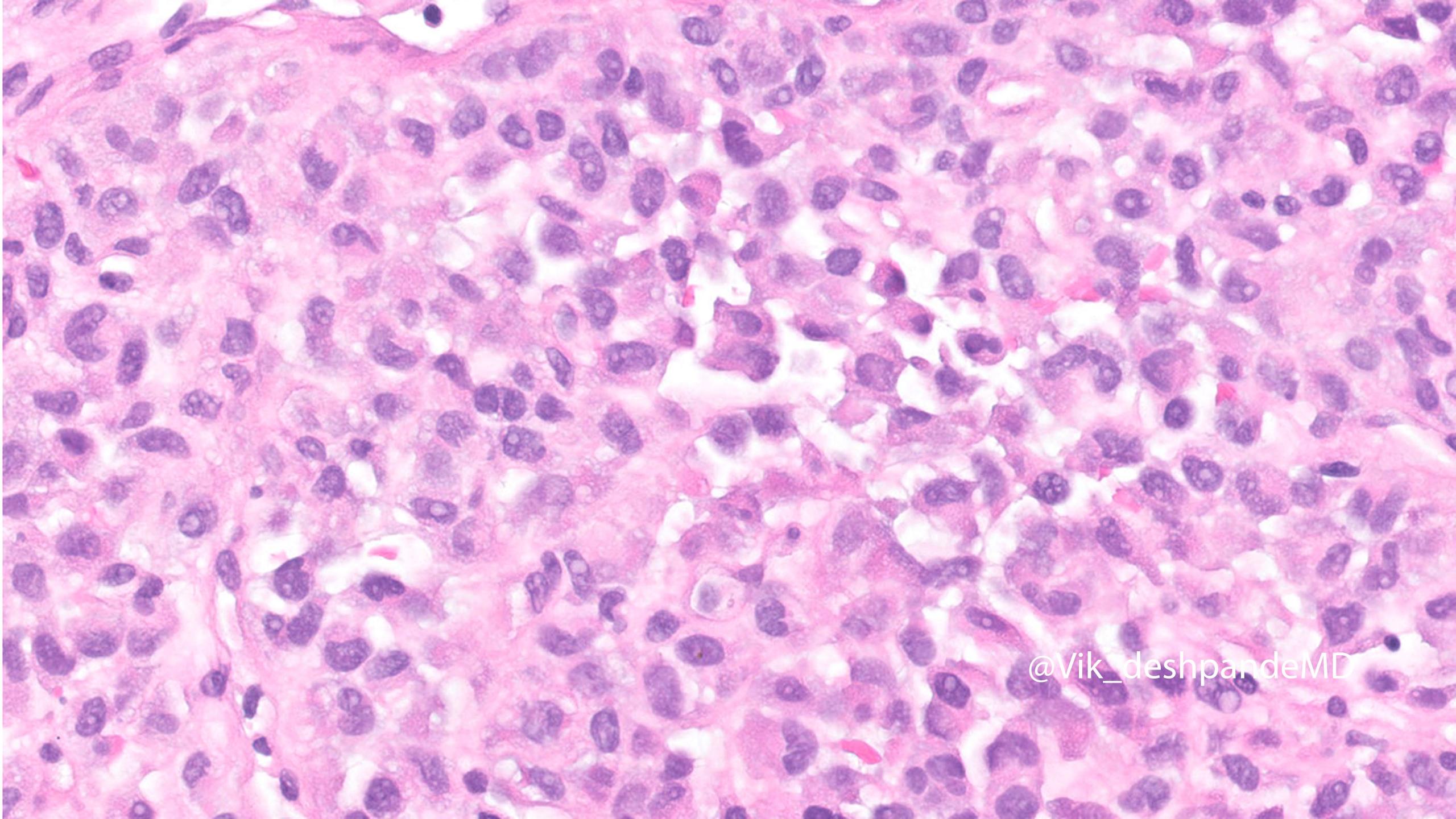


Desmin

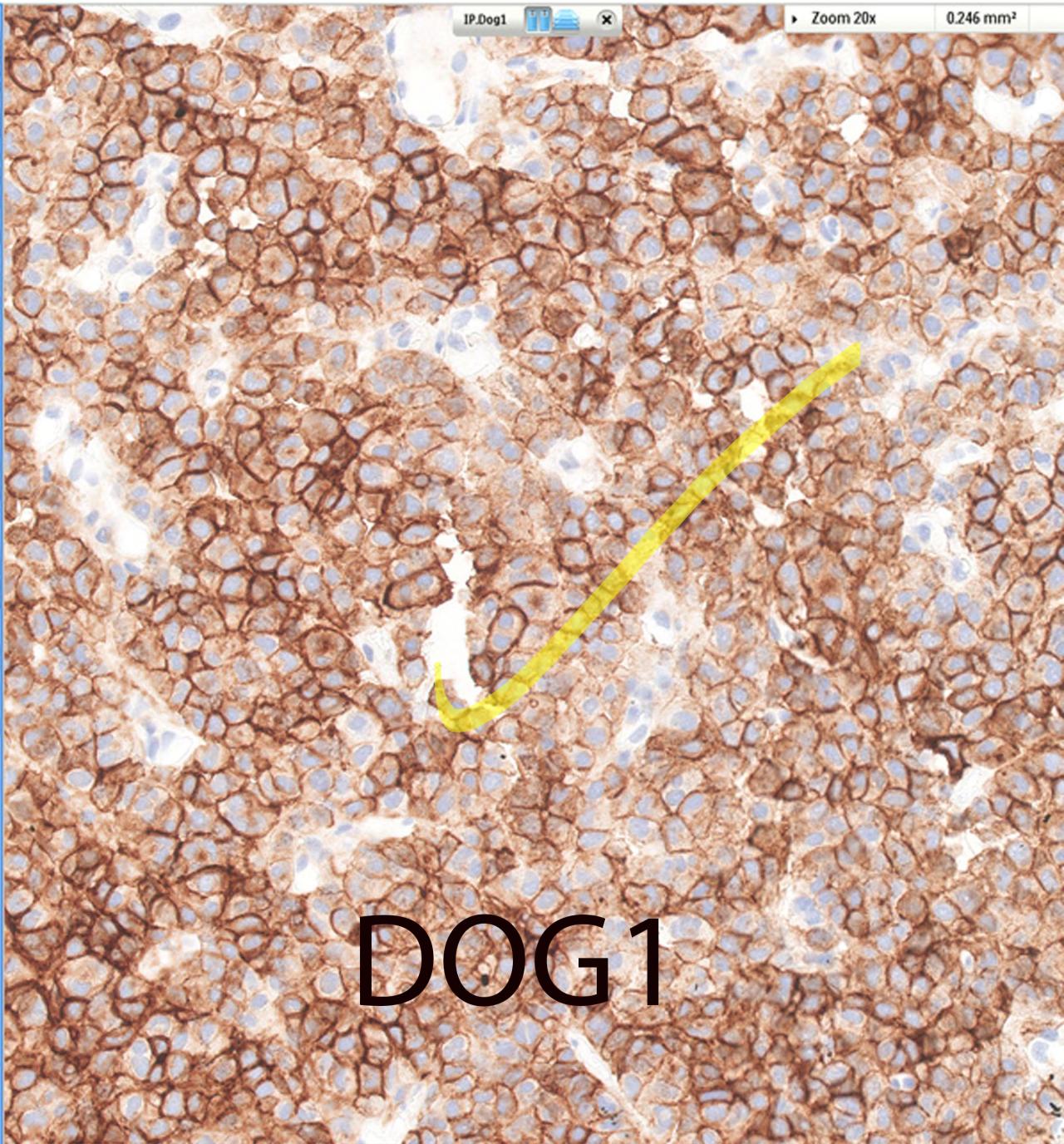
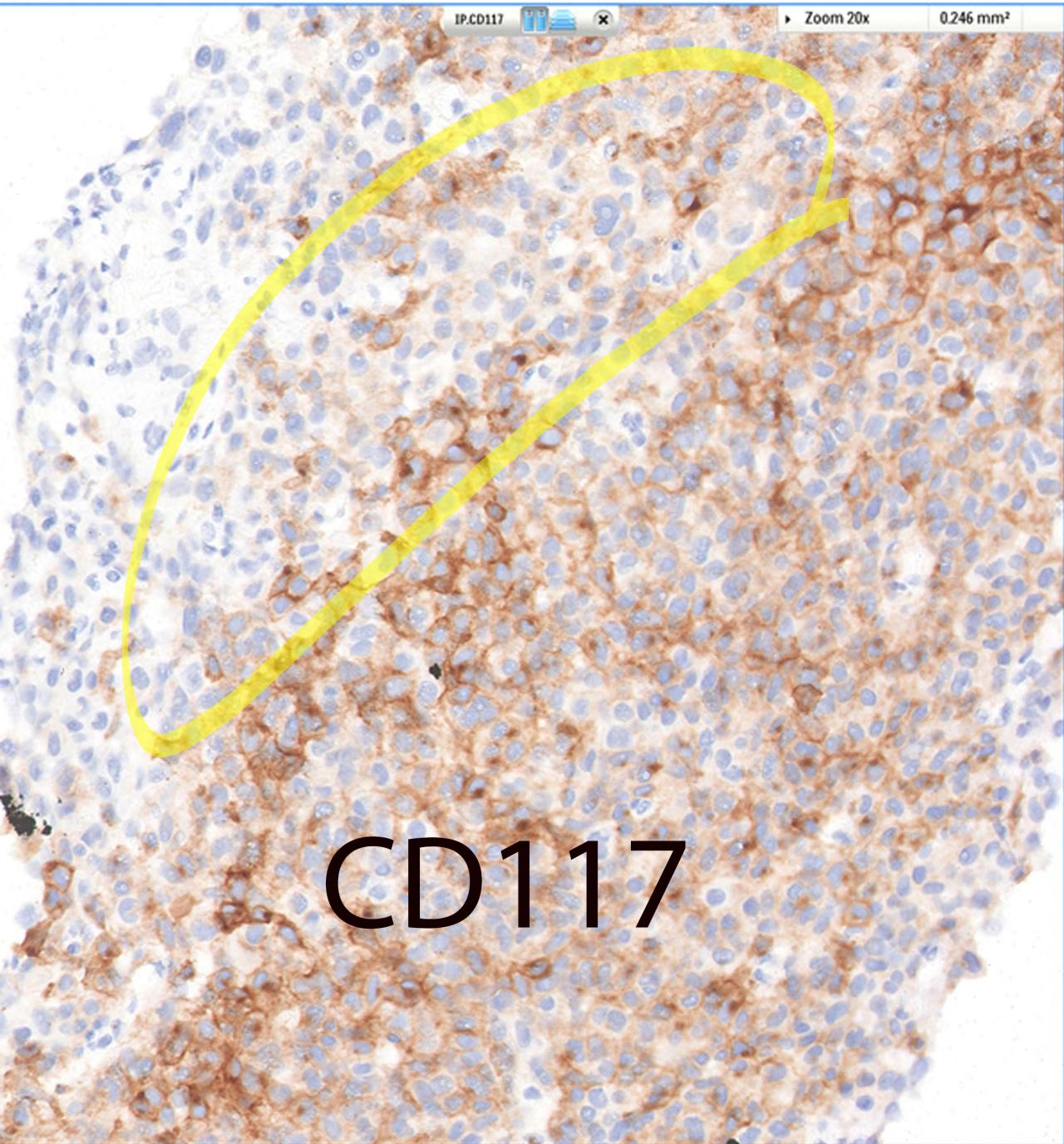


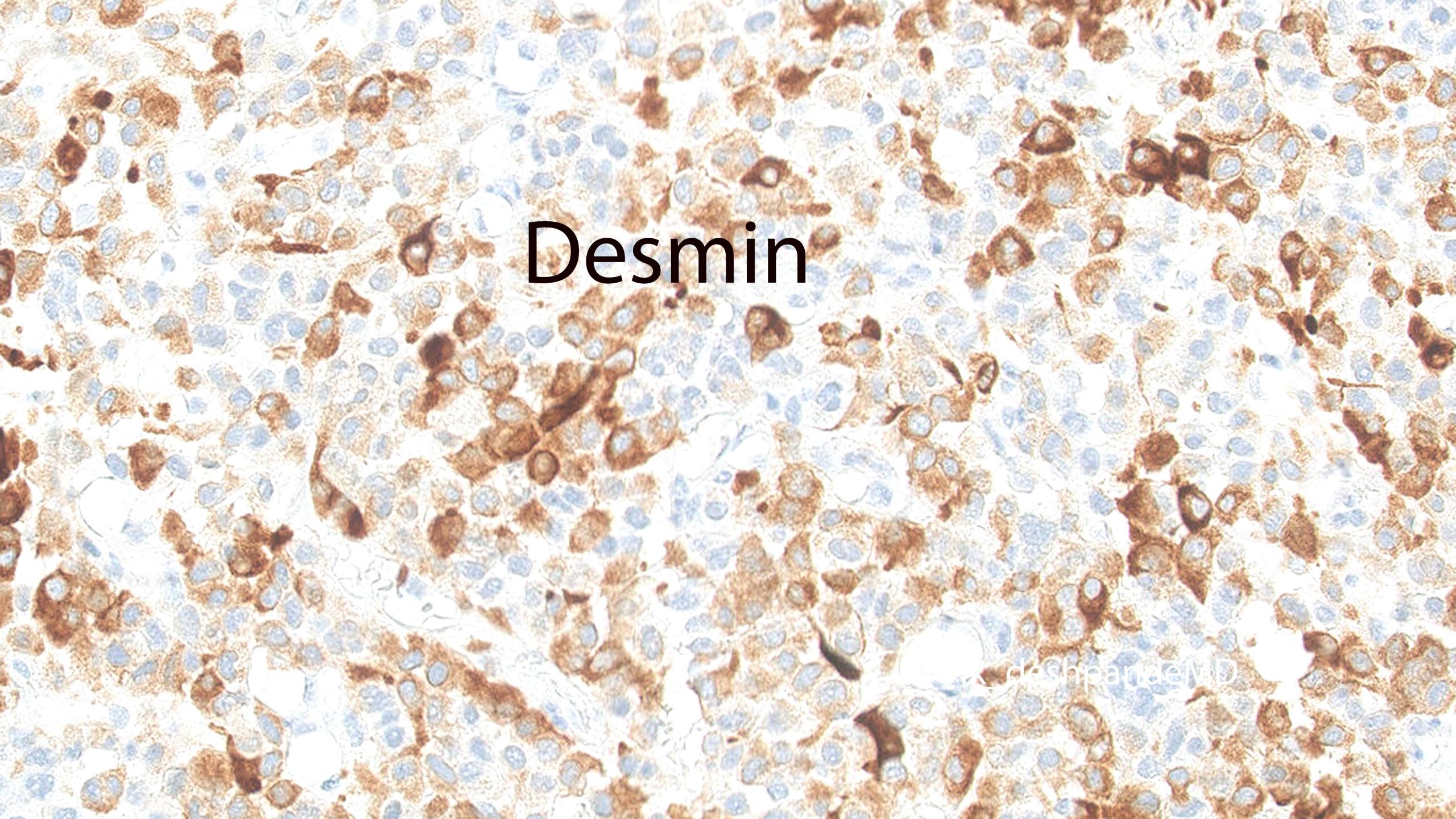
KIT





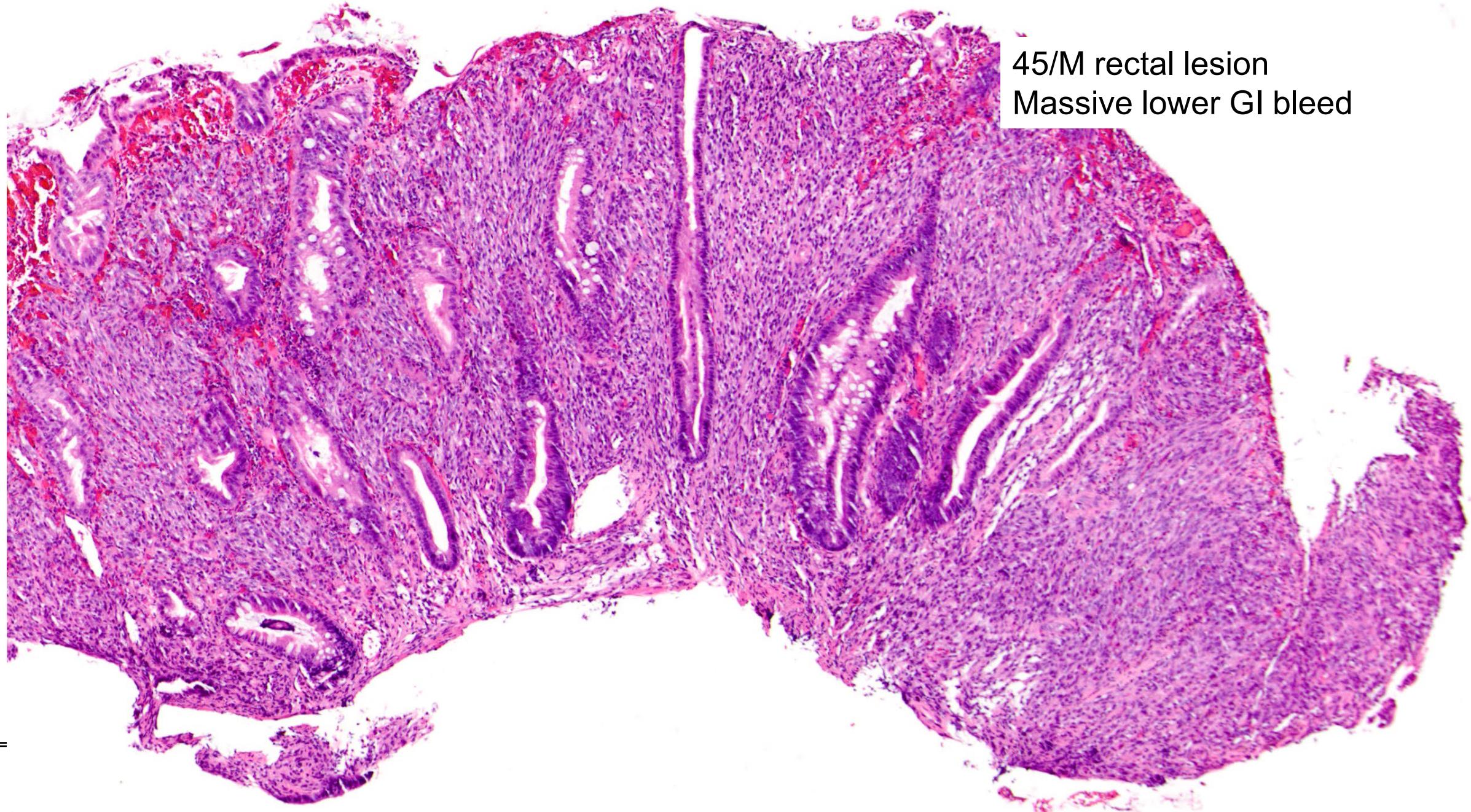
@Vik_deshpandeMD



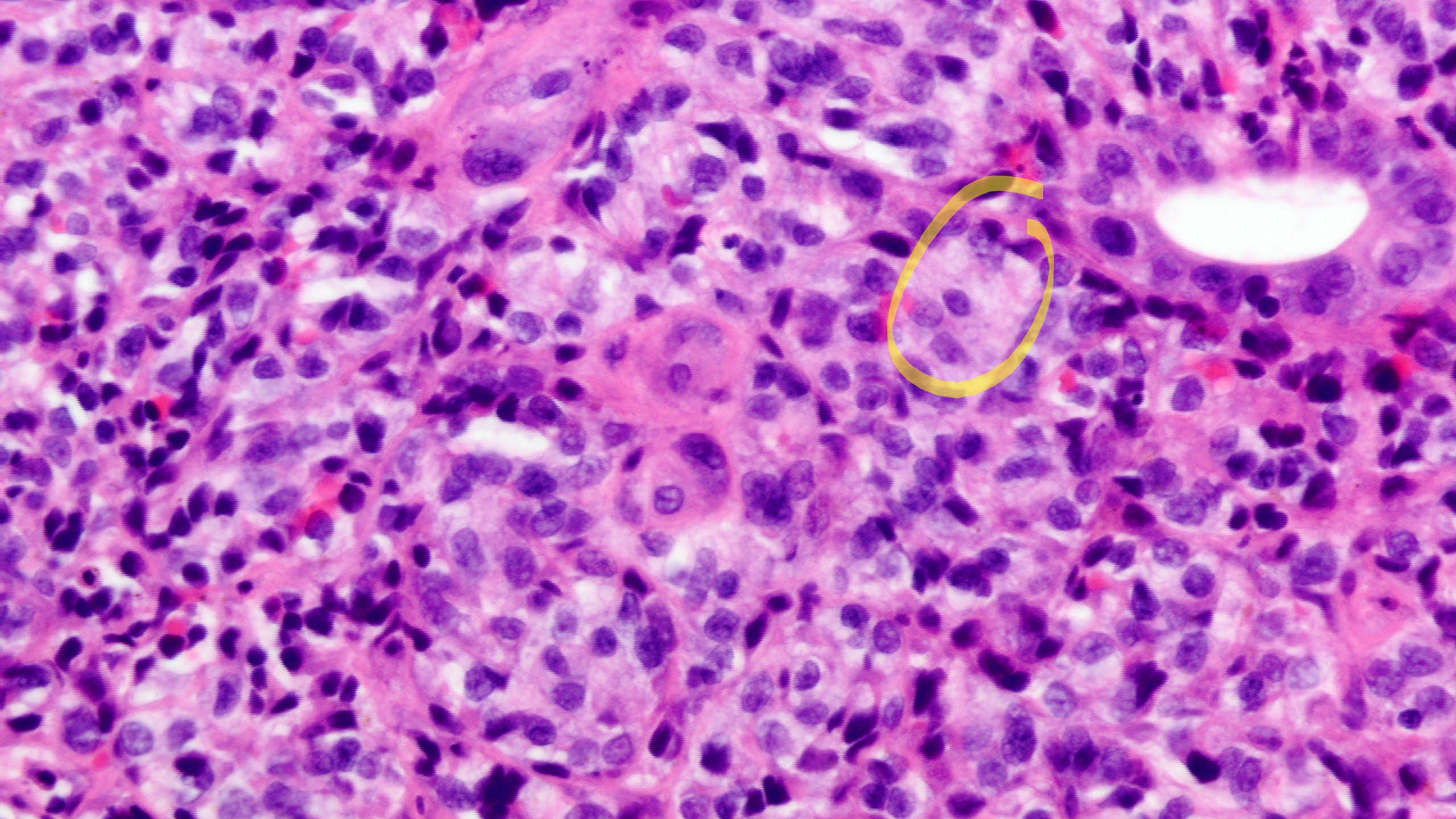


Desmin

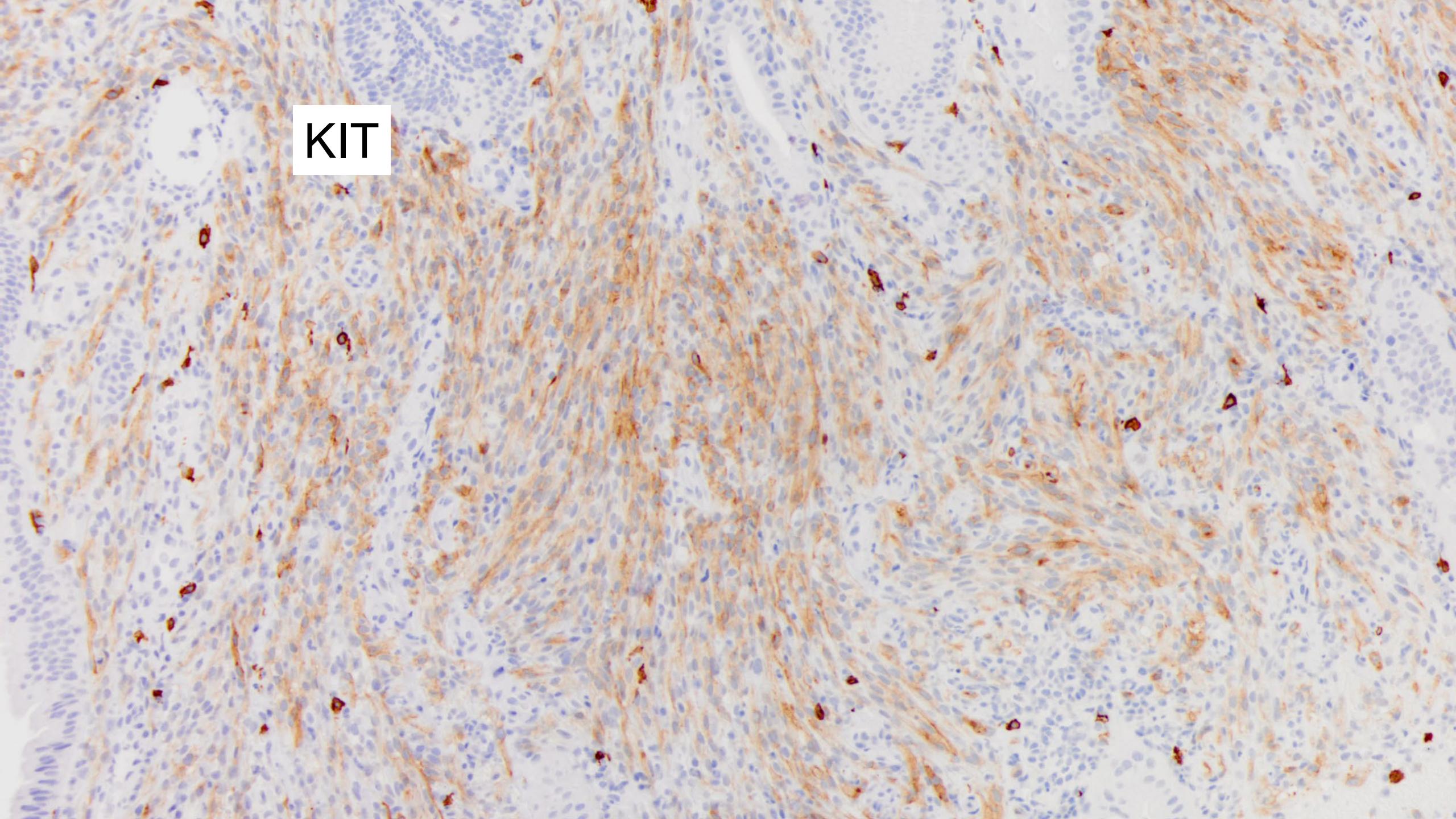
deshpandeMD

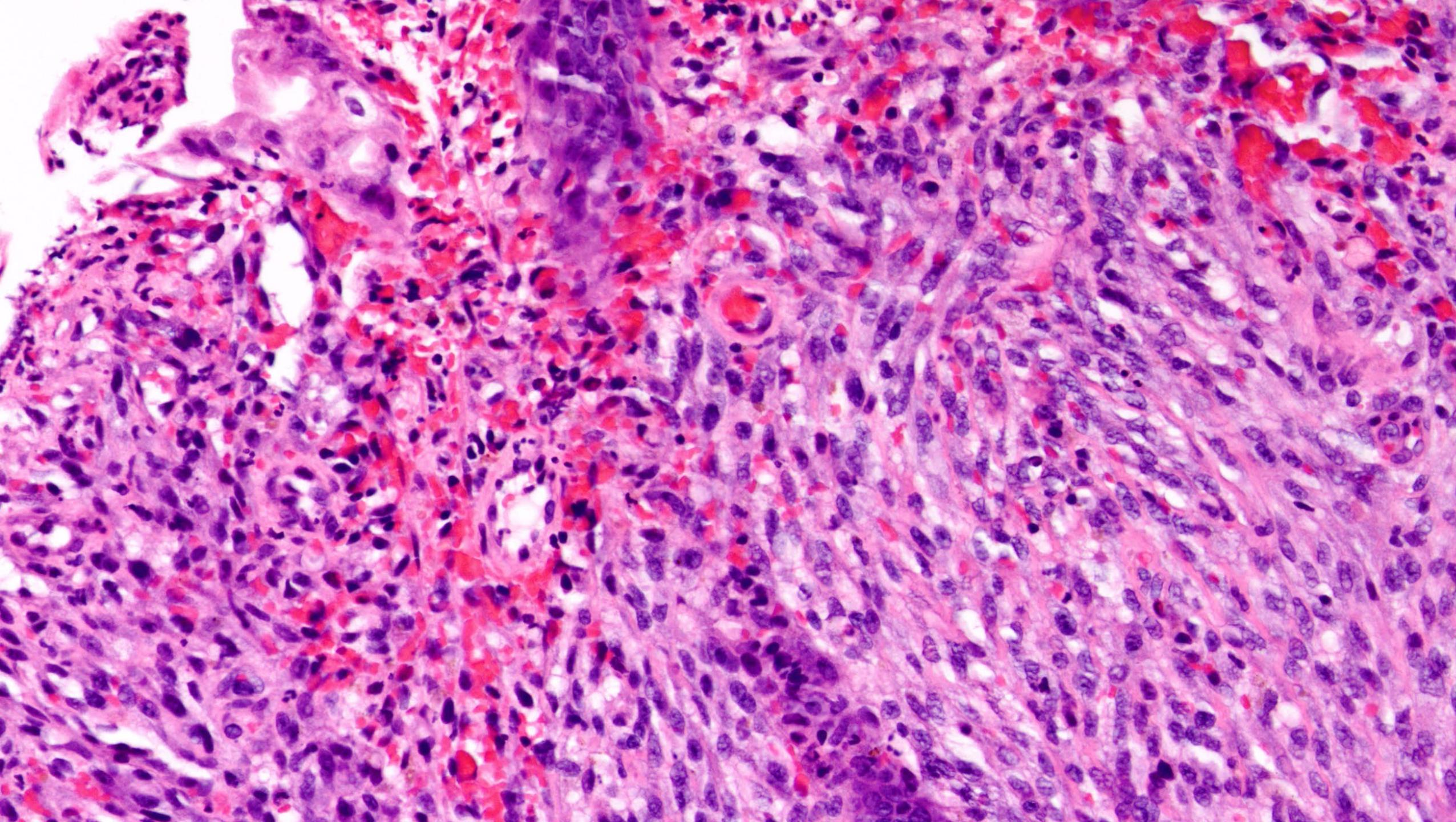


45/M rectal lesion
Massive lower GI bleed



KIT

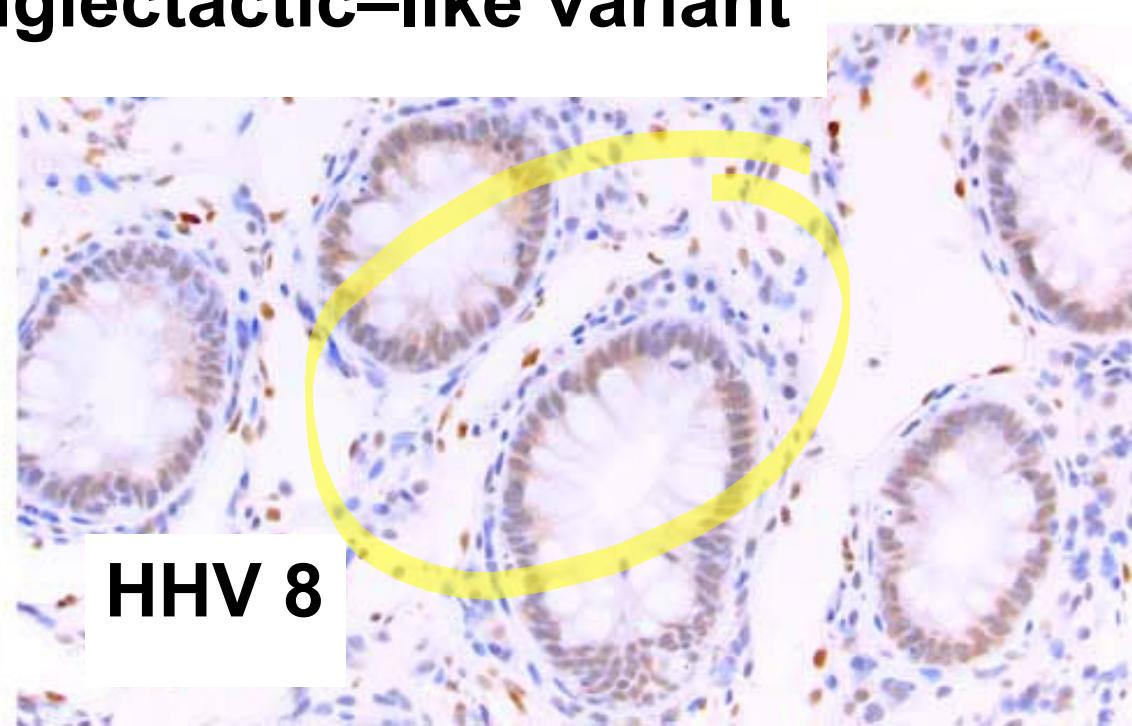
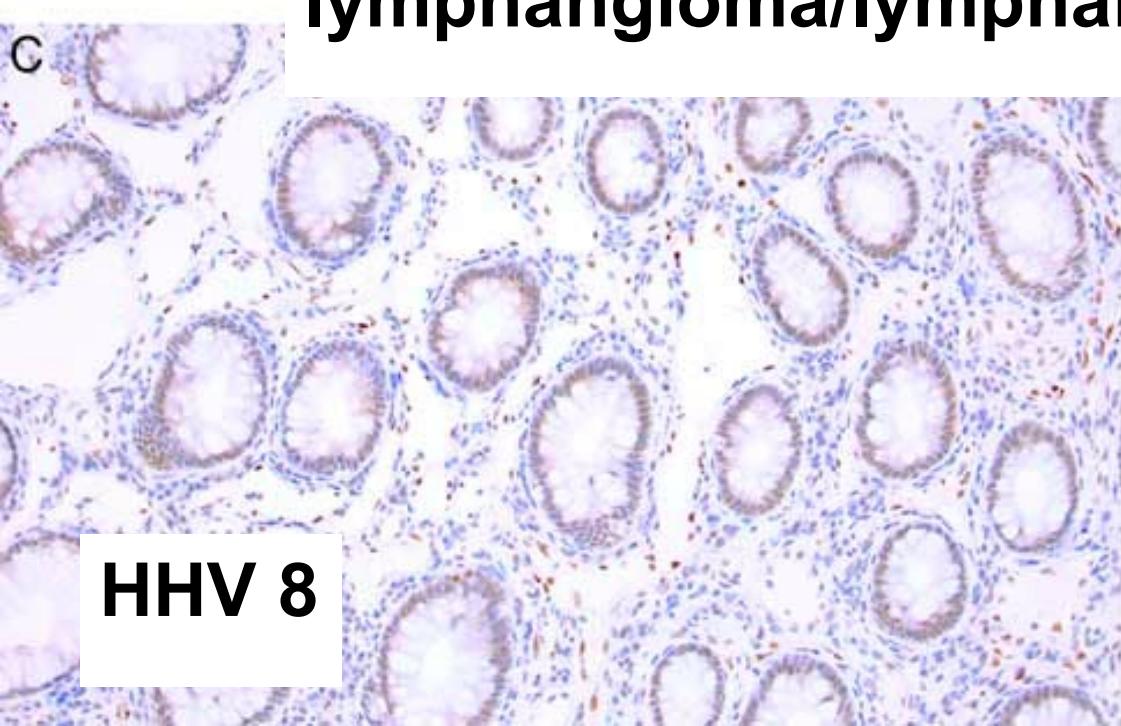
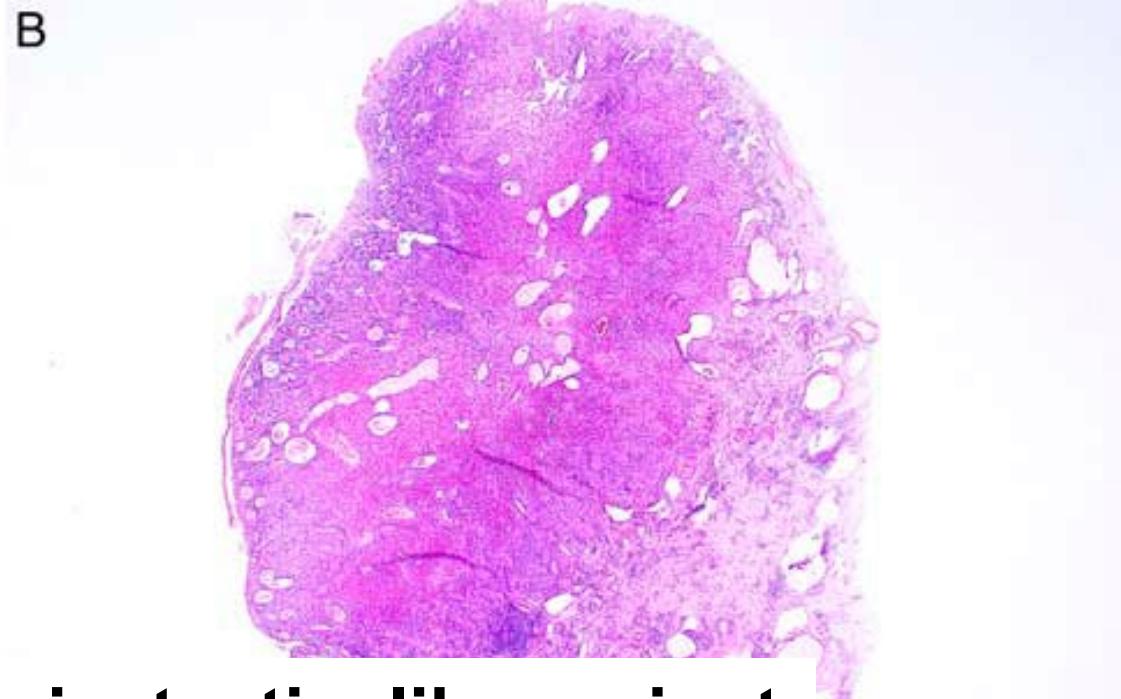
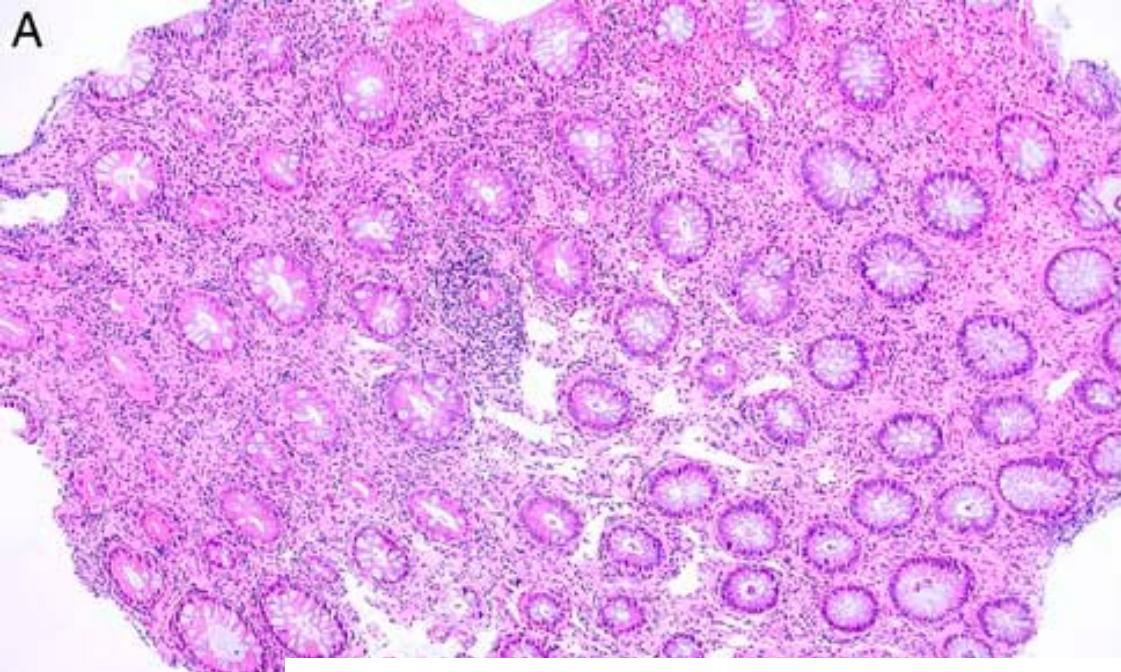




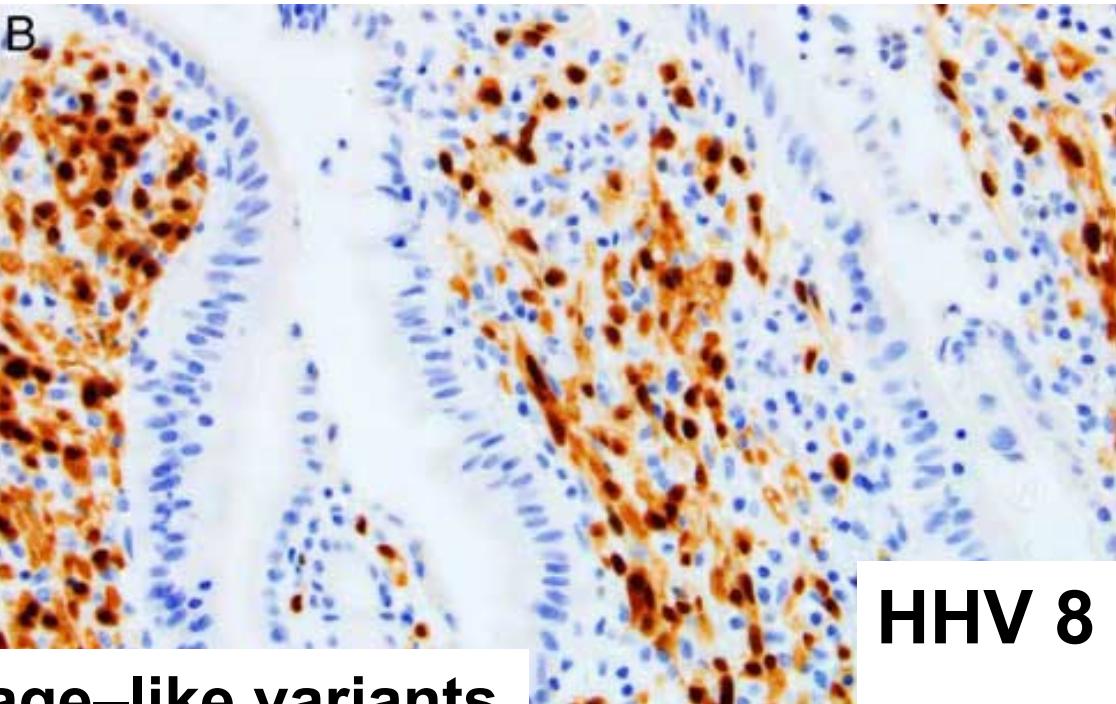
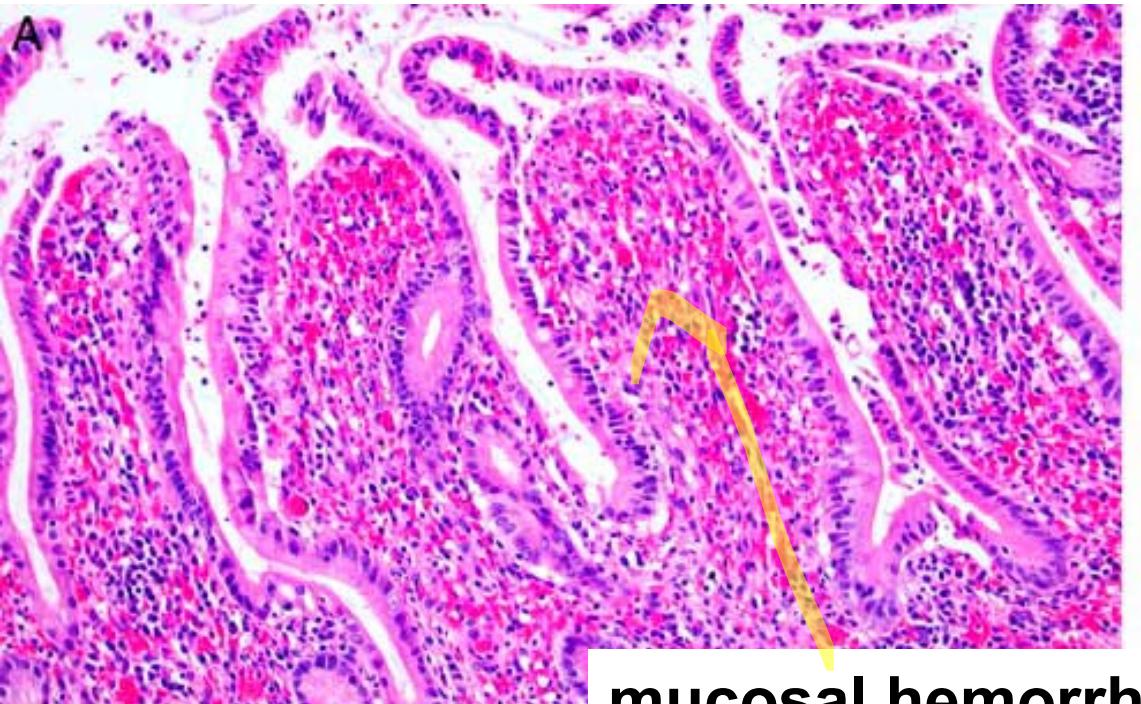
Kaposi sarcoma

ERG

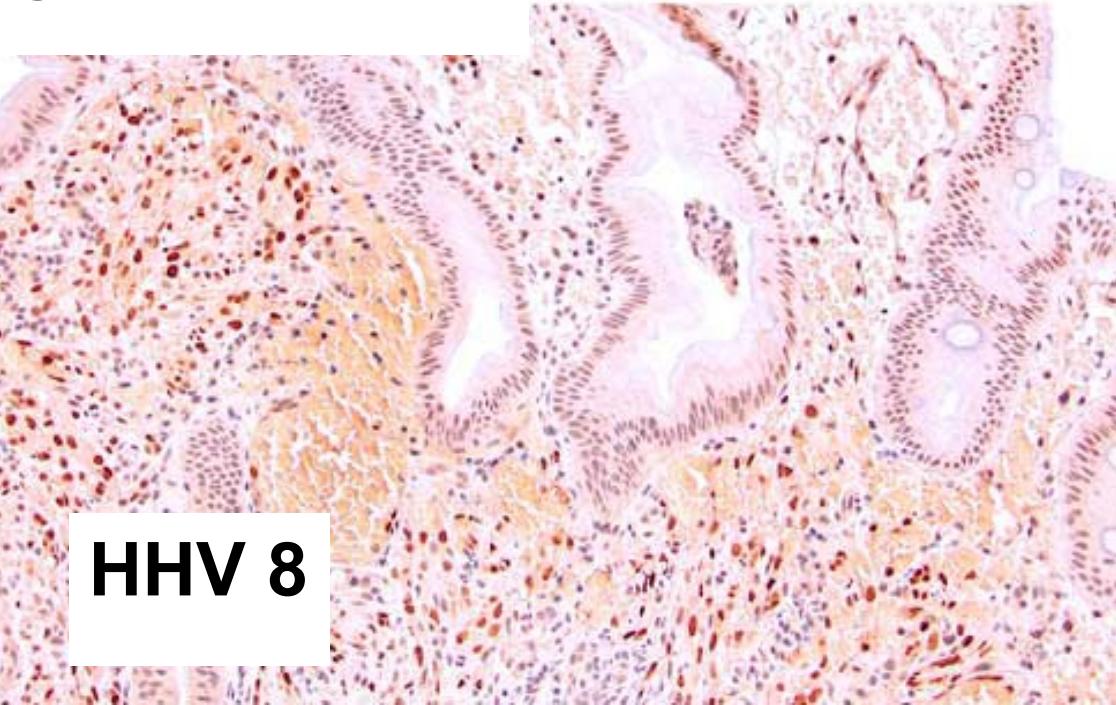
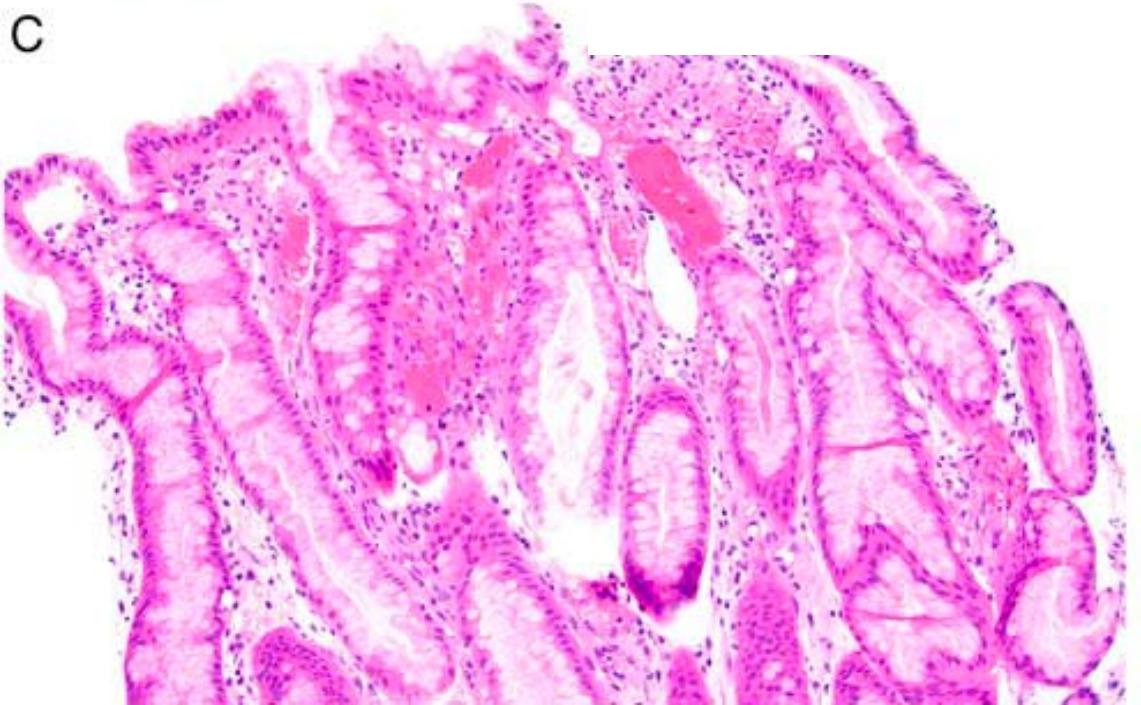
HHV8



HOOL



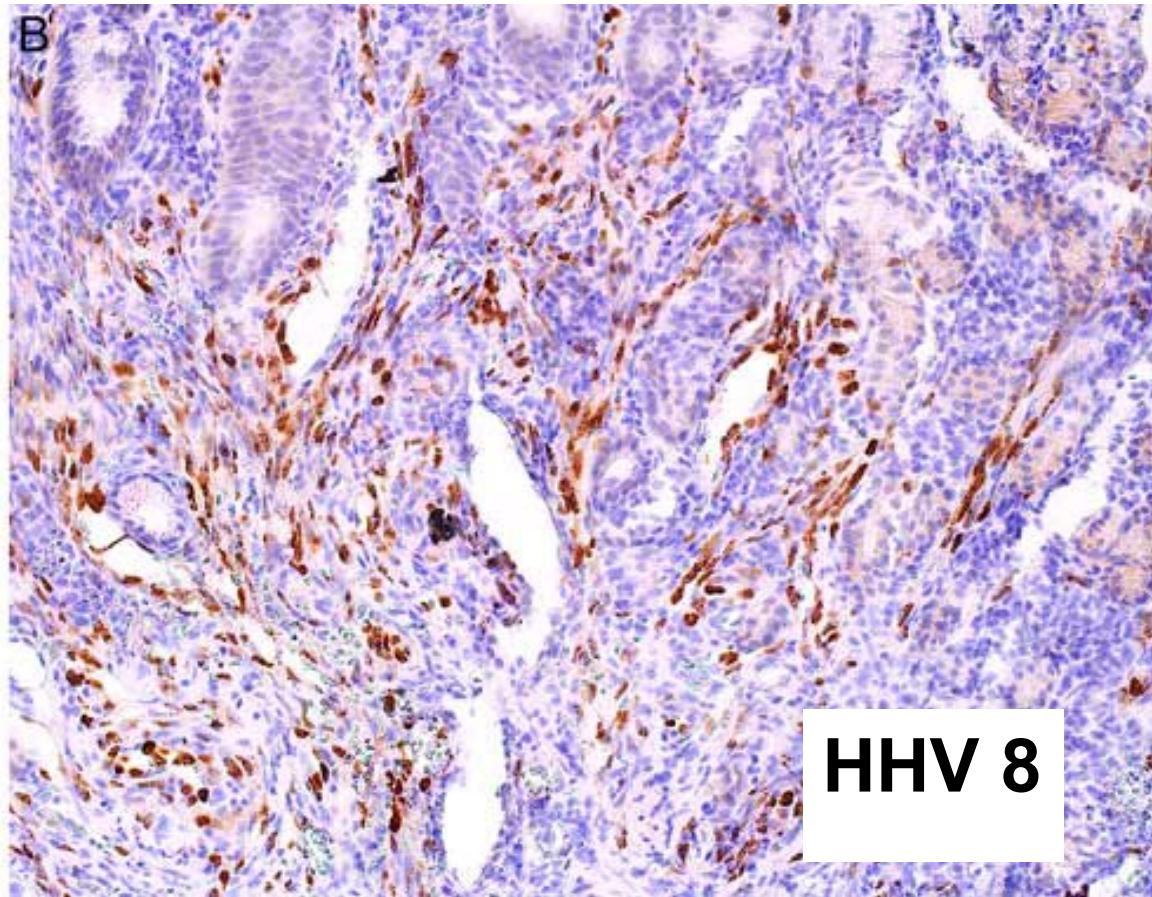
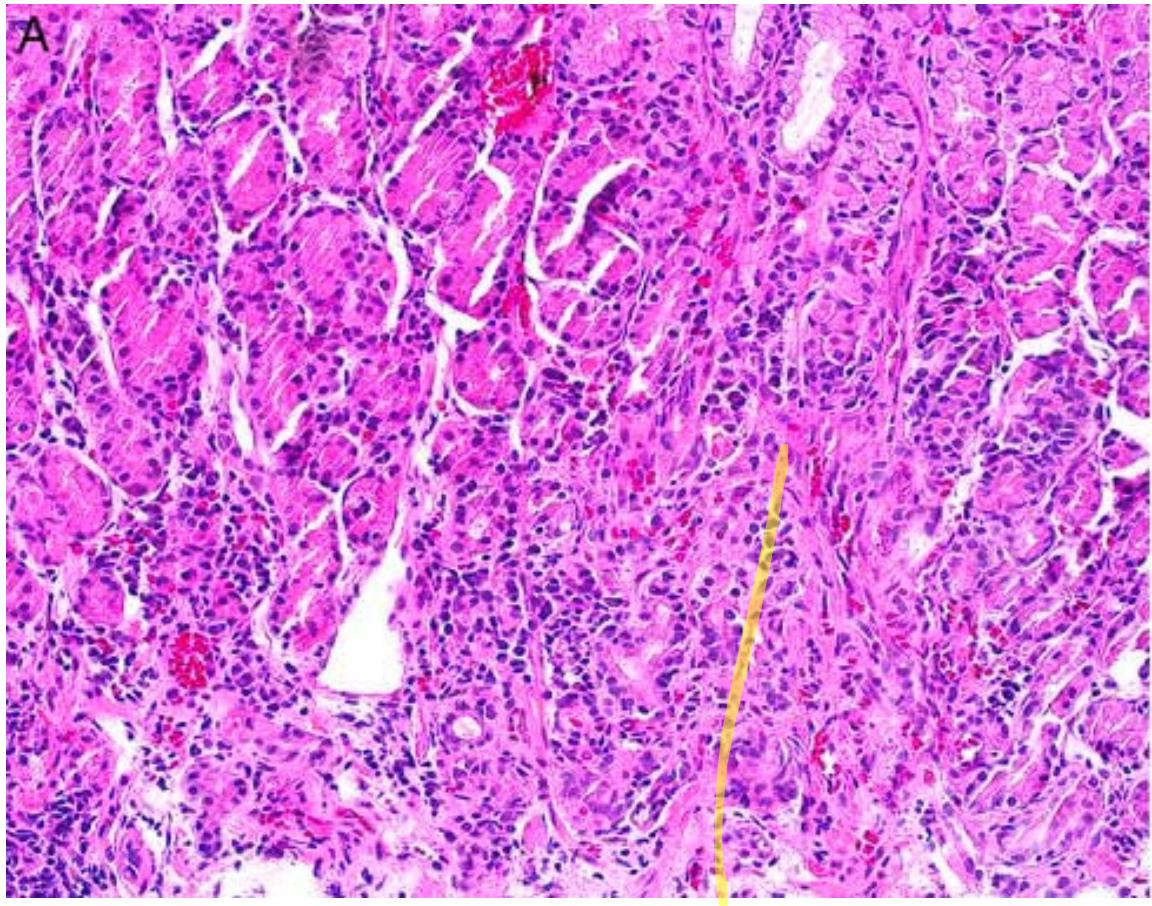
HHV 8

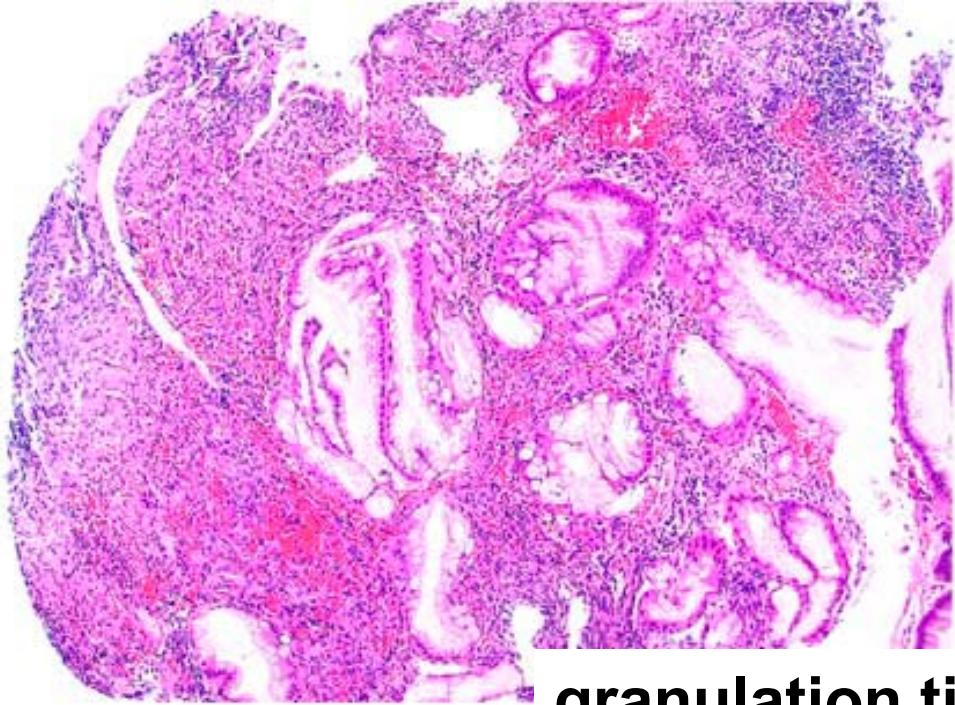


HHV 8

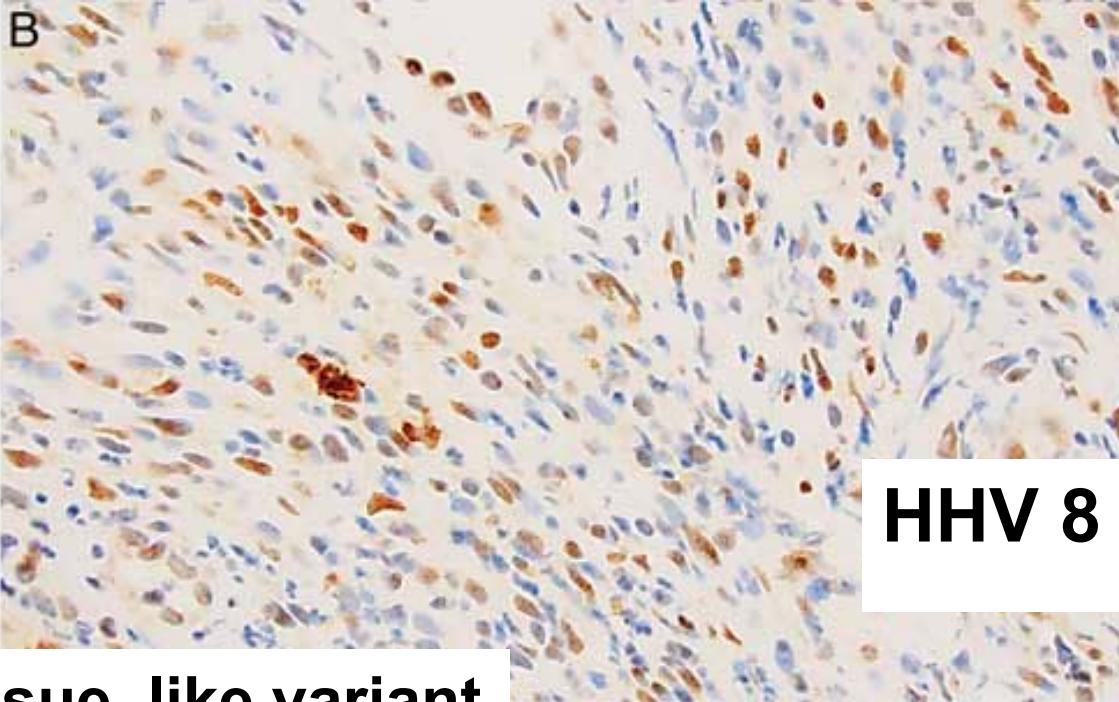
SCHOOL

mucosal inflammation–like variant

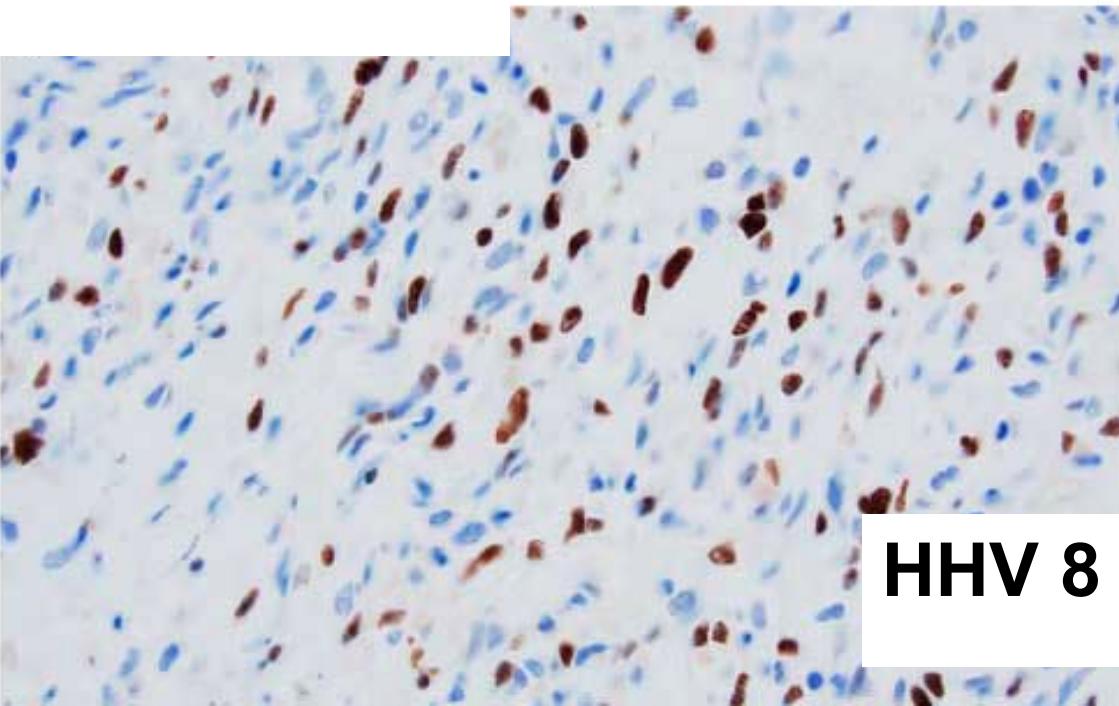
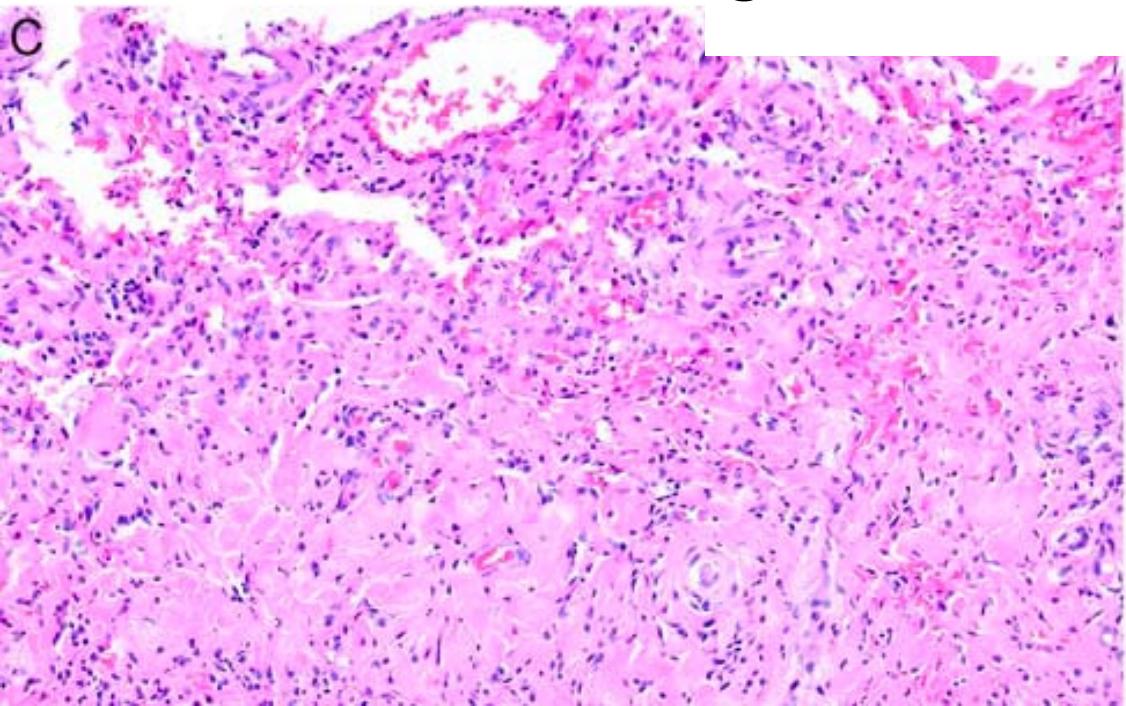


A

granulation tissue–like variant

B

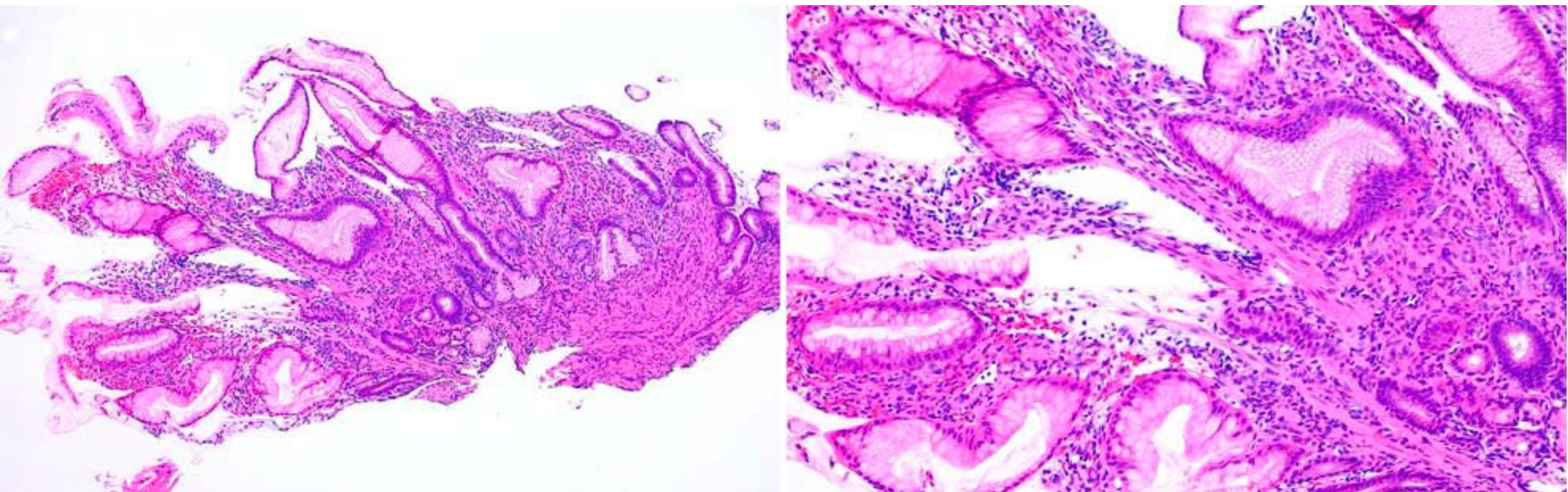
HHV 8

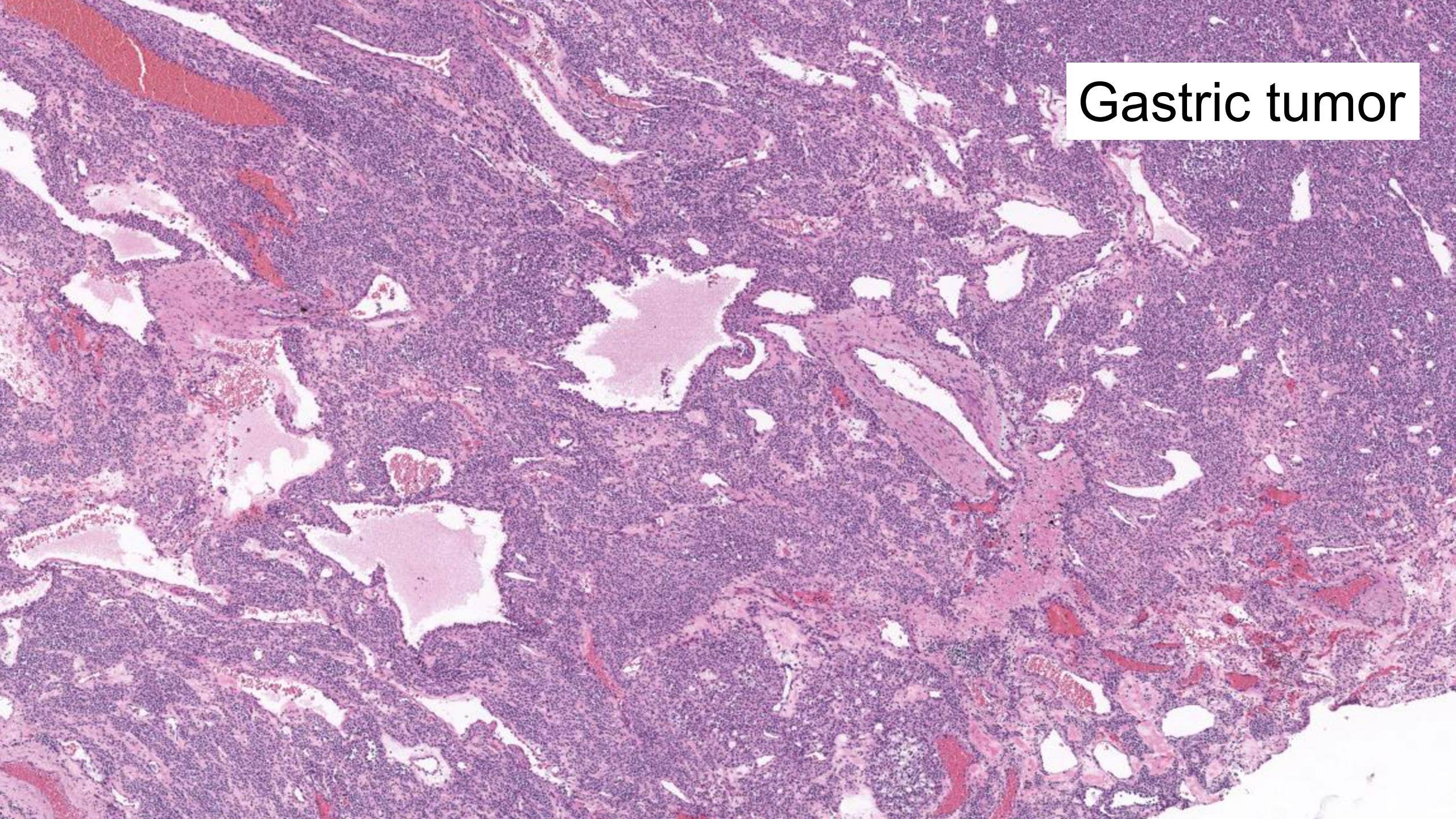
C

HHV 8

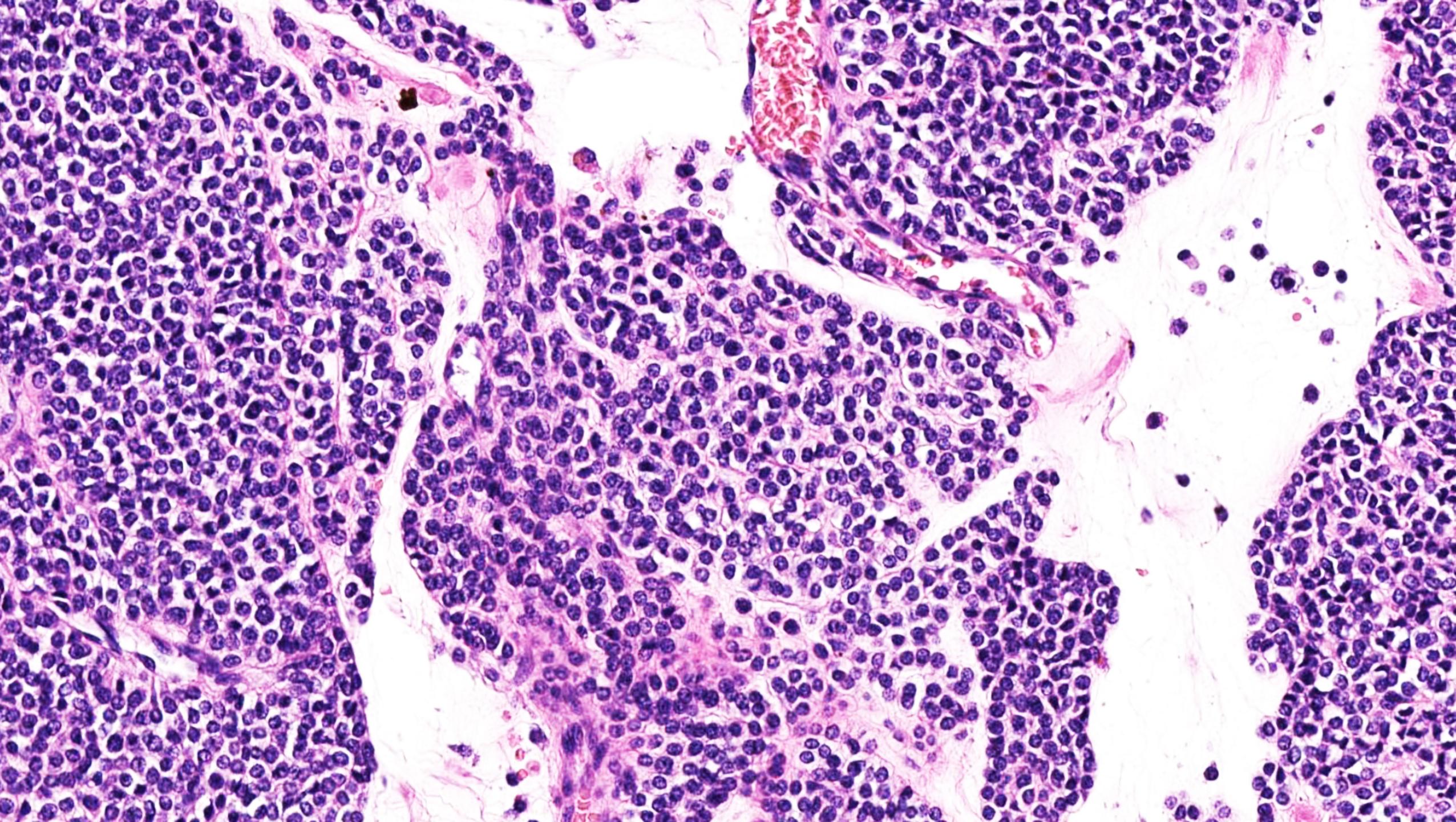
HOOL

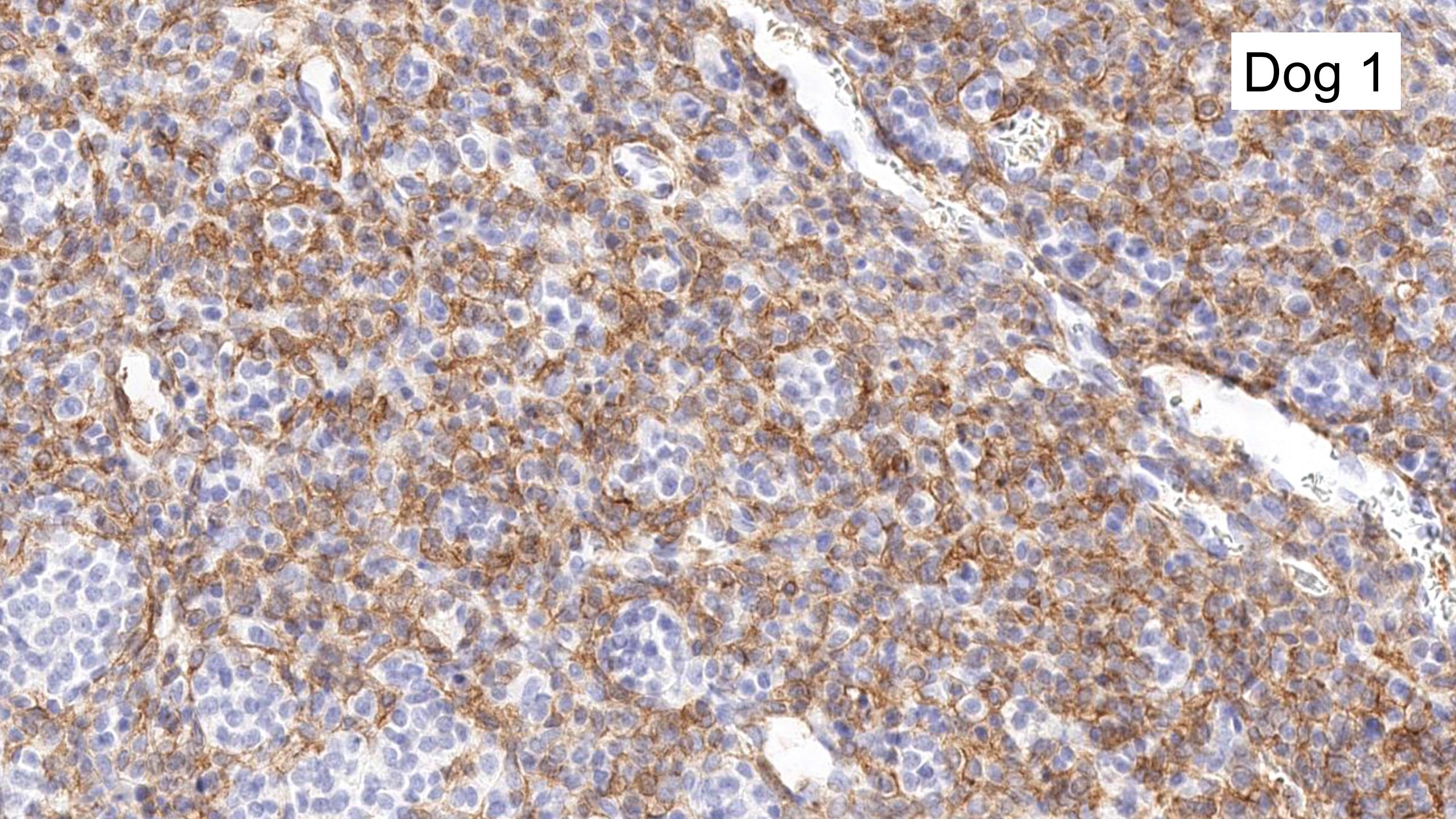
Mucosal prolapse-like variant



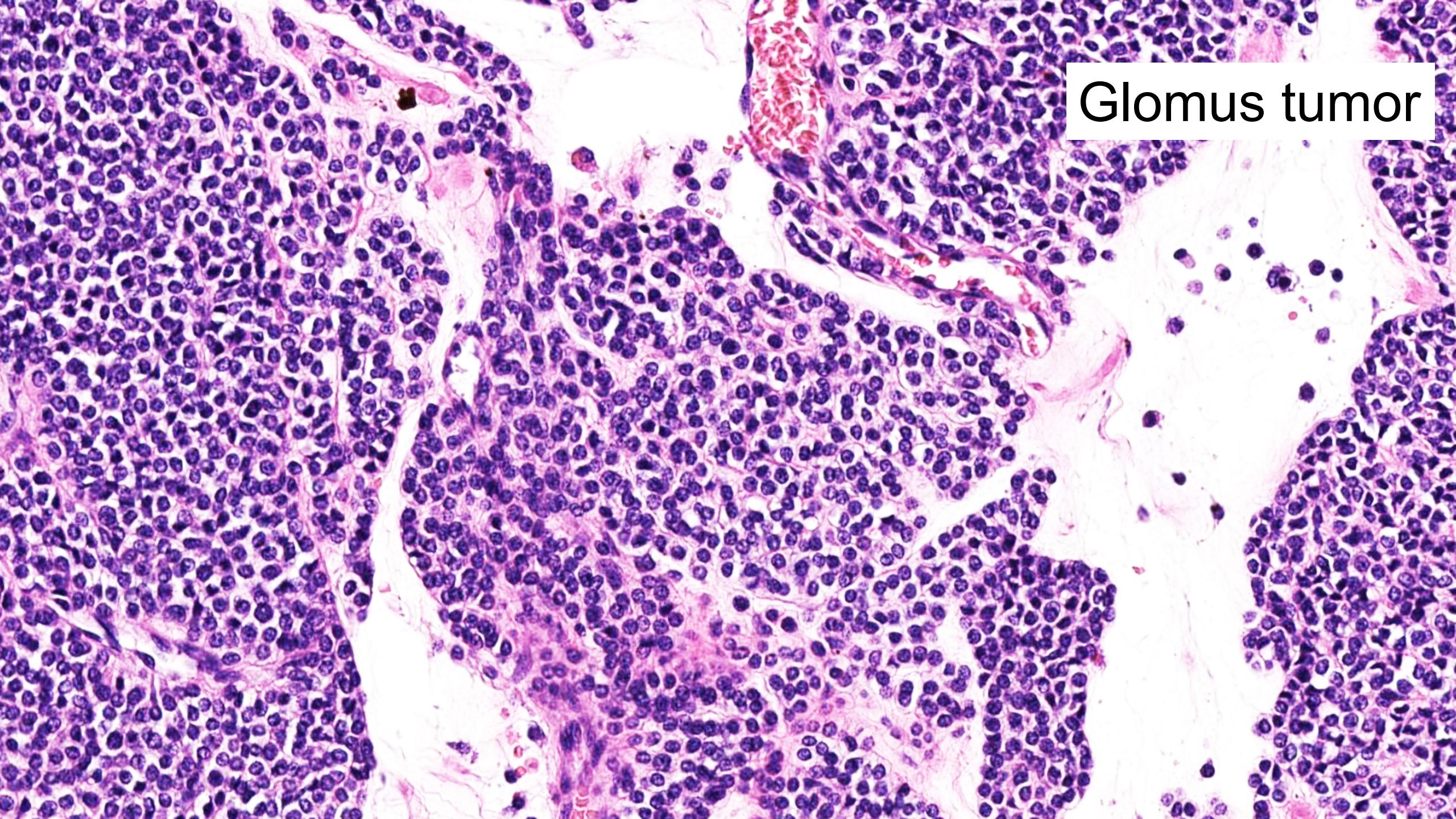
A histological slide showing a tissue sample with various cellular components. The background consists of a dense layer of small, dark-staining cells. Interspersed among them are several larger, more prominent areas. Some of these larger areas have a pale, eosinophilic appearance, while others are darker and more solid. A few red-stained blood vessels are visible. The overall pattern suggests a neoplastic process.

Gastric tumor



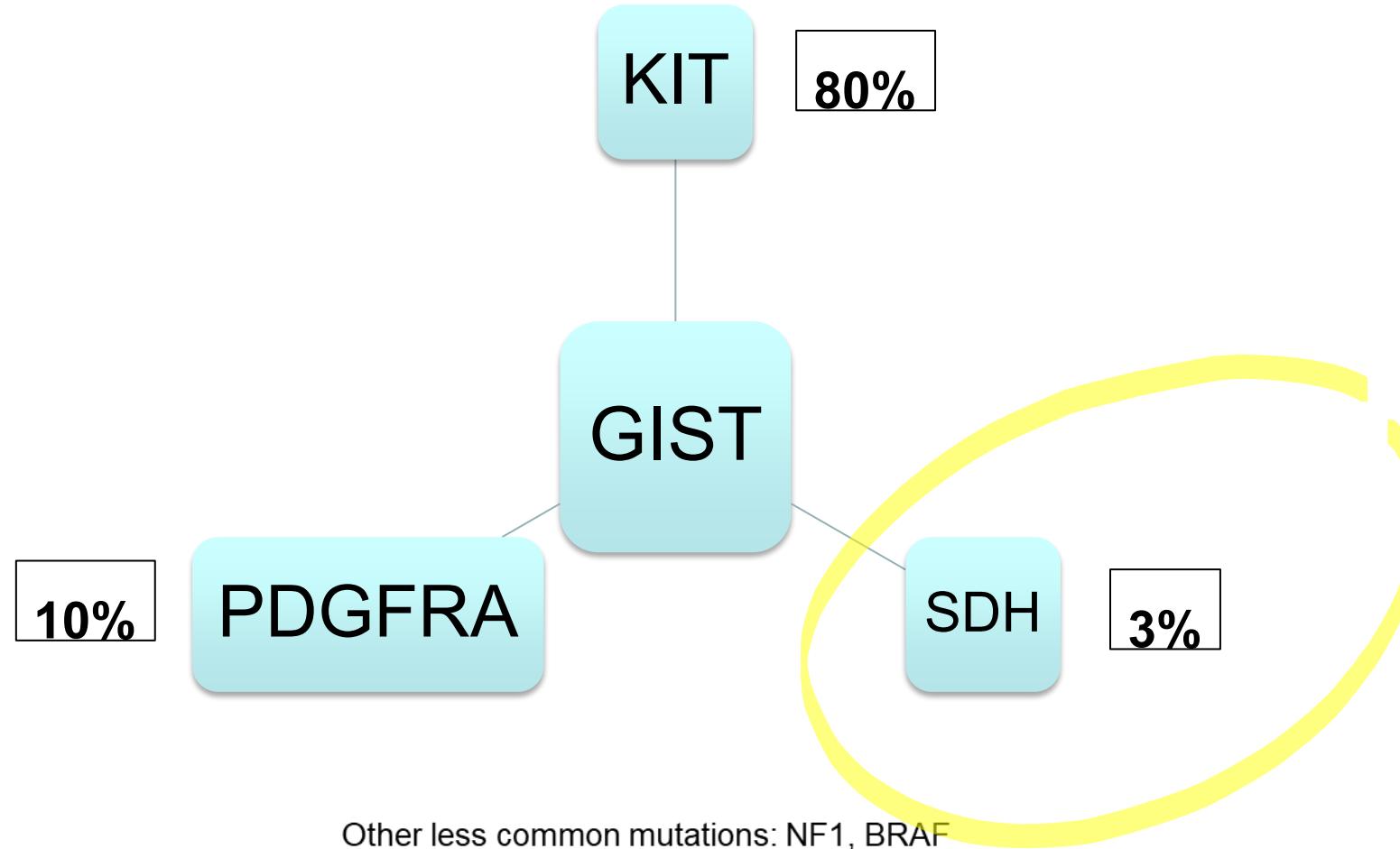


Dog 1

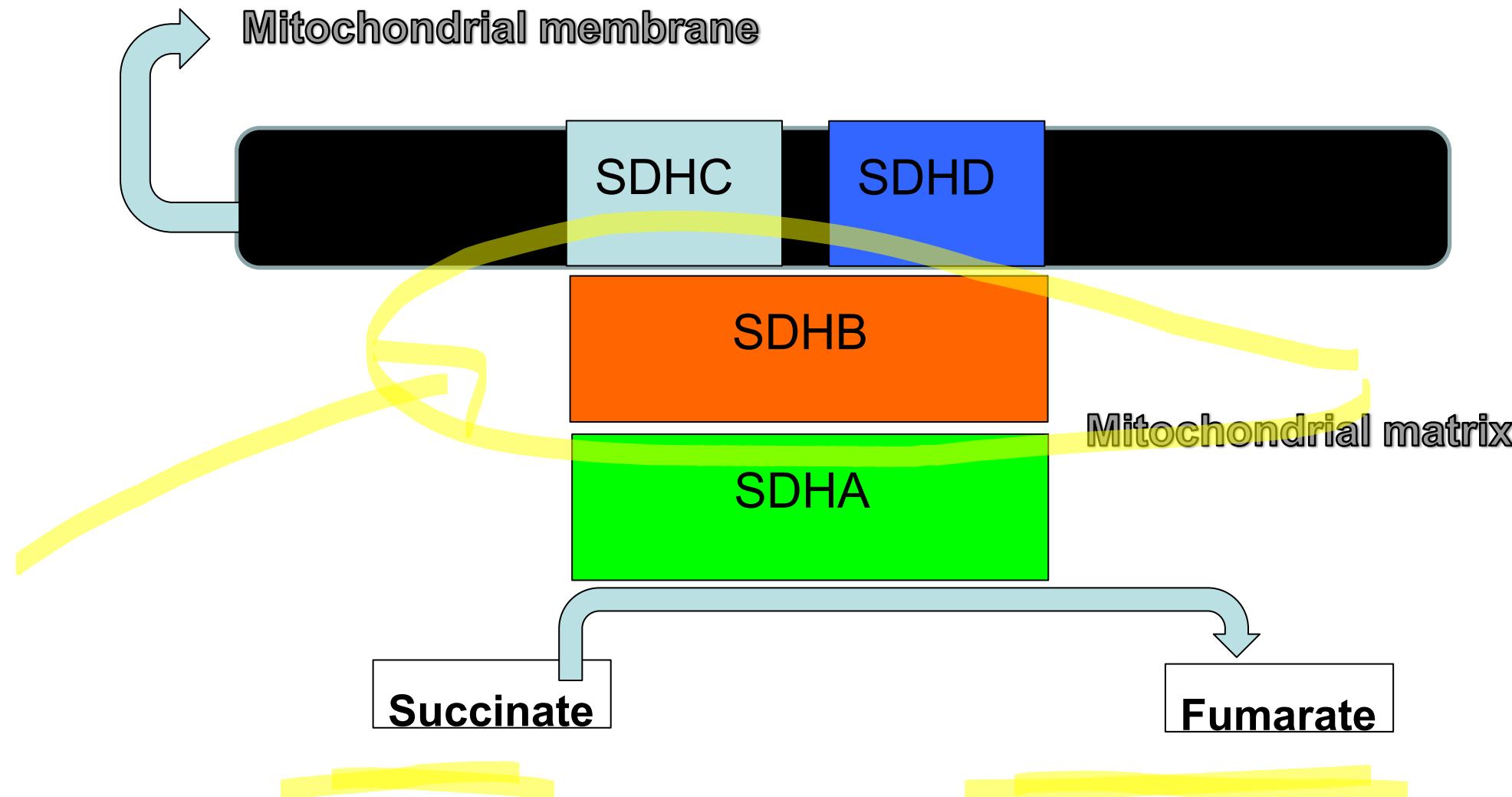
A hematoxylin-stained histological section of a glomus tumor. The image shows clusters of small, round to polygonal cells with dark purple nuclei and some pink-staining cytoplasmic areas. These clusters are separated by thin, wavy, pink-stained stromal bands.

Glomus tumor

GENETIC ALTERATIONS GIST



SDH mutations in GIST



SDH deficient GIST



Mass General Hospital Pathology D

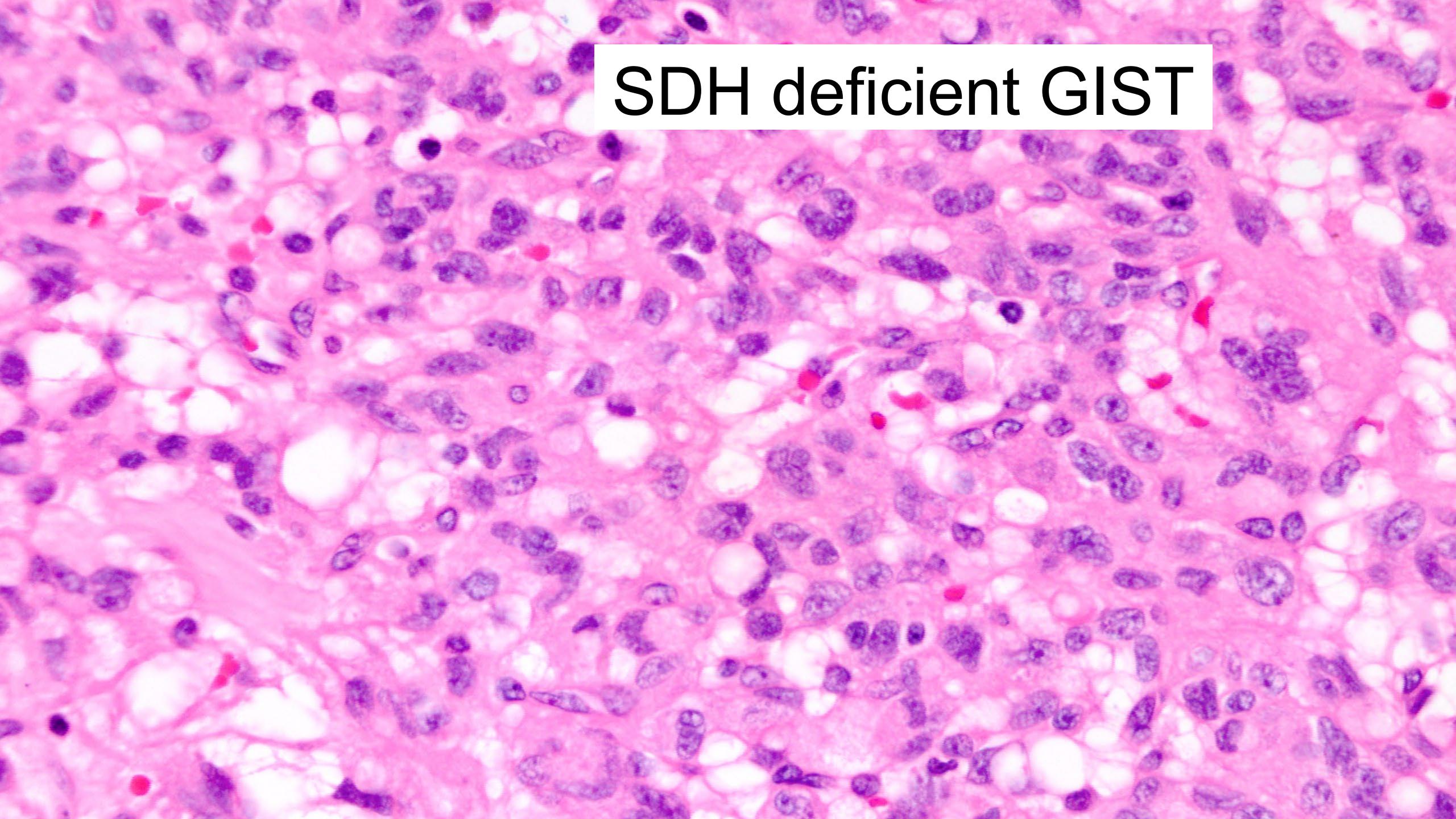


MASSACHUSETTS
GENERAL HOSPITAL

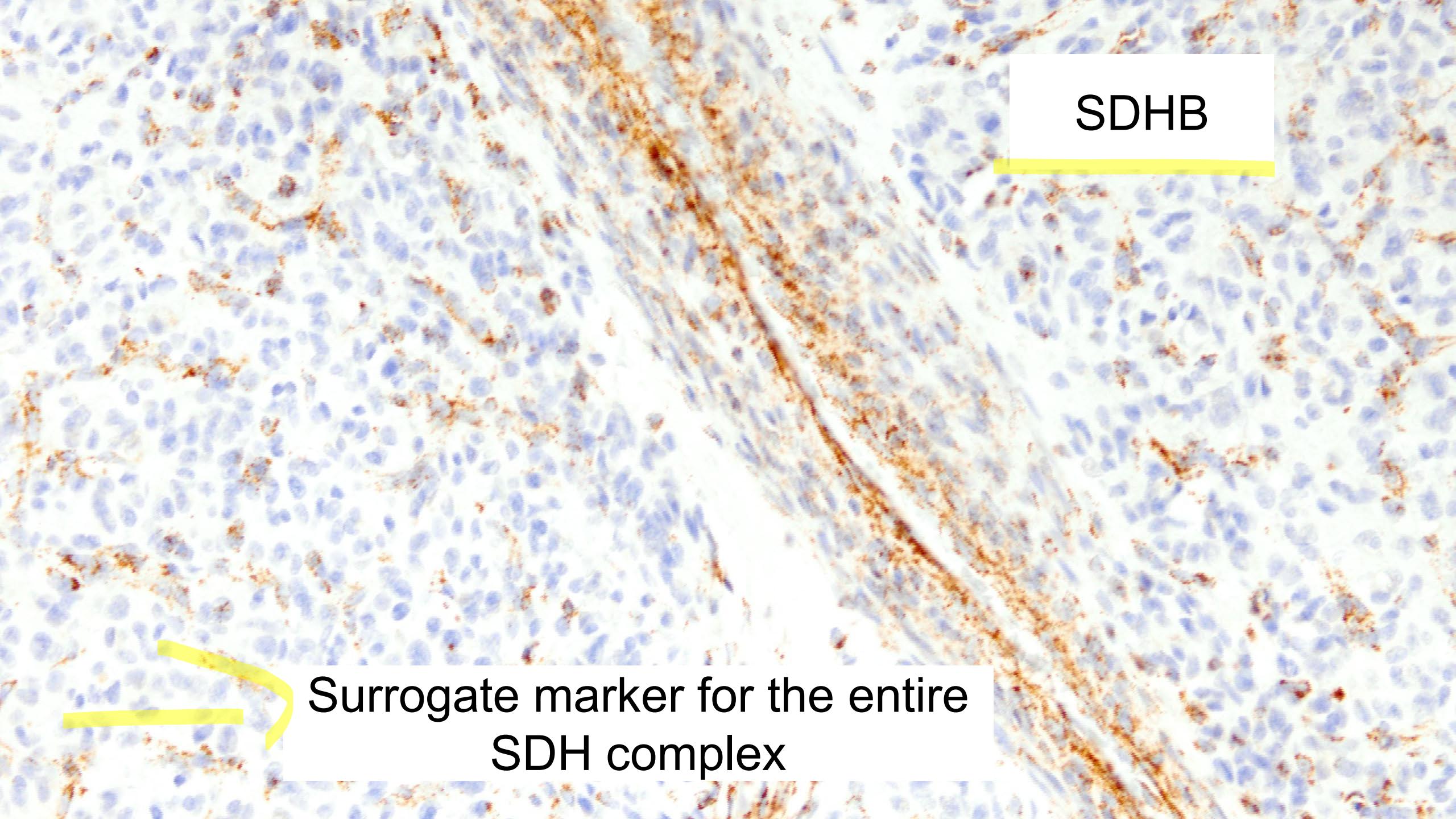
HARVARD
MEDICAL SCHOOL

SDH deficient GIST

This image shows a hematoxylin and eosin (H&E) stained histological section of a Gastrointestinal Stromal Tumor (GIST). The tumor is highlighted by a thick yellow line, showing a dense cellular area with spindle-shaped cells and some areas of more epithelioid-like cells. The surrounding tissue appears relatively normal. A white rectangular box in the upper right corner contains the text "SDH deficient GIST".



SDH deficient GIST



SDHB

Surrogate marker for the entire
SDH complex

SDH deficient GIST

- Majority <40
- Conventional criteria fail to predict aggressive behavior
- Association with syndrome
 - Carney Stratakis syndrome
 - Carney triad
- Do not respond to targeted therapy
 - Imatinib

Plexiform Fibromyxoma

- 5th decade
- Benign tumor almost always arises in stomach (antrum)
 - Muscle layer
- Complete excision is curative
- Vascular invasion is often present and has no apparent significance
- *MALAT1-GLI1* fusions and *GLI1* polysomy

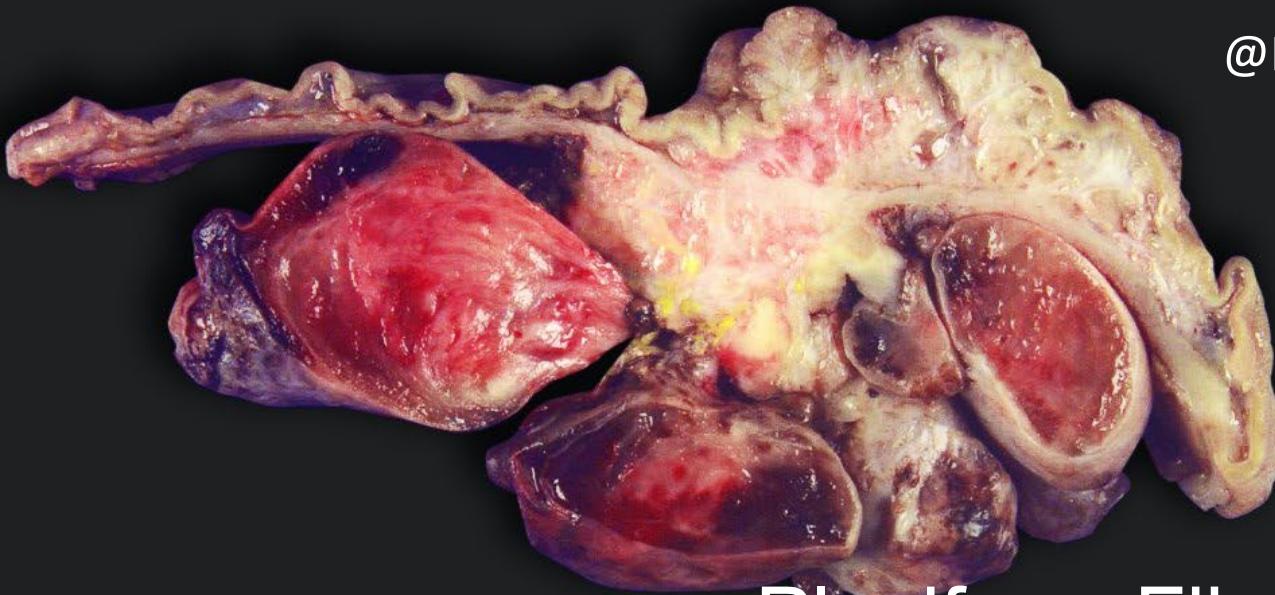


@HubertLauMD

Plexiform Fibromyxoma

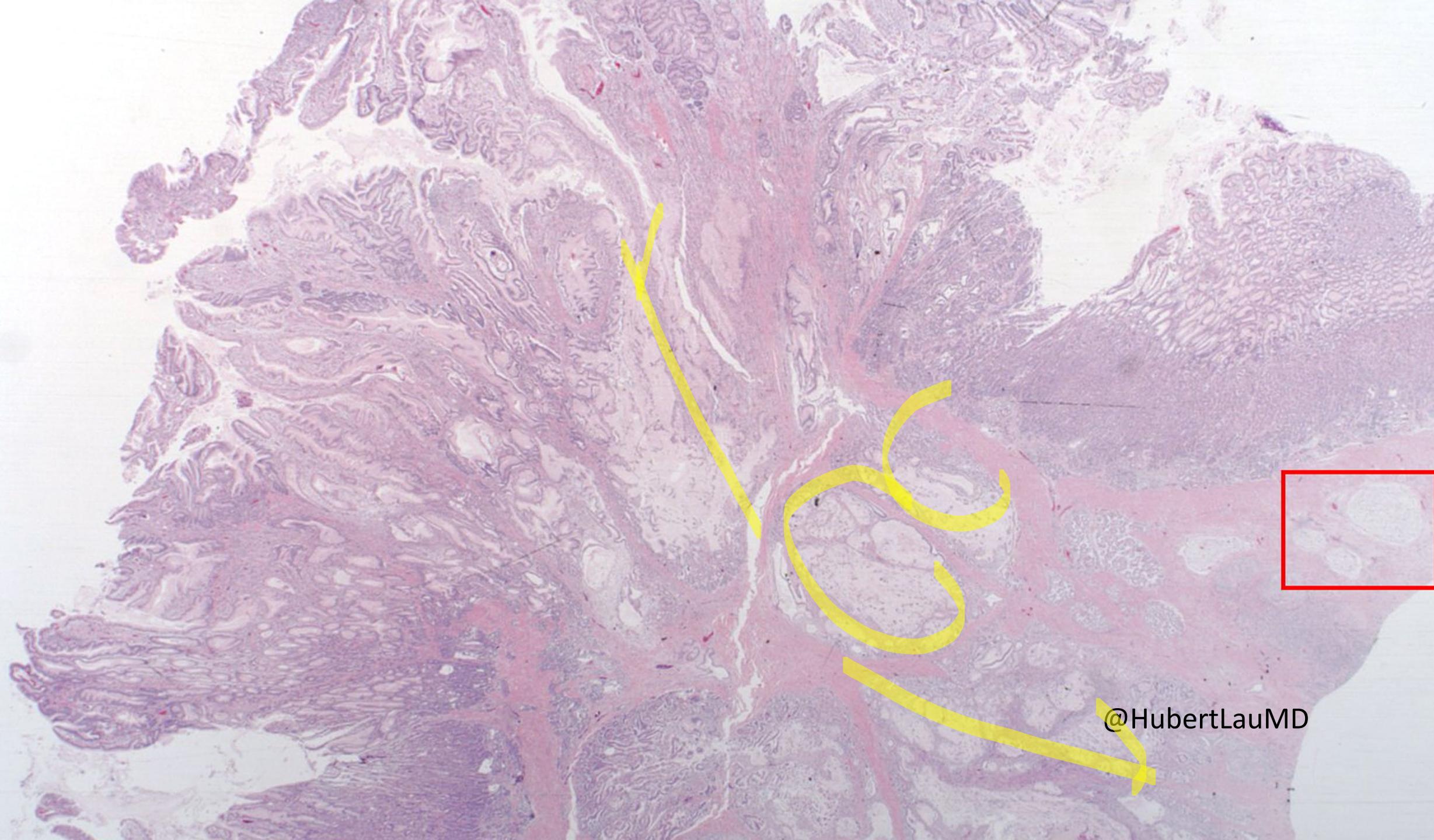
cross-sections

@HubertLauMD

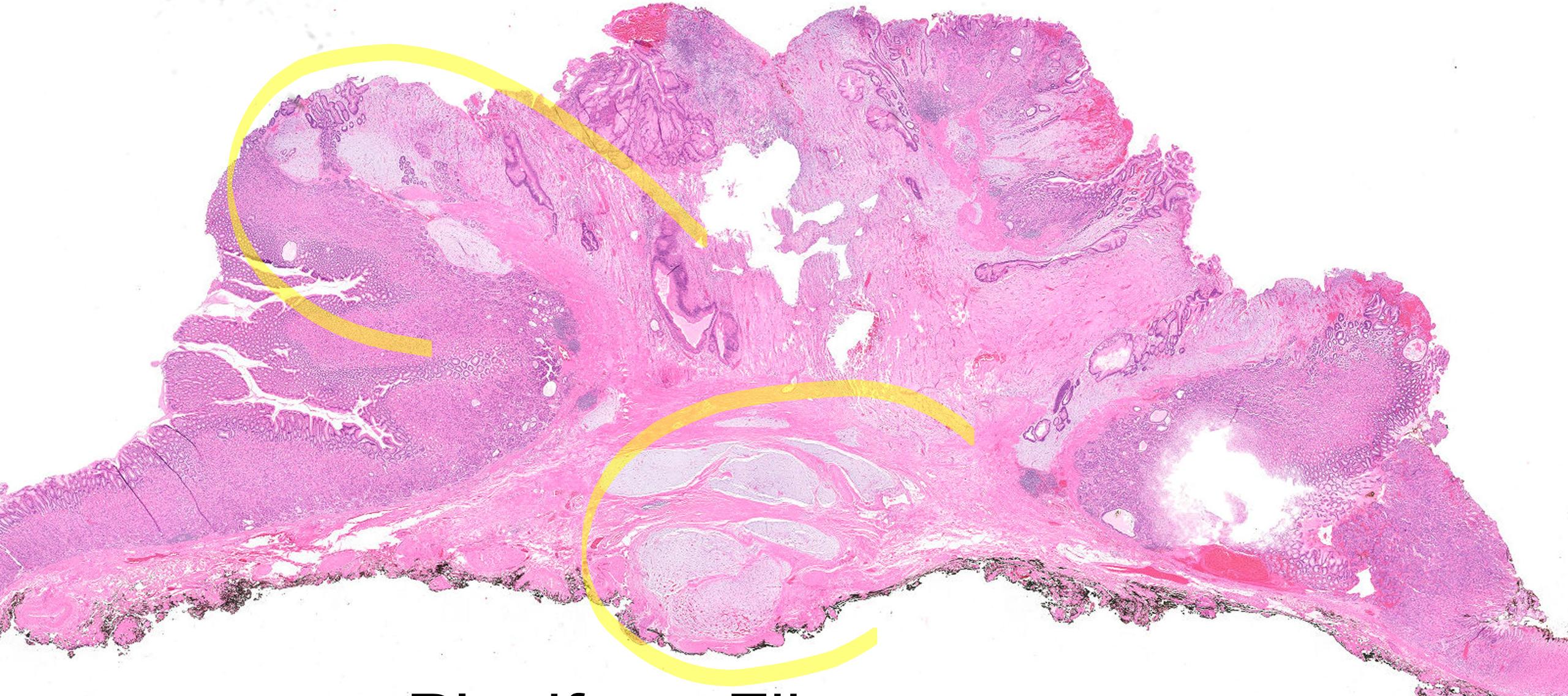


Plexiform Fibromyxoma

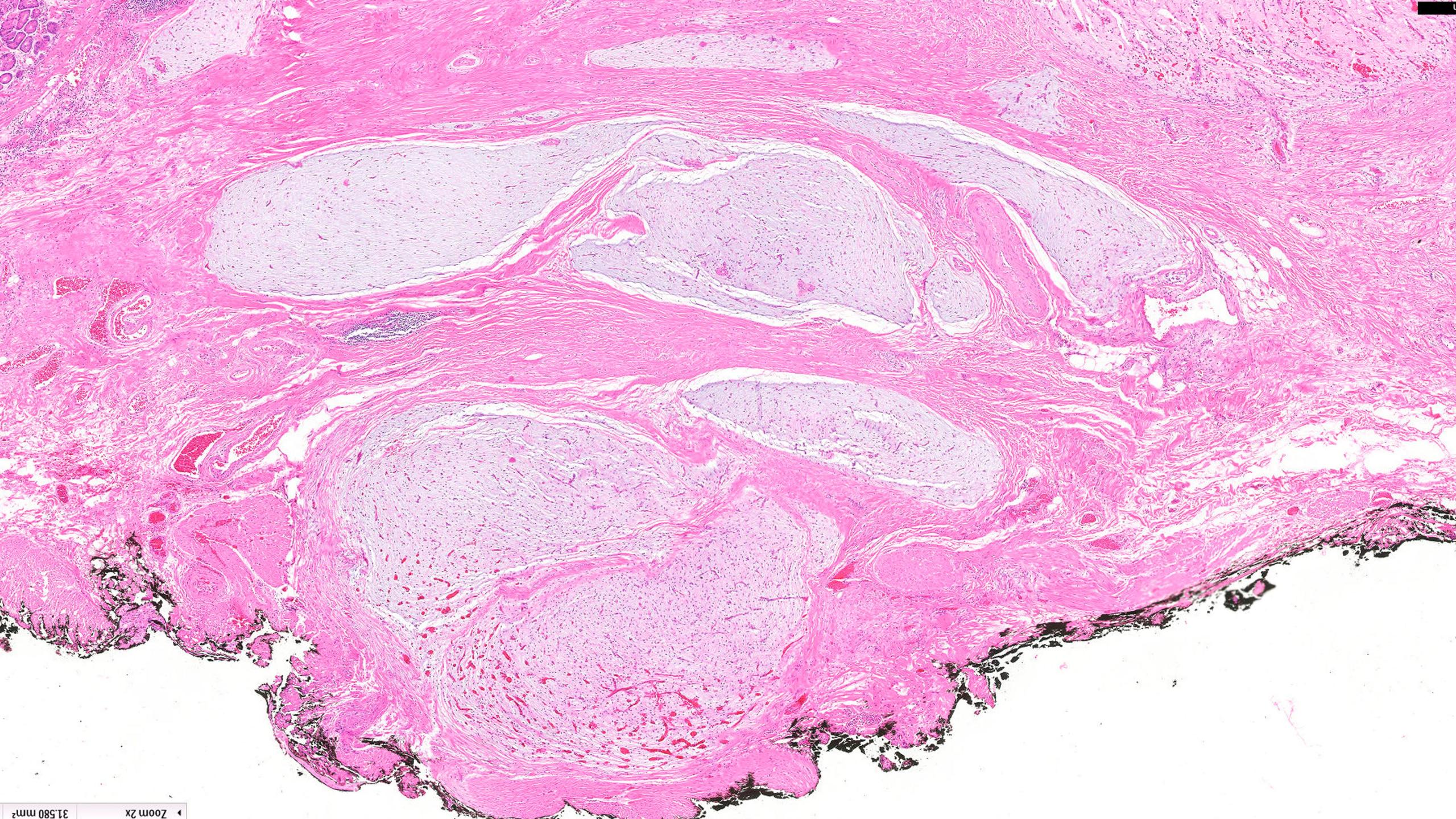


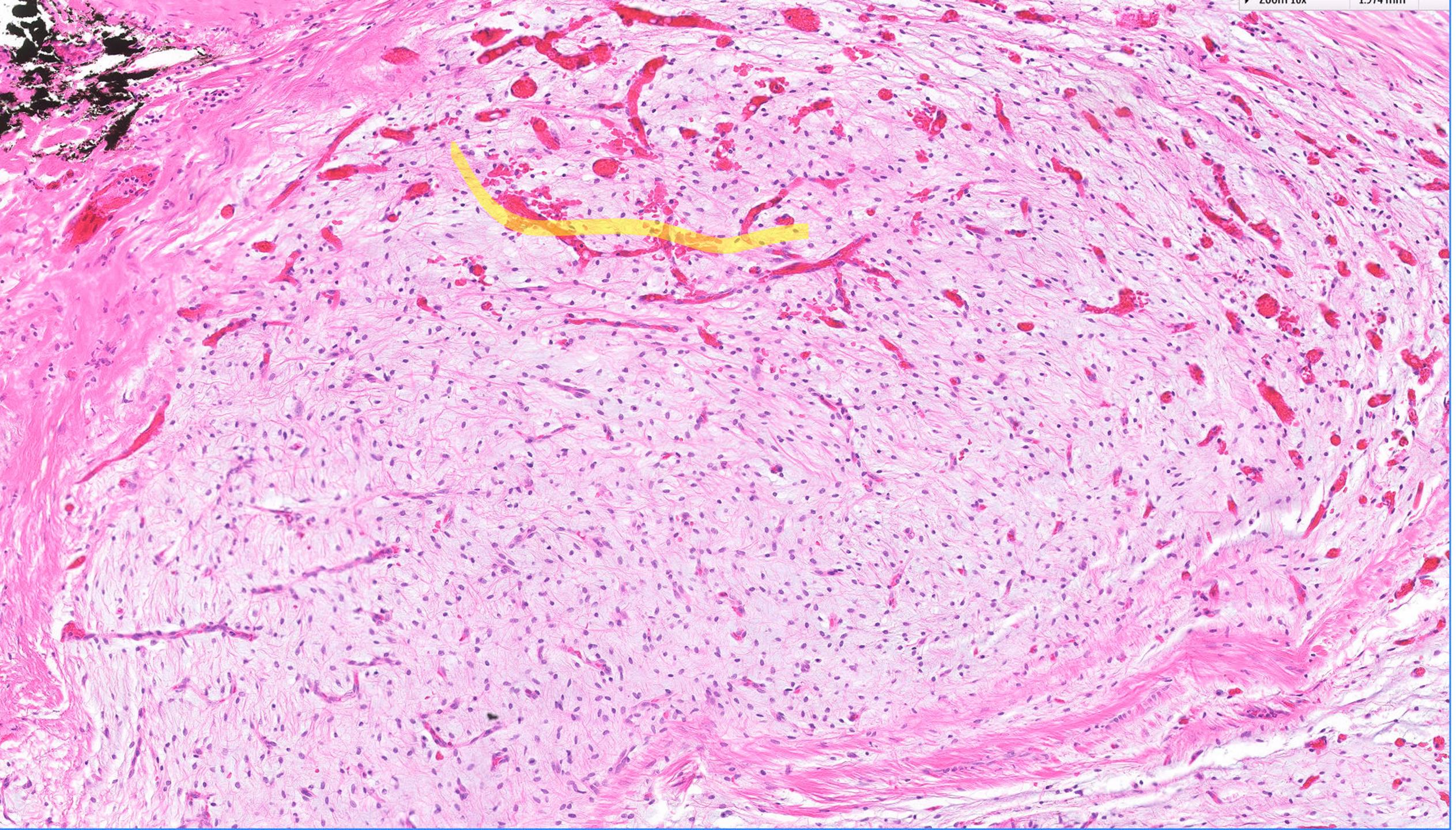


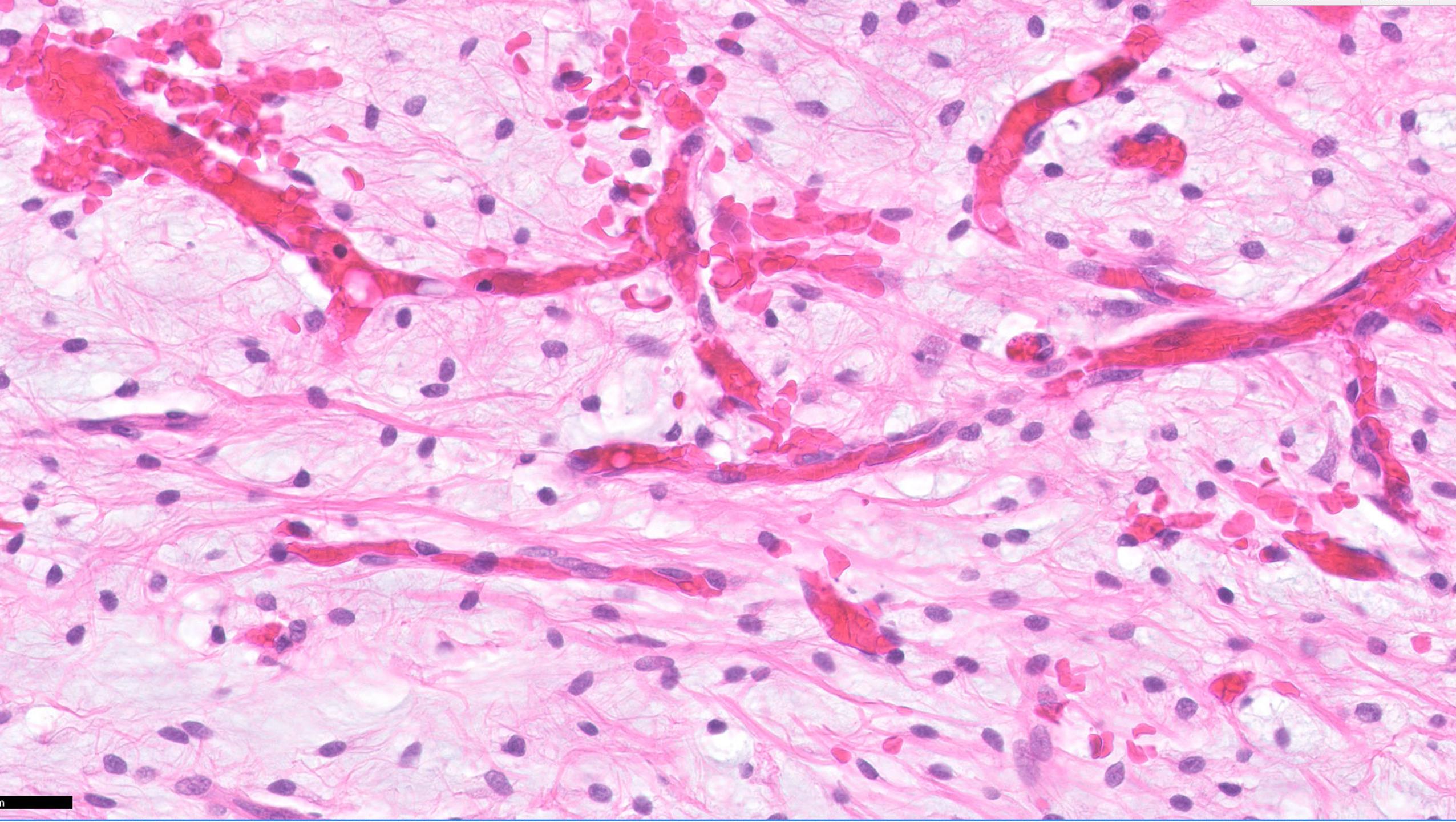
@HubertLauMD



Plexiform Fibromyxoma







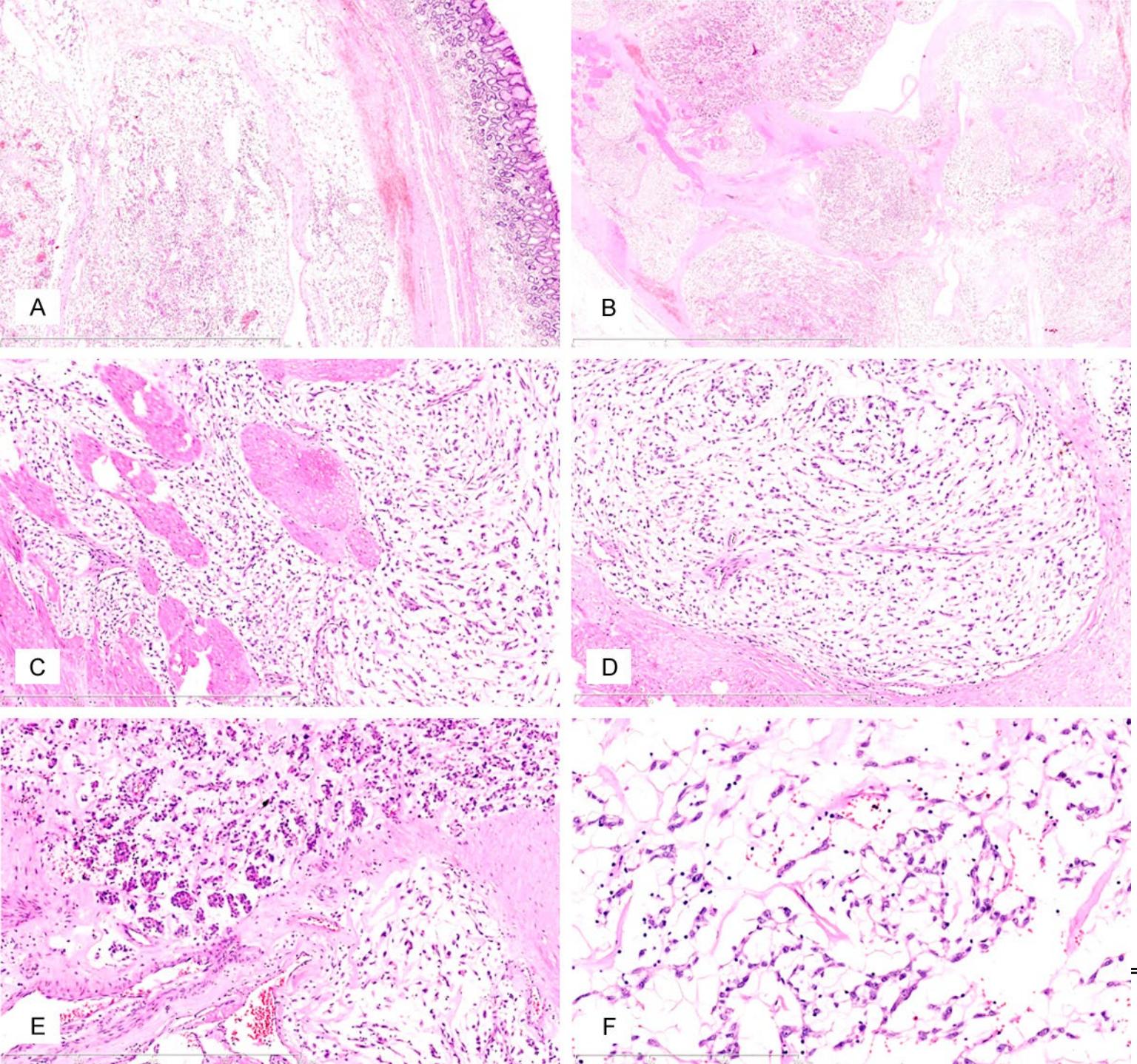
GLI-1

expression

C



HARVARD
MEDICAL SCHOOL



Myxoid GIST



HARVARD
MEDICAL SCHOOL

GIST treated with imatinib



Plexiform Fibromyxoma

- 5th decade
- Benign tumor almost always arises in stomach (antrum)
- Complete excision is curative
- Vascular invasion is often present and has no apparent significance
- *MALAT1-GLI1* fusions and *GLI1* polysomy



Gastroblastoma

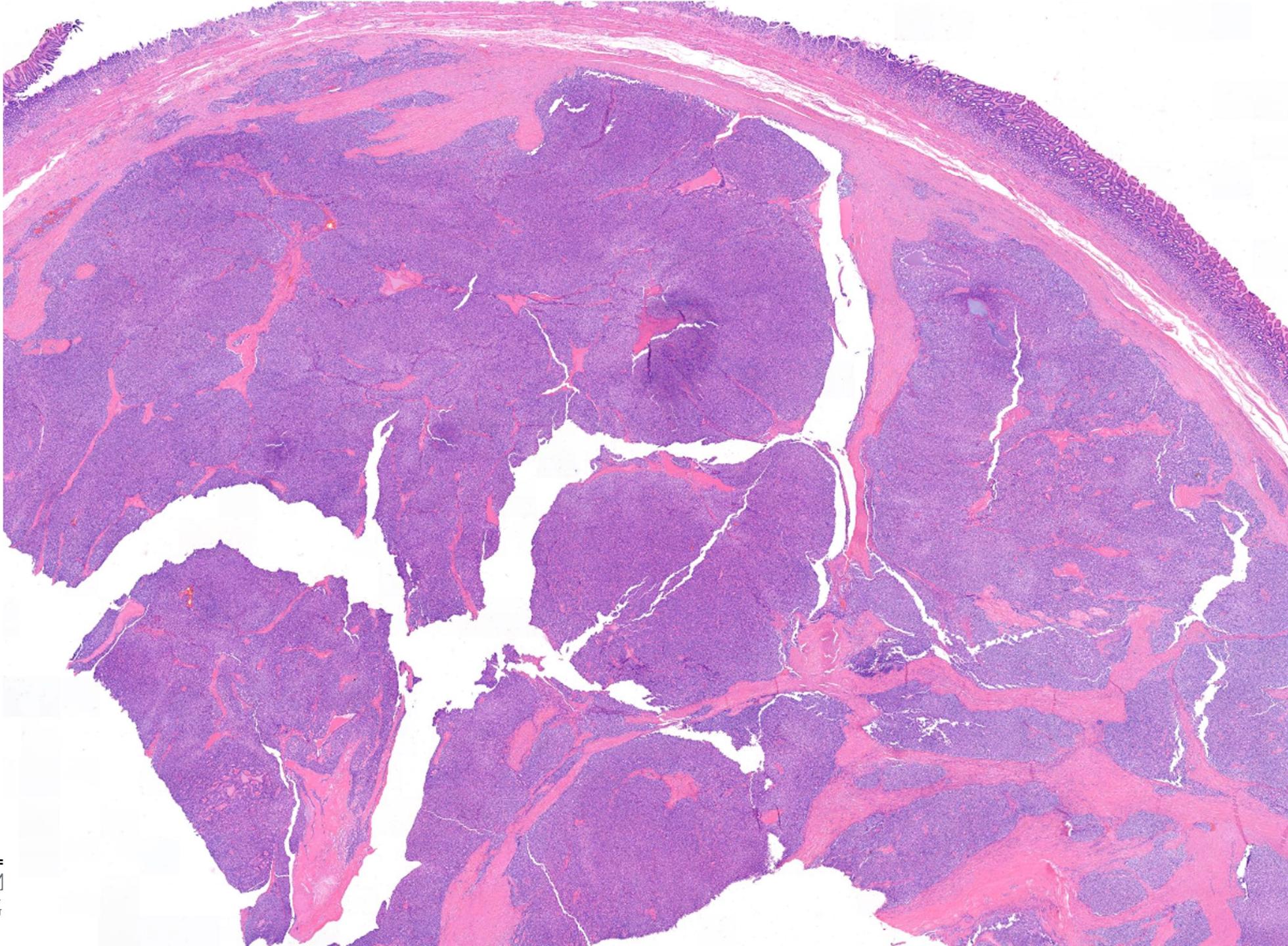
MALAT1-GLI1

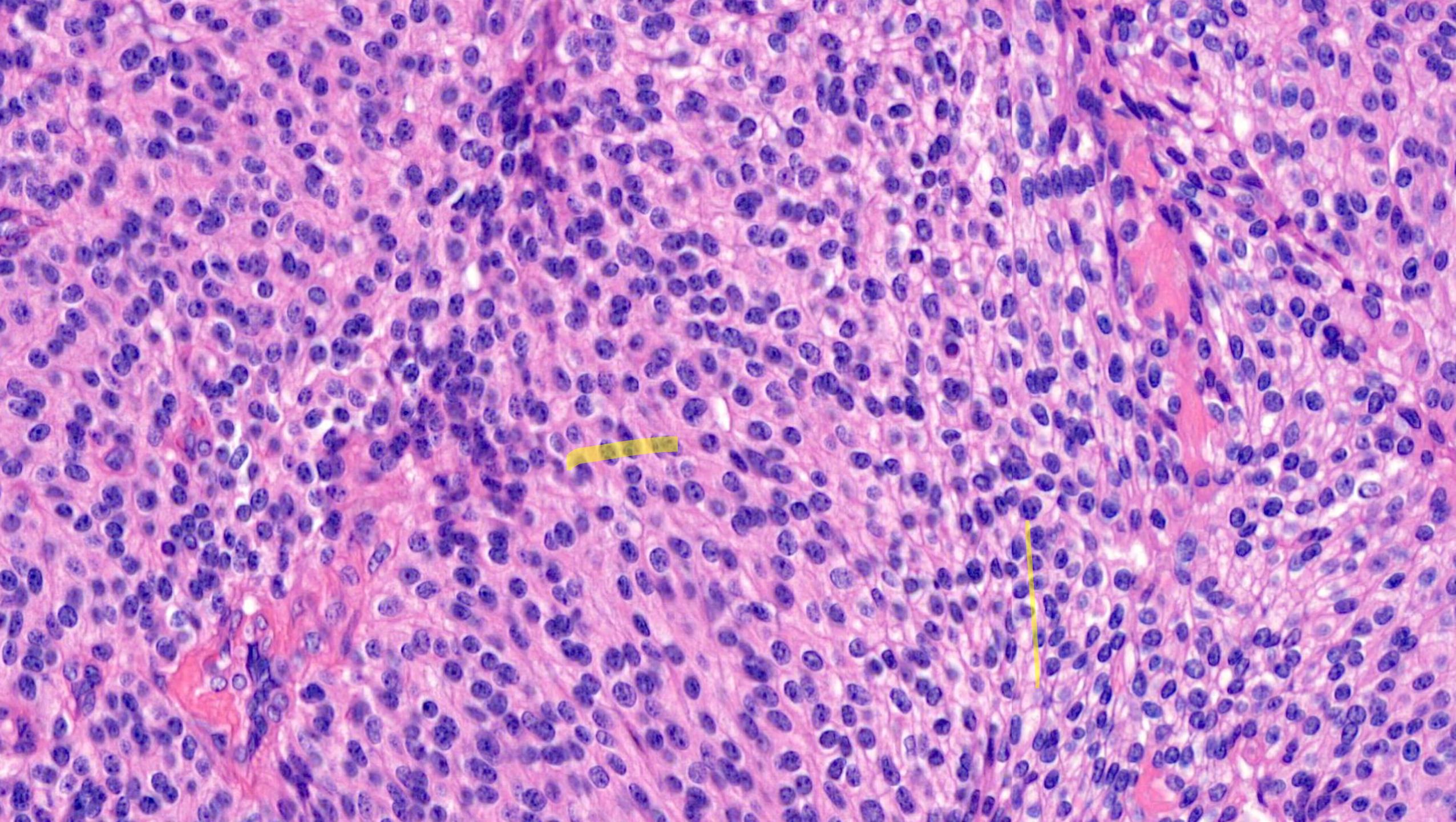


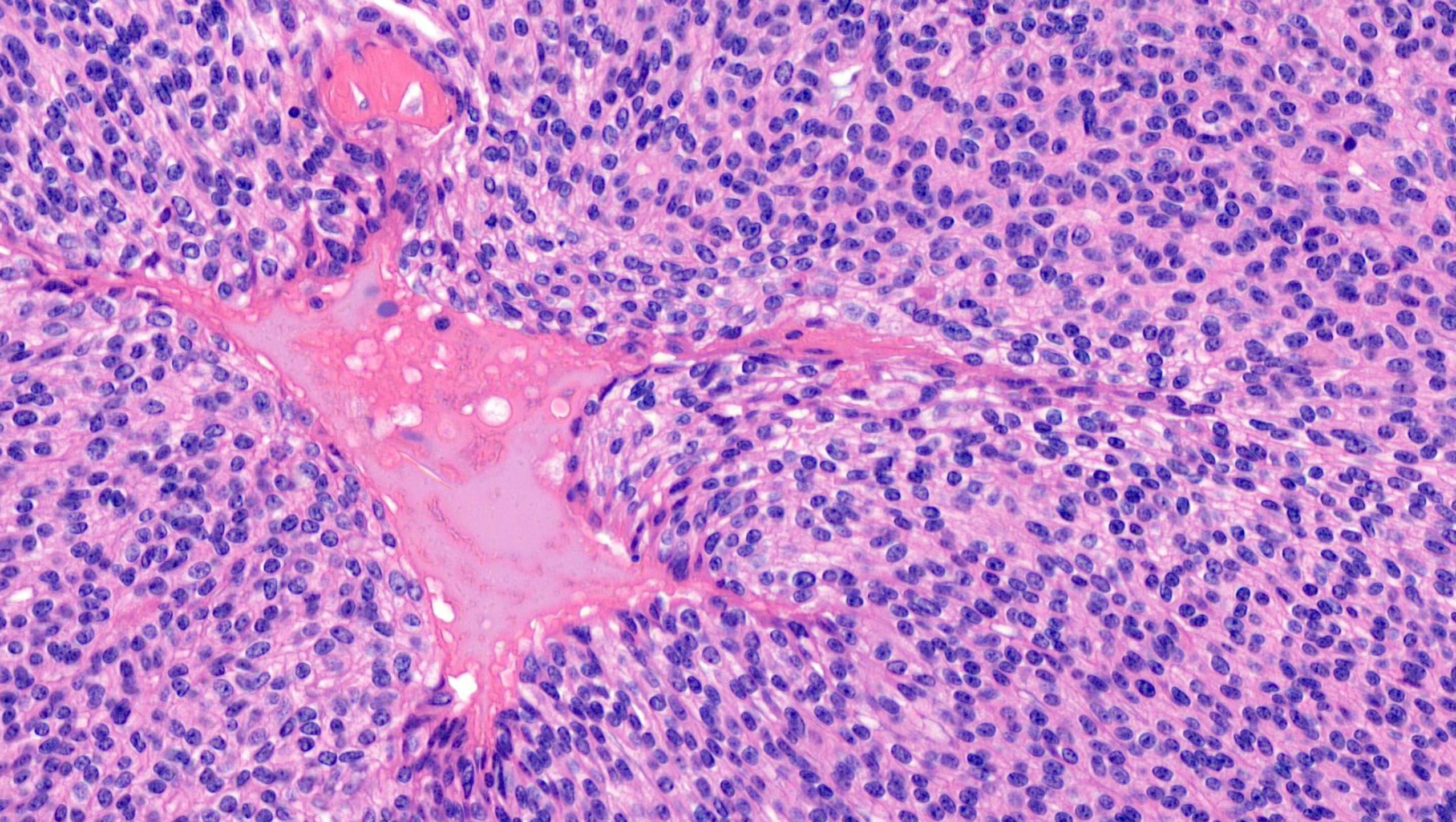
MASSACHUSETTS
GENERAL HOSPITAL



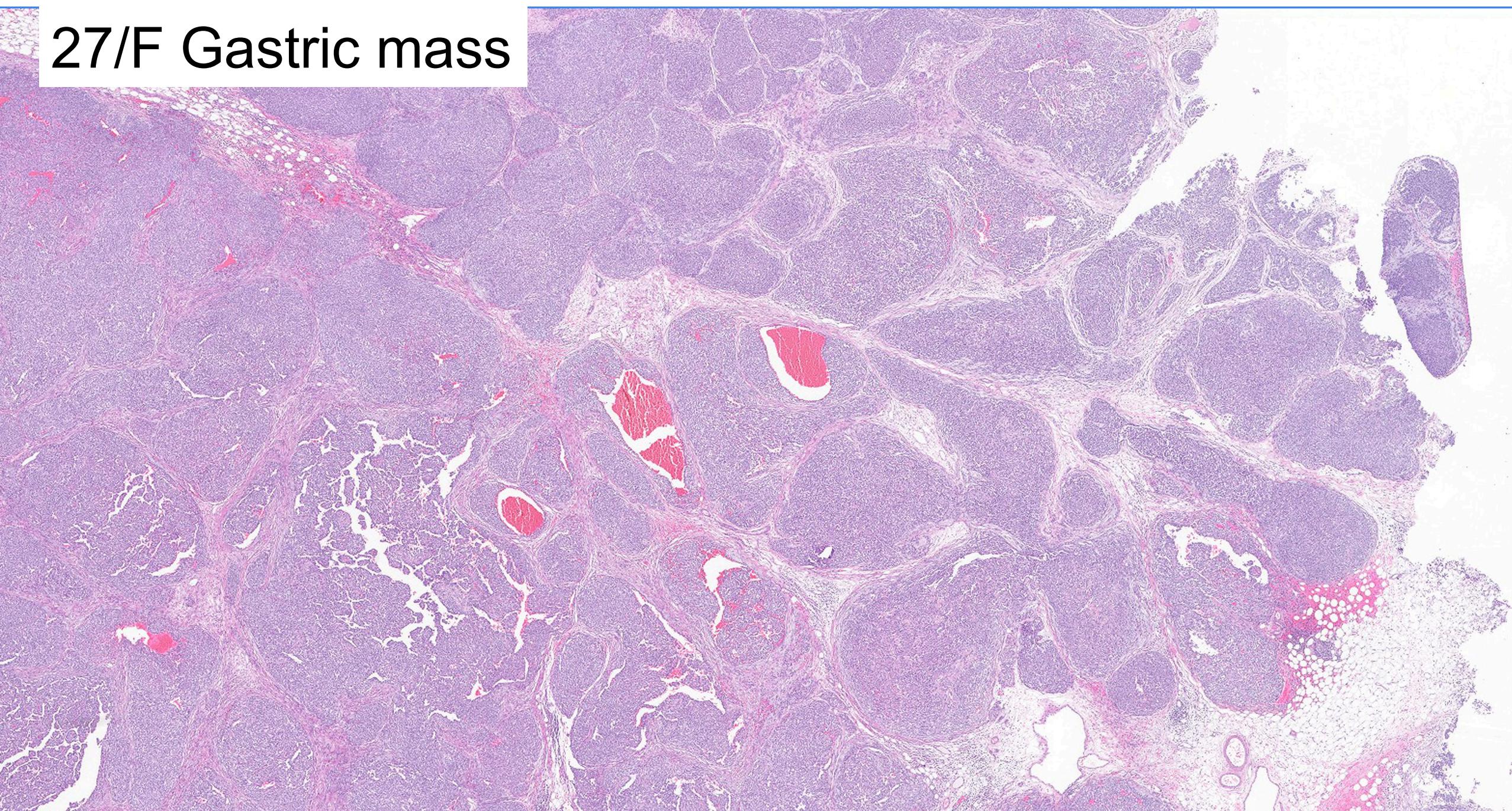
HARVARD
MEDICAL SCHOOL

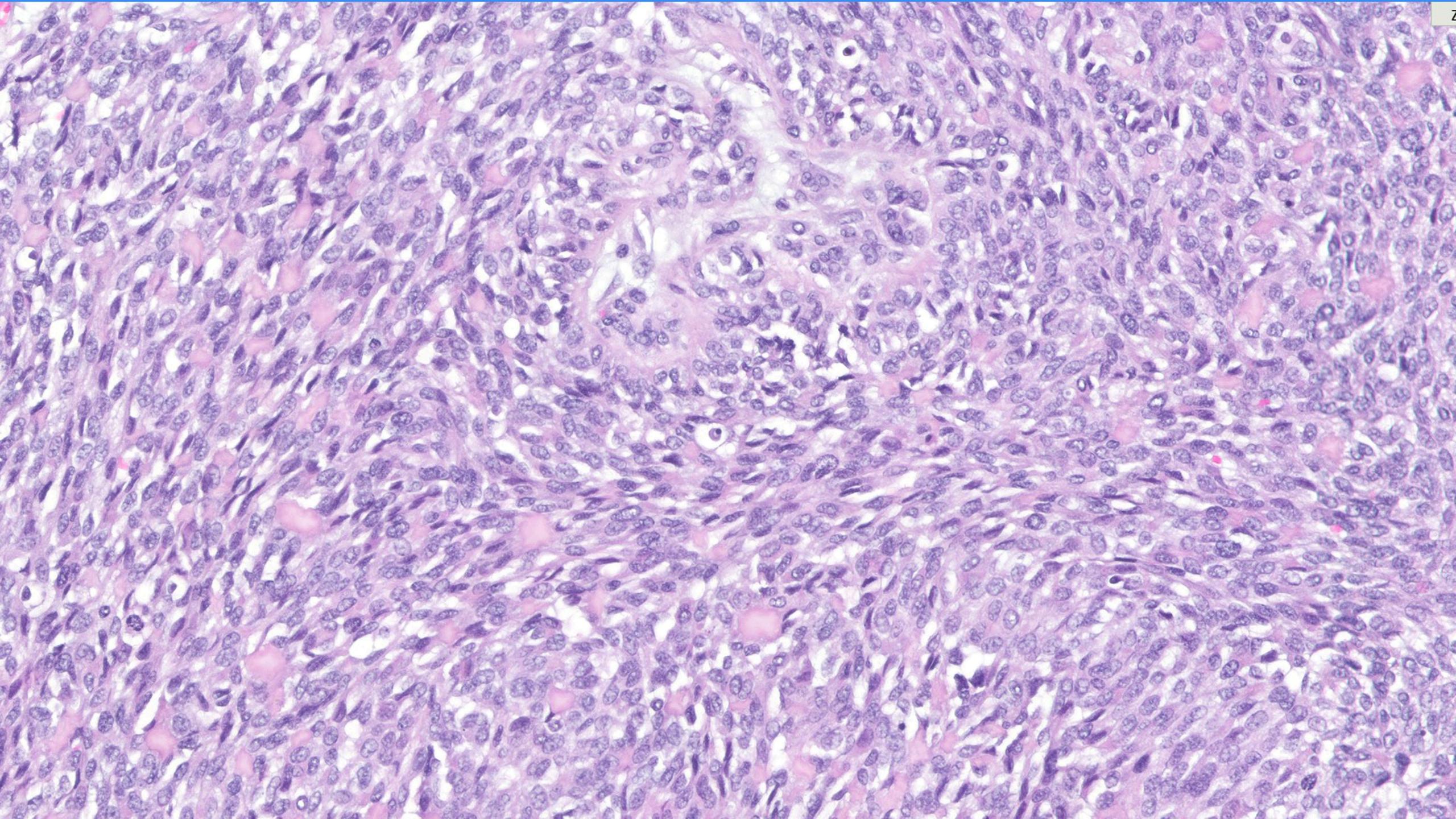


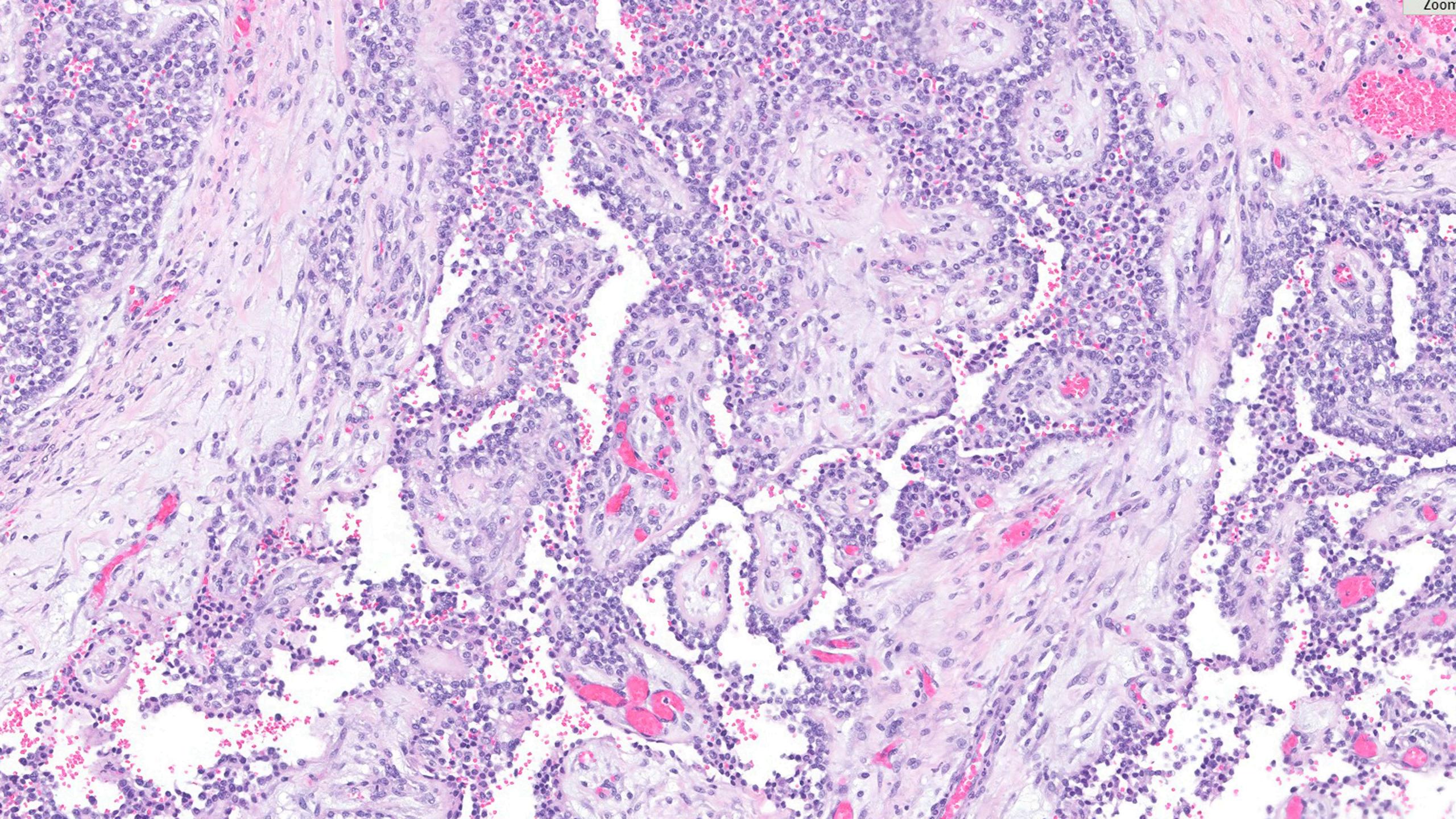




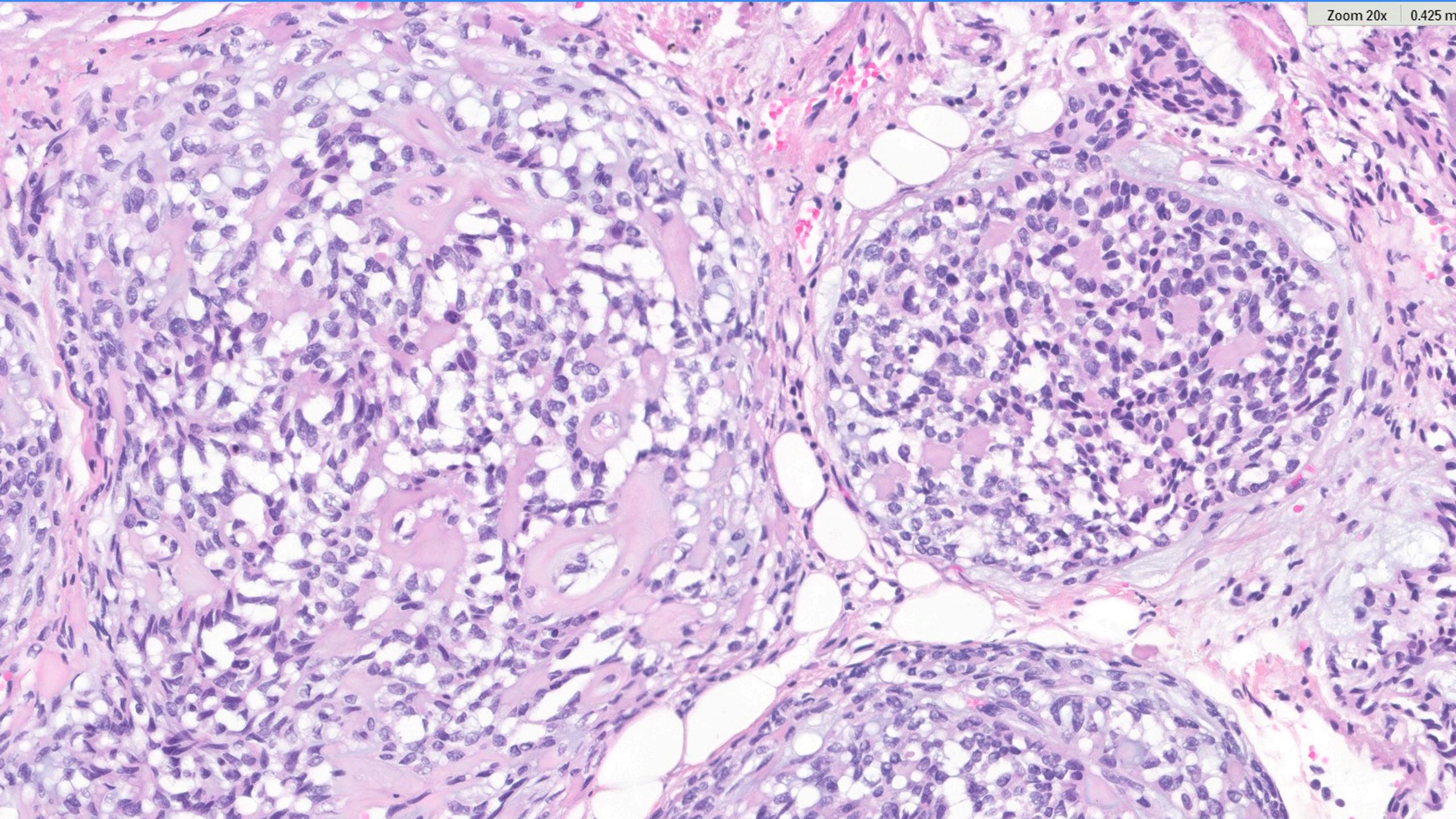
27/F Gastric mass

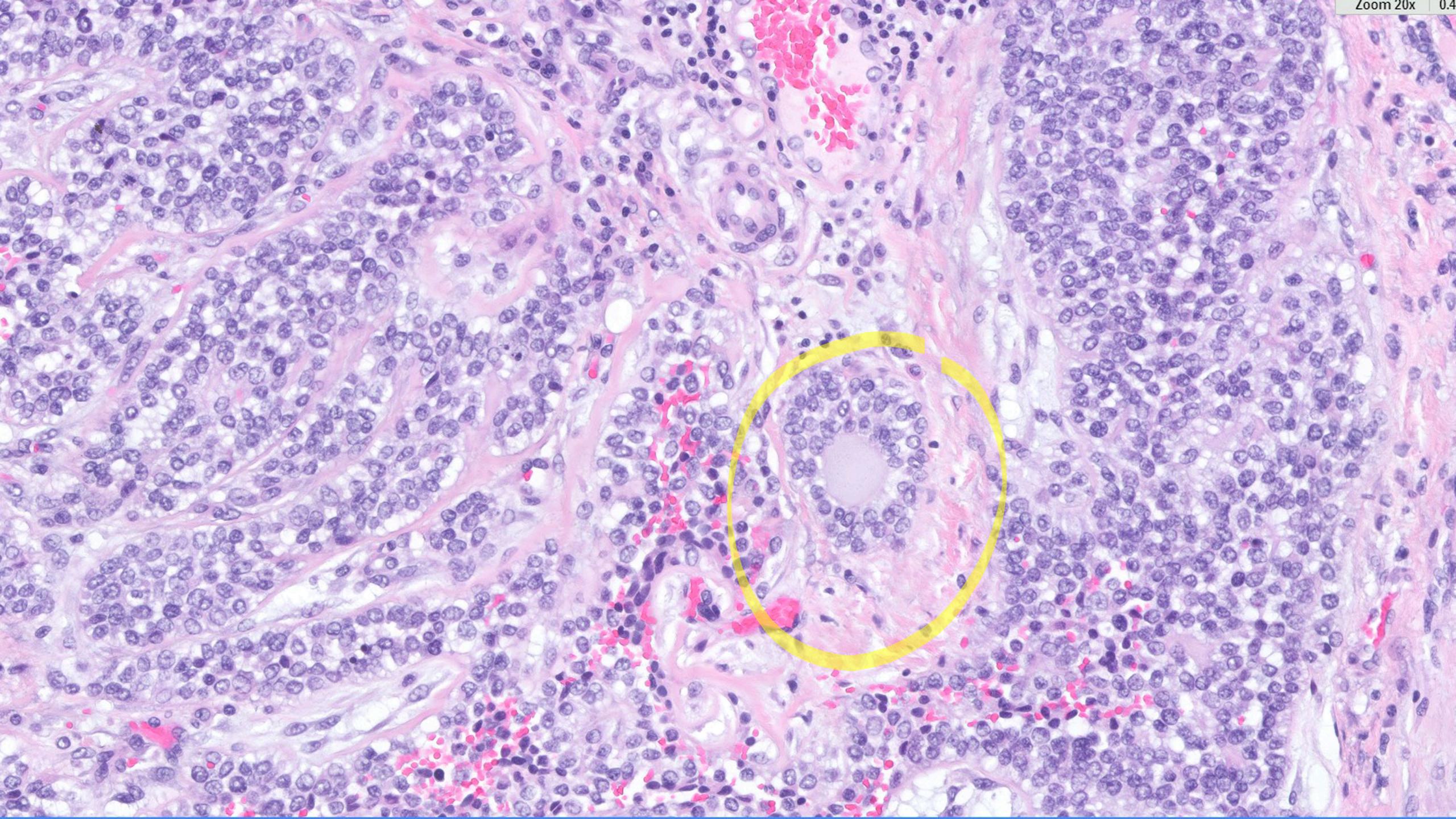


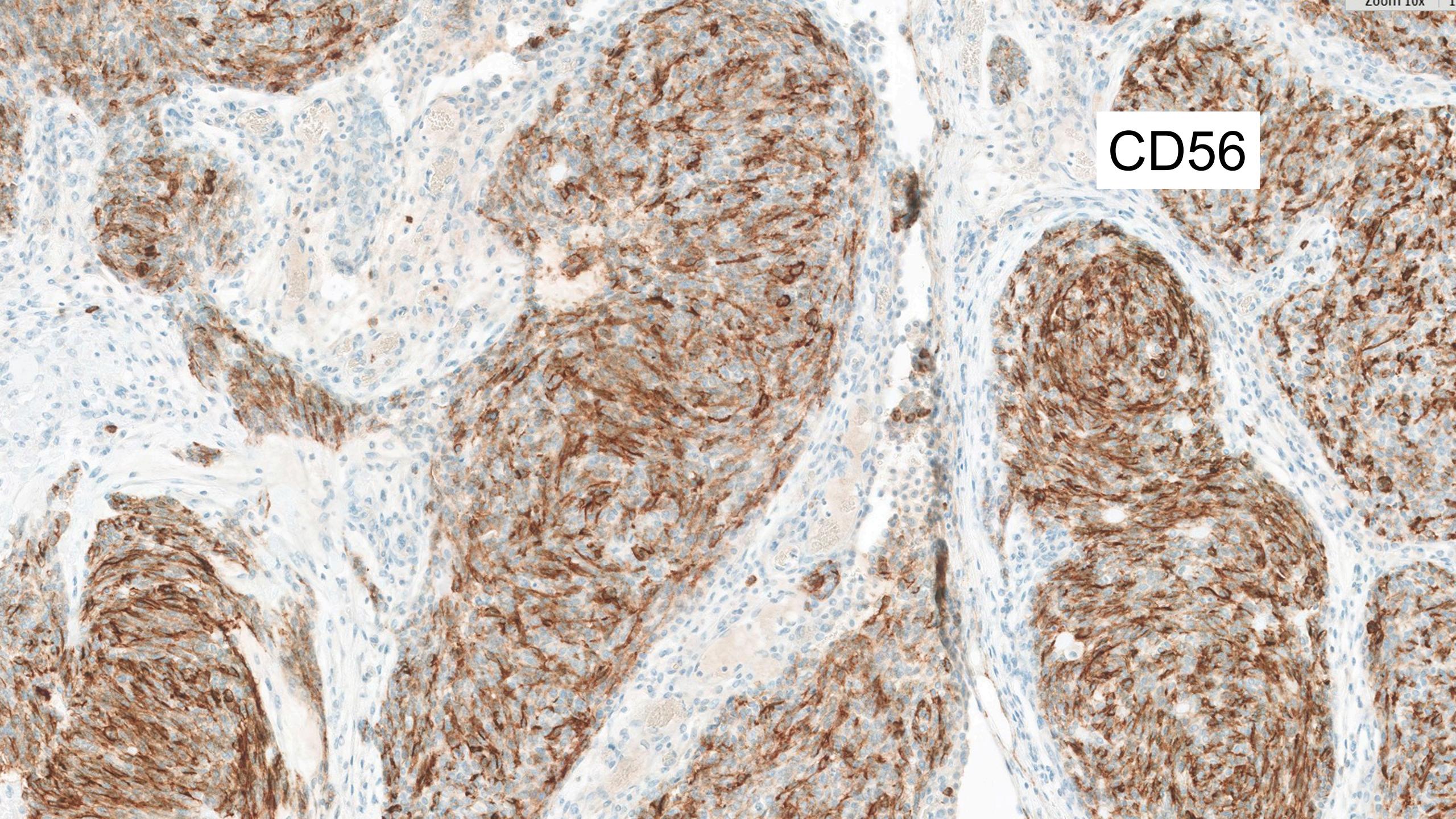




Zoom 20x | 0.425 m



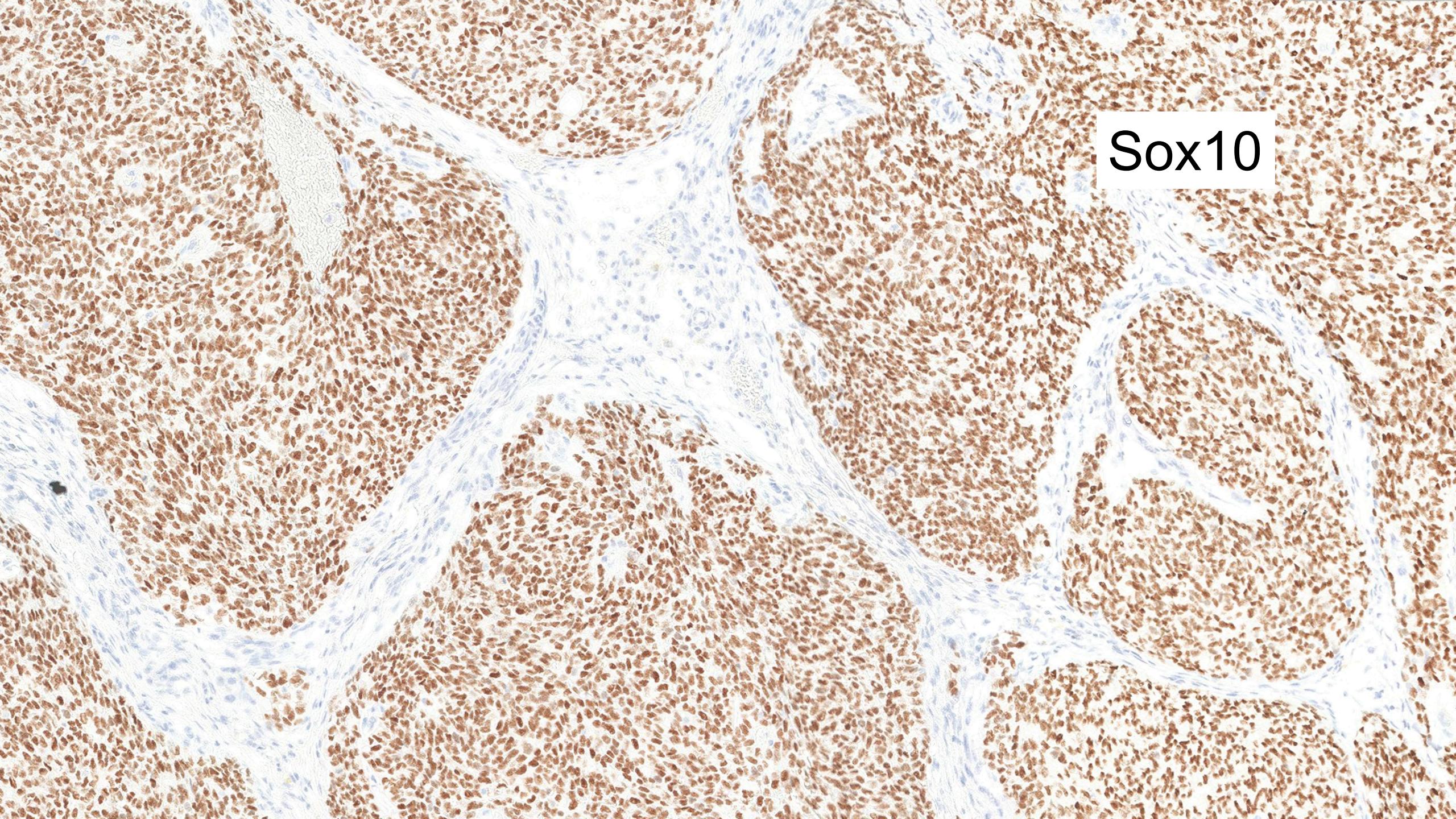




CD56

S100

This image shows immunohistochemical staining for the protein S100. The staining is performed on tissue sections, likely from a peripheral nerve biopsy, as indicated by the label 'S100' in the top right corner. The brown color represents S100-positive fibers, which are primarily located in the periphery of the nerve fascicles. These fibers appear to be myelinated, based on their thick, brown-stained appearance. The surrounding tissue, including the epineurium and perineurium, shows sparse, small brown spots, characteristic of S100 expression in Schwann cells. The overall pattern is consistent with a diagnosis of a peripheral neuropathy, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). A scale bar is visible in the bottom right corner.



Sox10

EWSR1-ATF1

GI tract Clear Cell Sarcoma

Malignant Gastrointestinal neuroectodermal tumor

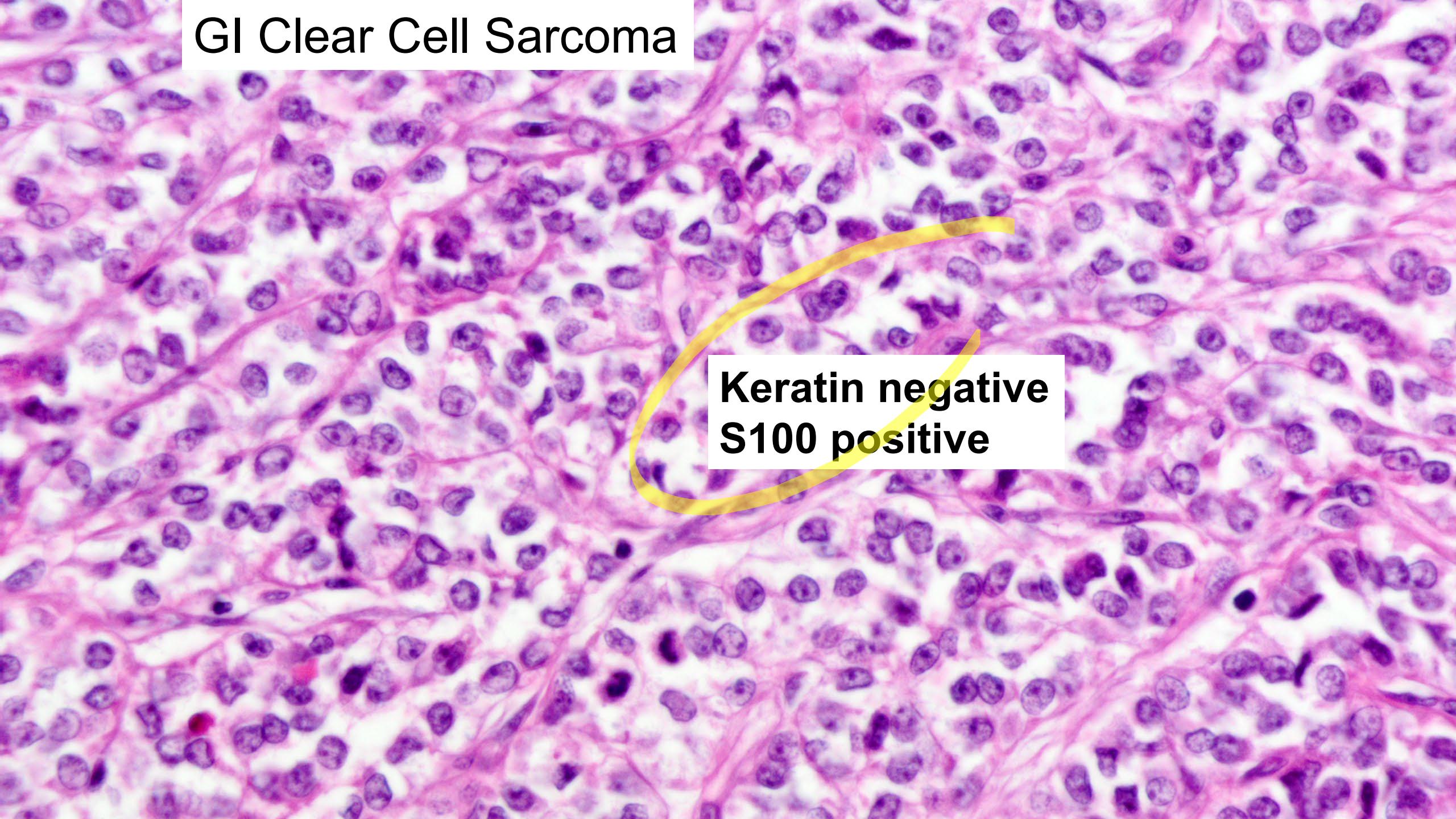


MASSACHUSETTS
GENERAL HOSPITAL



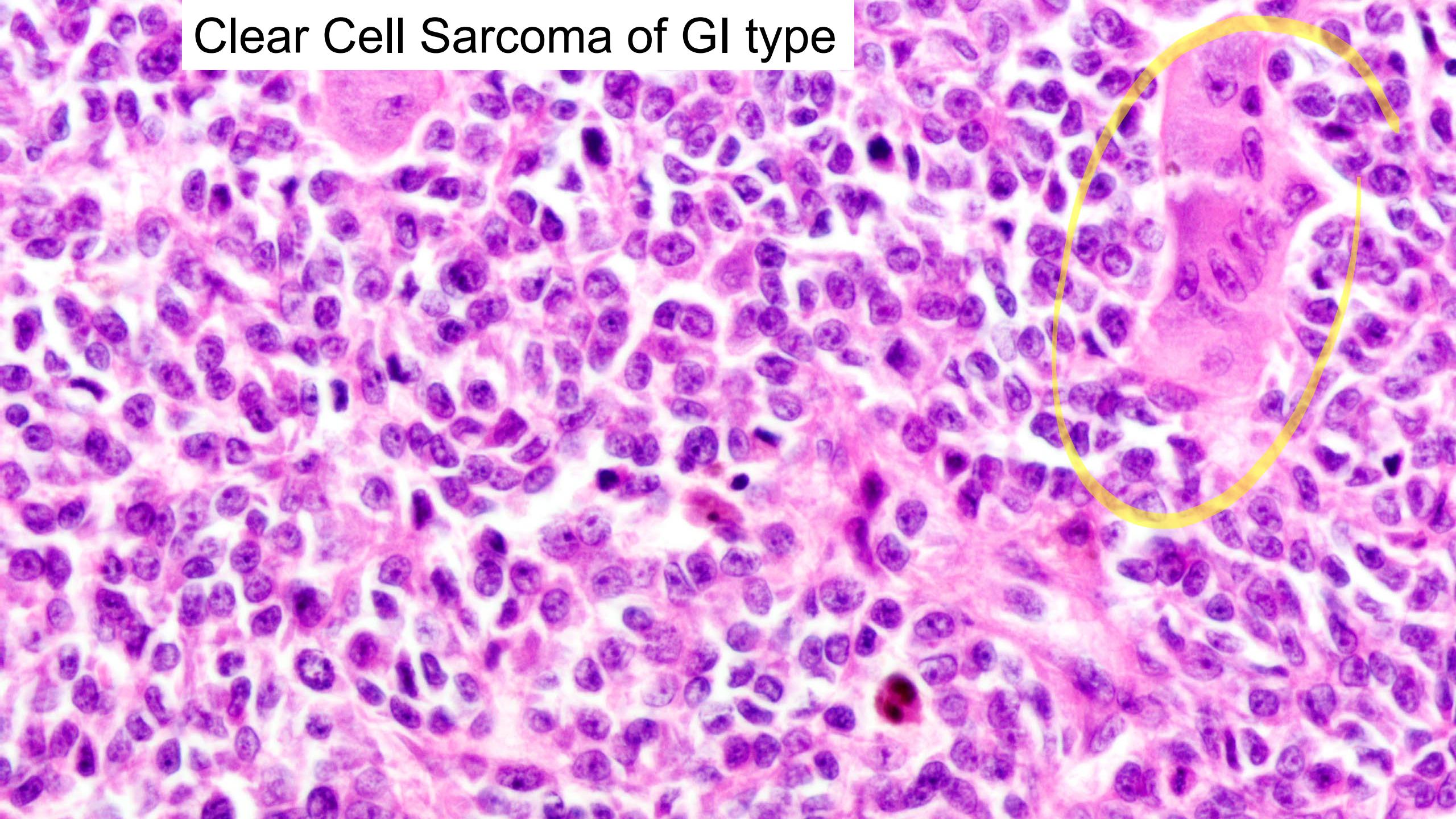
HARVARD
MEDICAL SCHOOL

GI Clear Cell Sarcoma

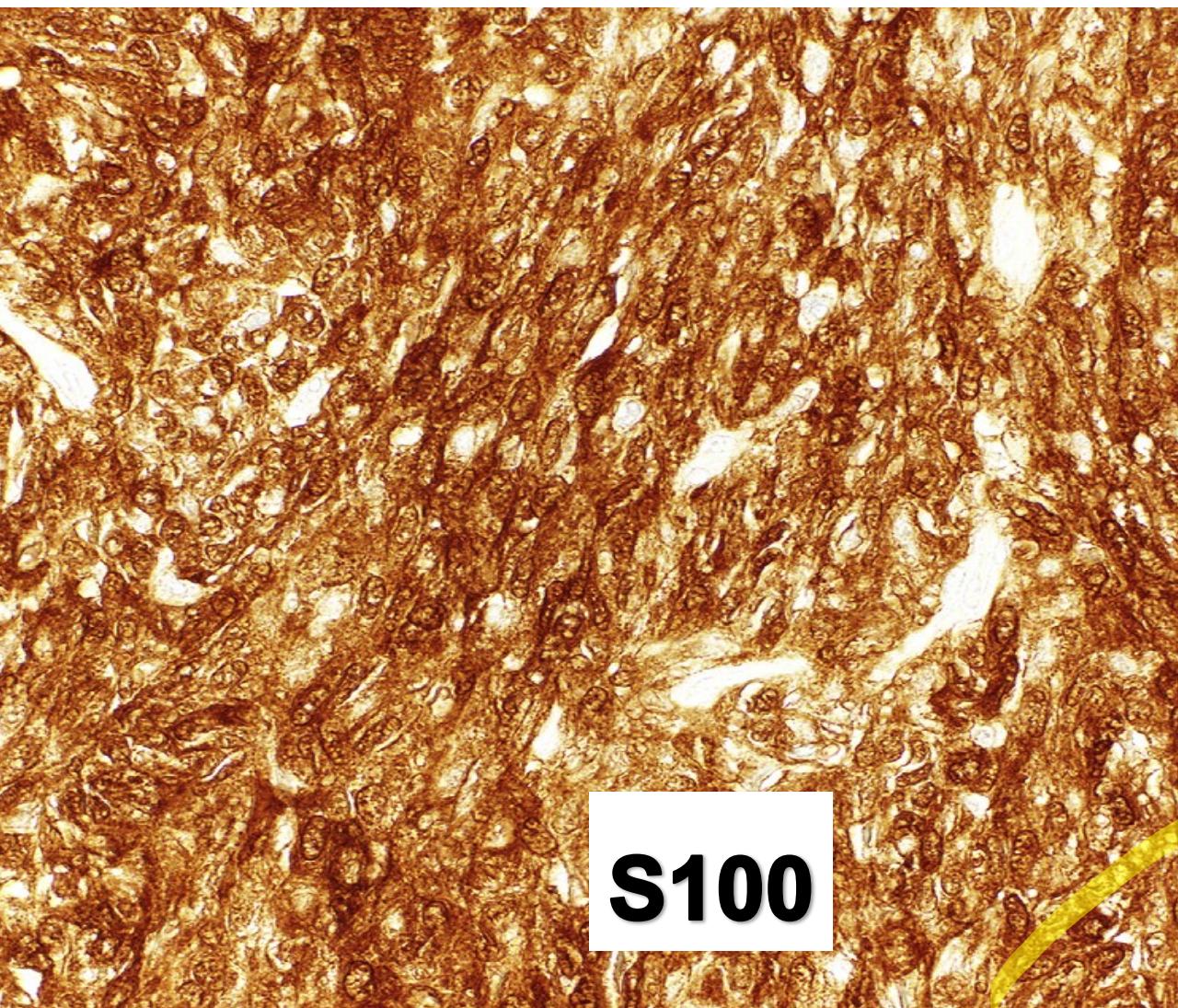


**Keratin negative
S100 positive**

Clear Cell Sarcoma of GI type



GI Clear Cell Sarcoma



Immunohistochemistry

- Positive
 - S100
- Negative
 - HMB-45, Mart-1, MiTF
- EWSR1-ATF1 or
- EWSR1-CREB1 fusion
- Aggressive clinical course

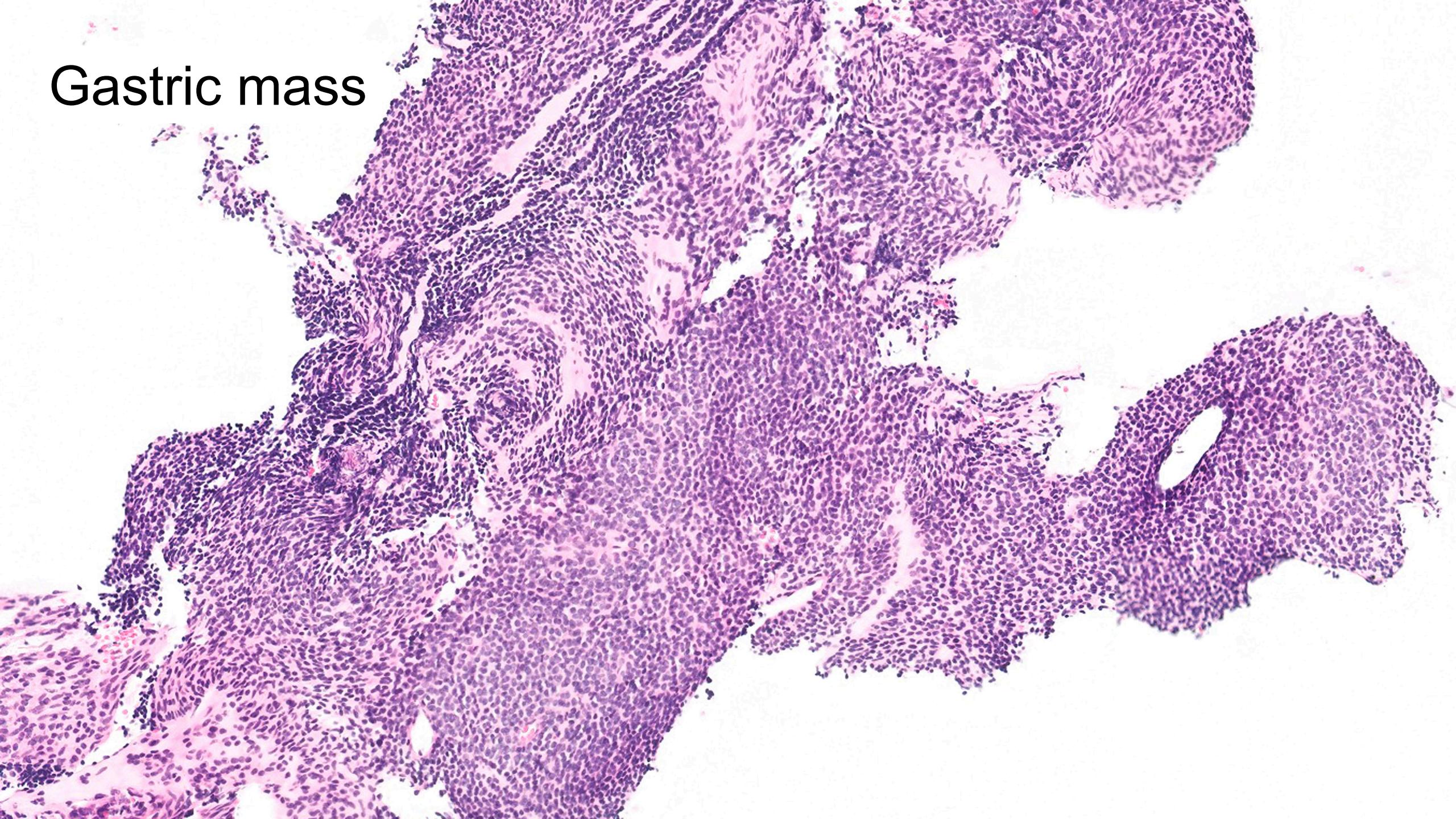


MASSACHUSETTS
GENERAL HOSPITAL



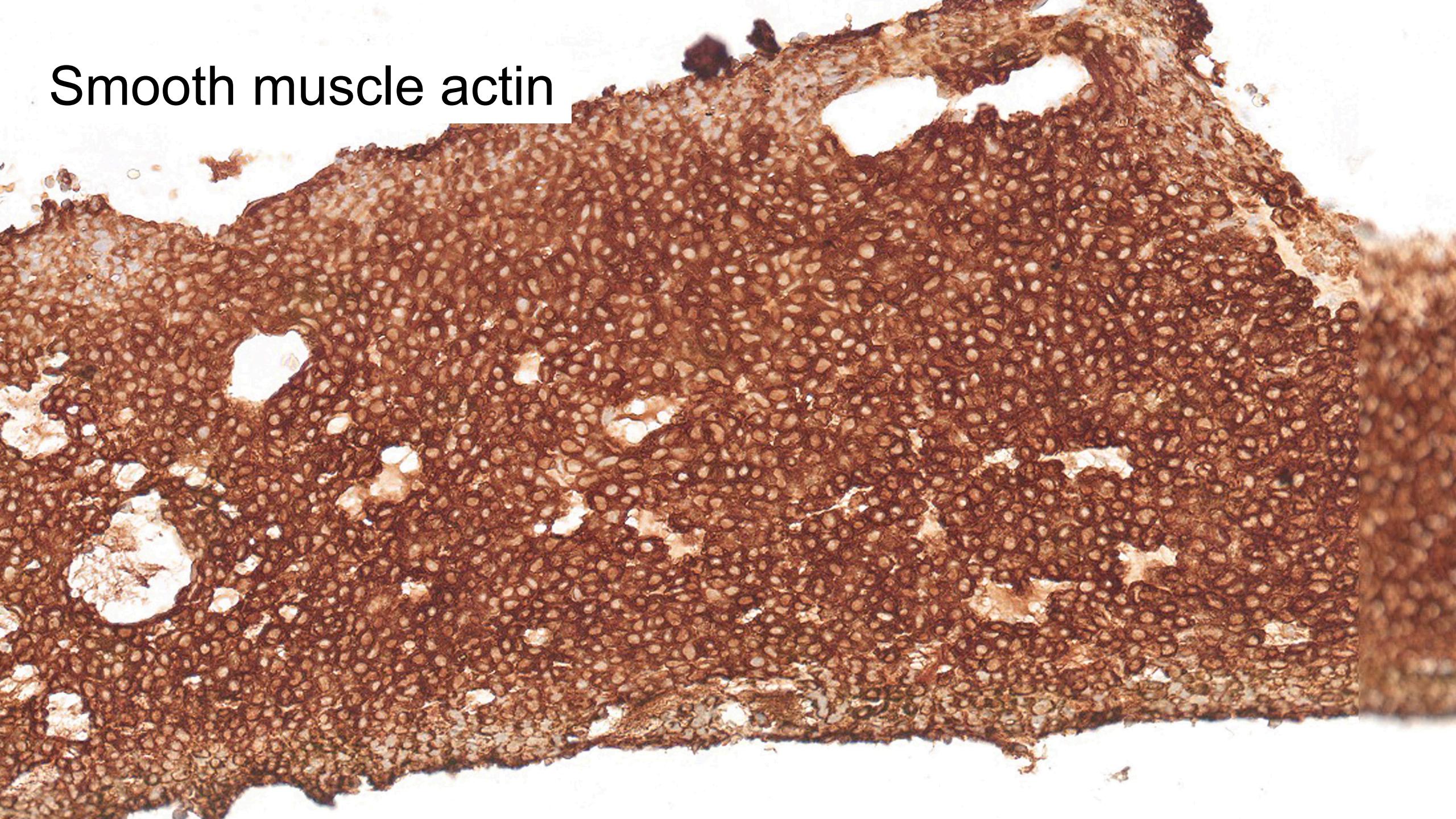
HARVARD
MEDICAL SCHOOL

Gastric mass

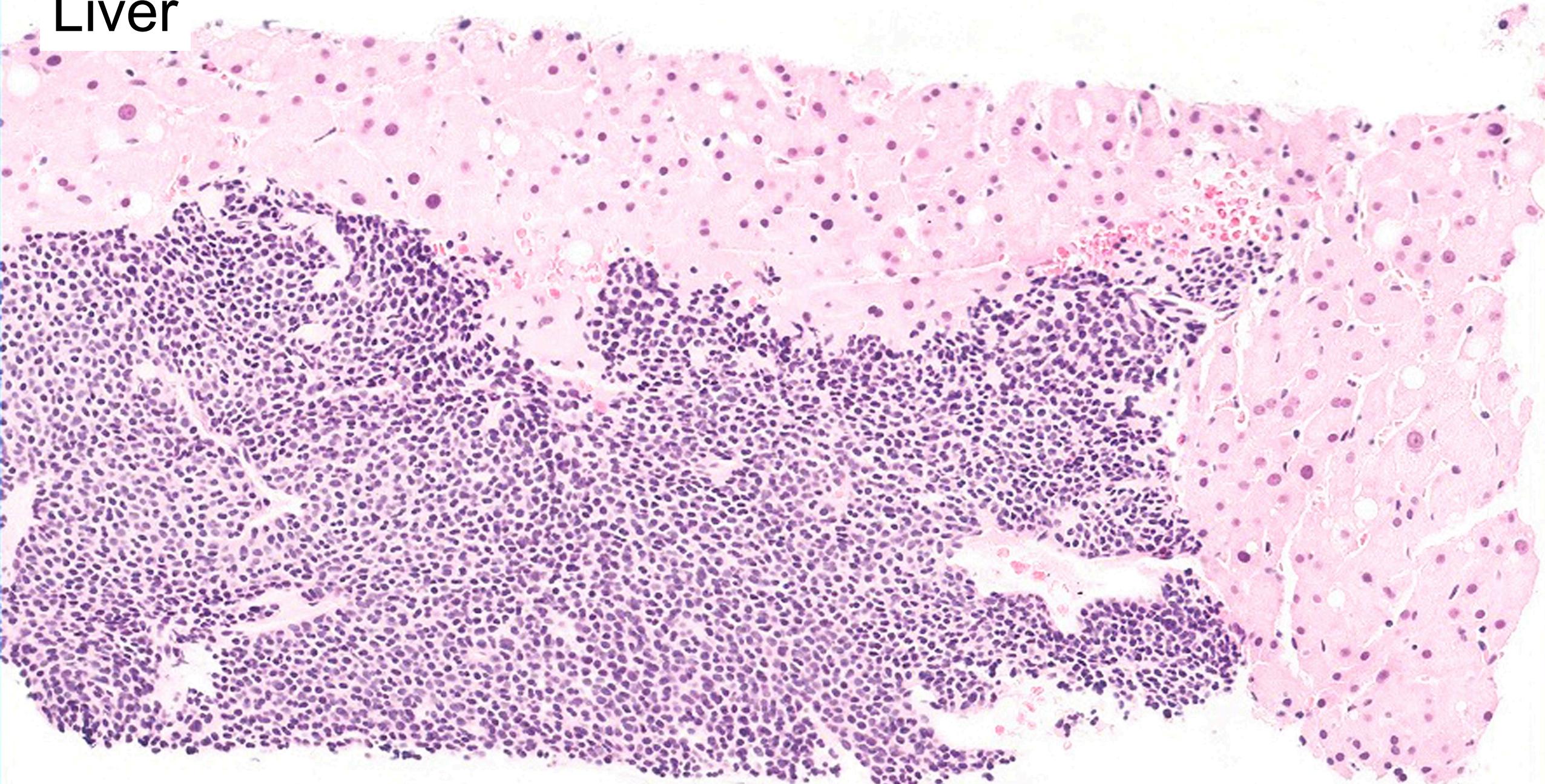


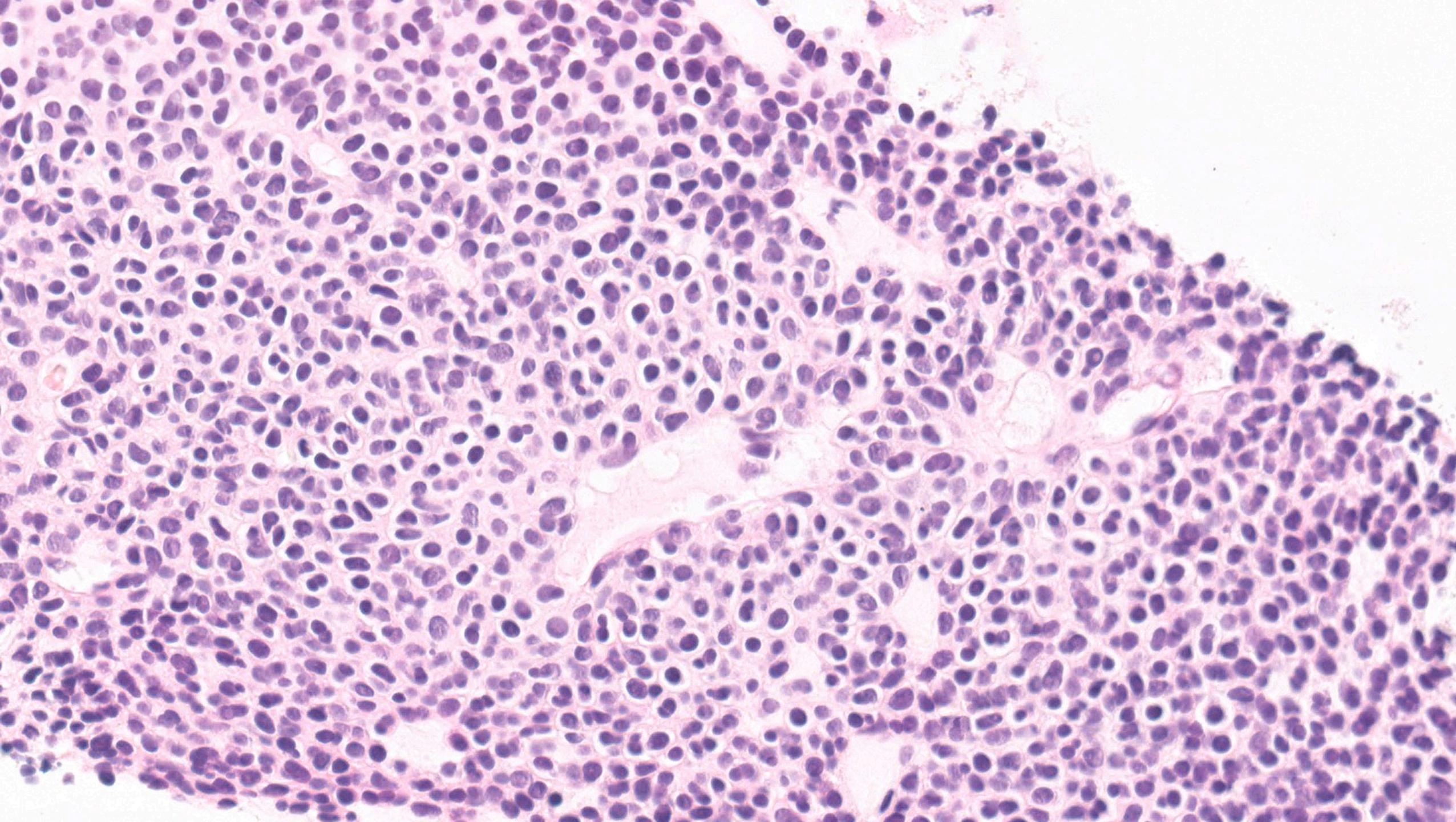


Smooth muscle actin



Liver







Malignant Glomus

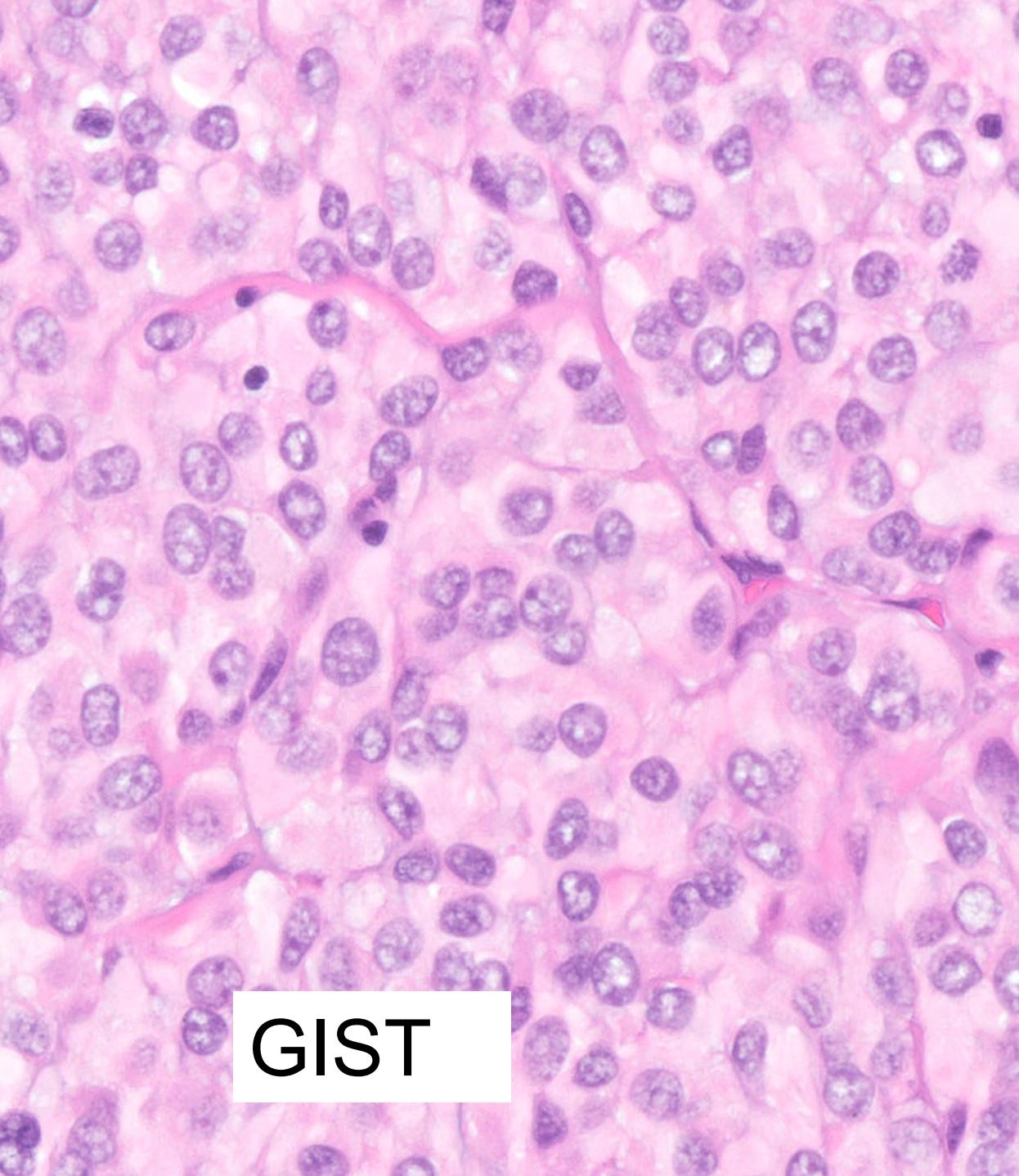
- Marked nuclear atypia (with any level of mitotic activity) or atypical mitotic figures
- An infiltrative growth pattern, high cellularity, and spindled morphology are also features significantly more common in malignant glomus tumors



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL



GIST



Glomus

Deep leiomyomas (muscularis propria)

In order of frequency

Esophagus

Stomach

Small intestine

Colon

muscularis propria



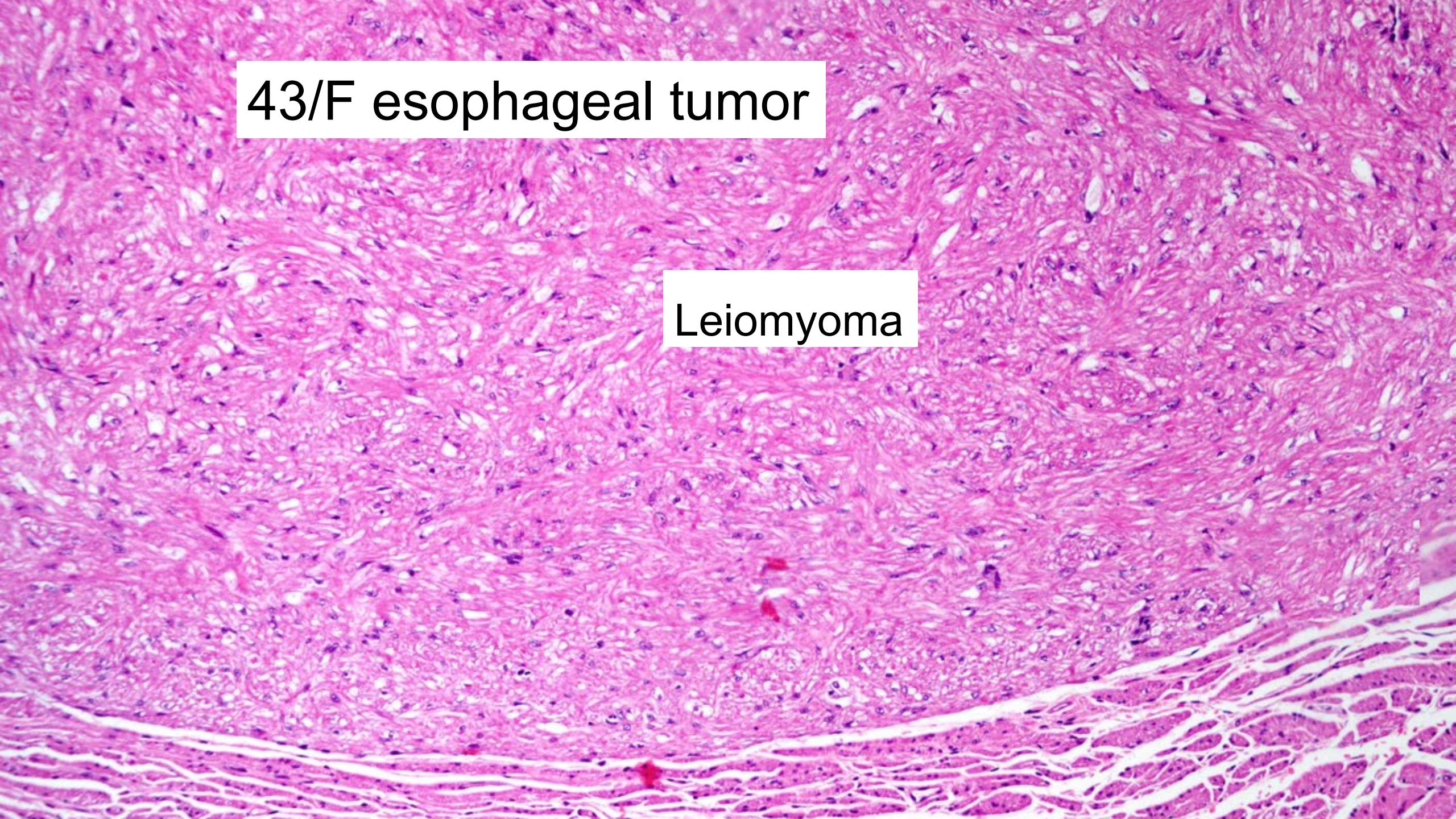
MASSACHUSETTS
GENERAL HOSPITAL

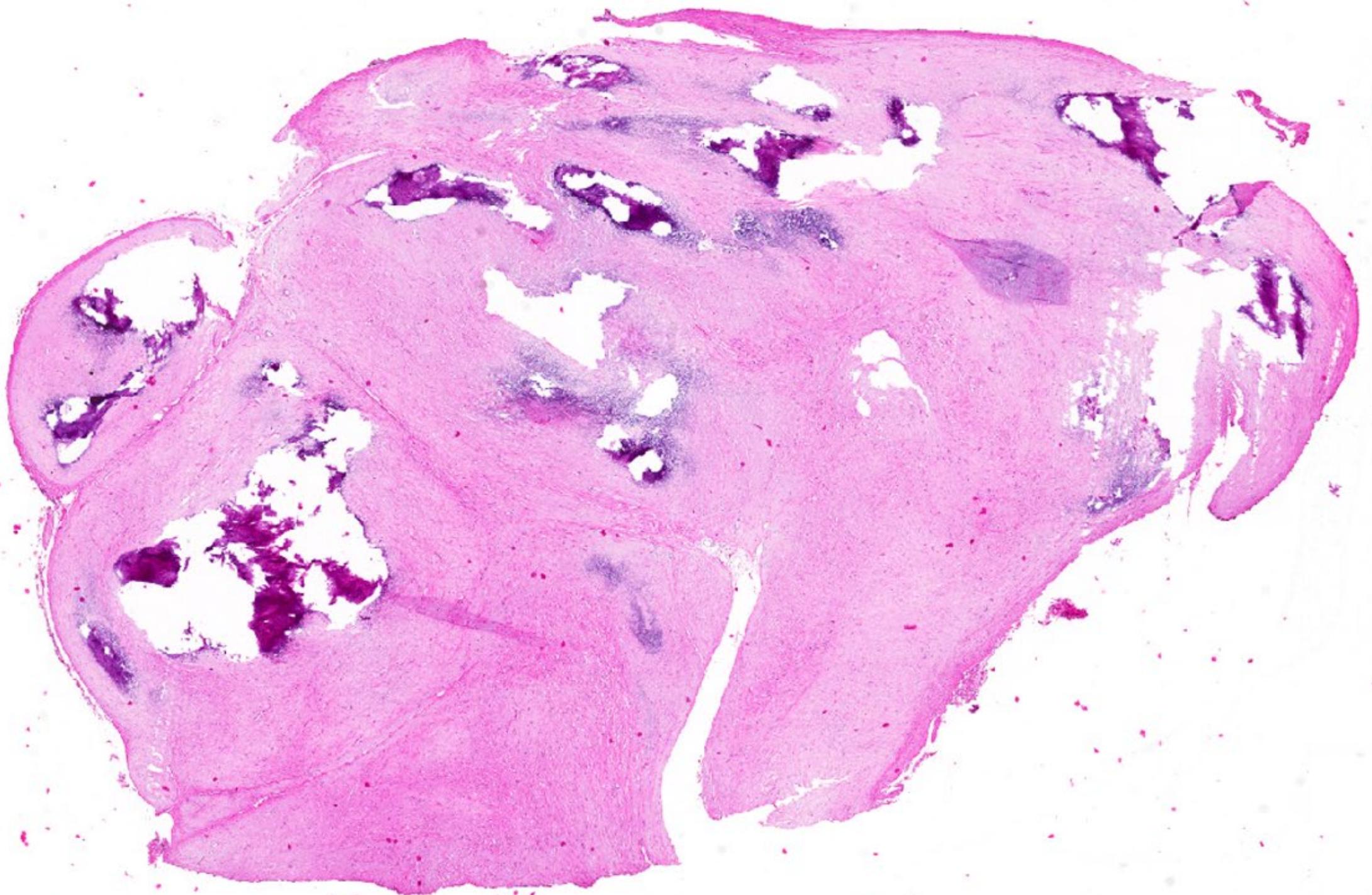


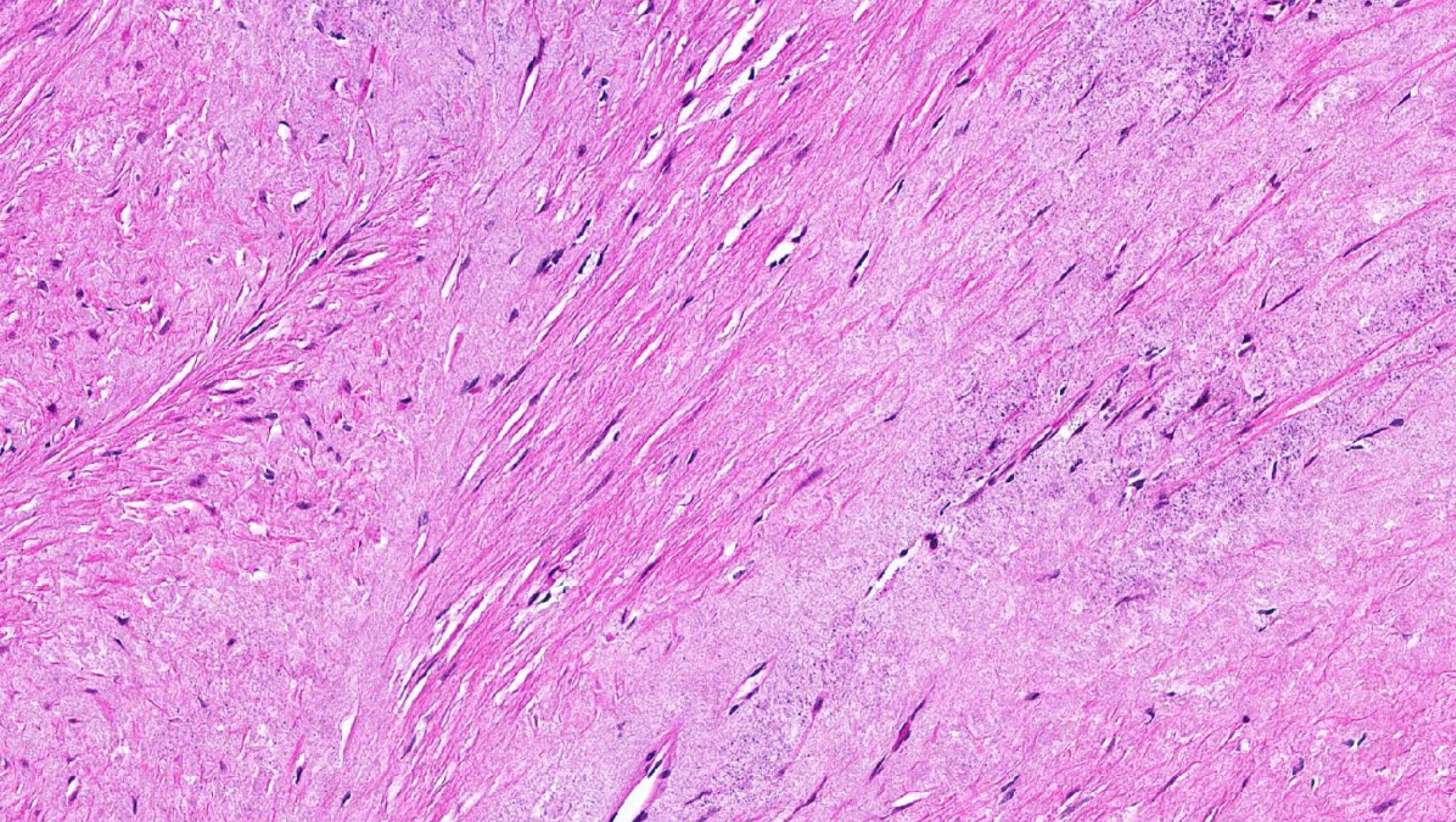
HARVARD
MEDICAL SCHOOL

43/F esophageal tumor

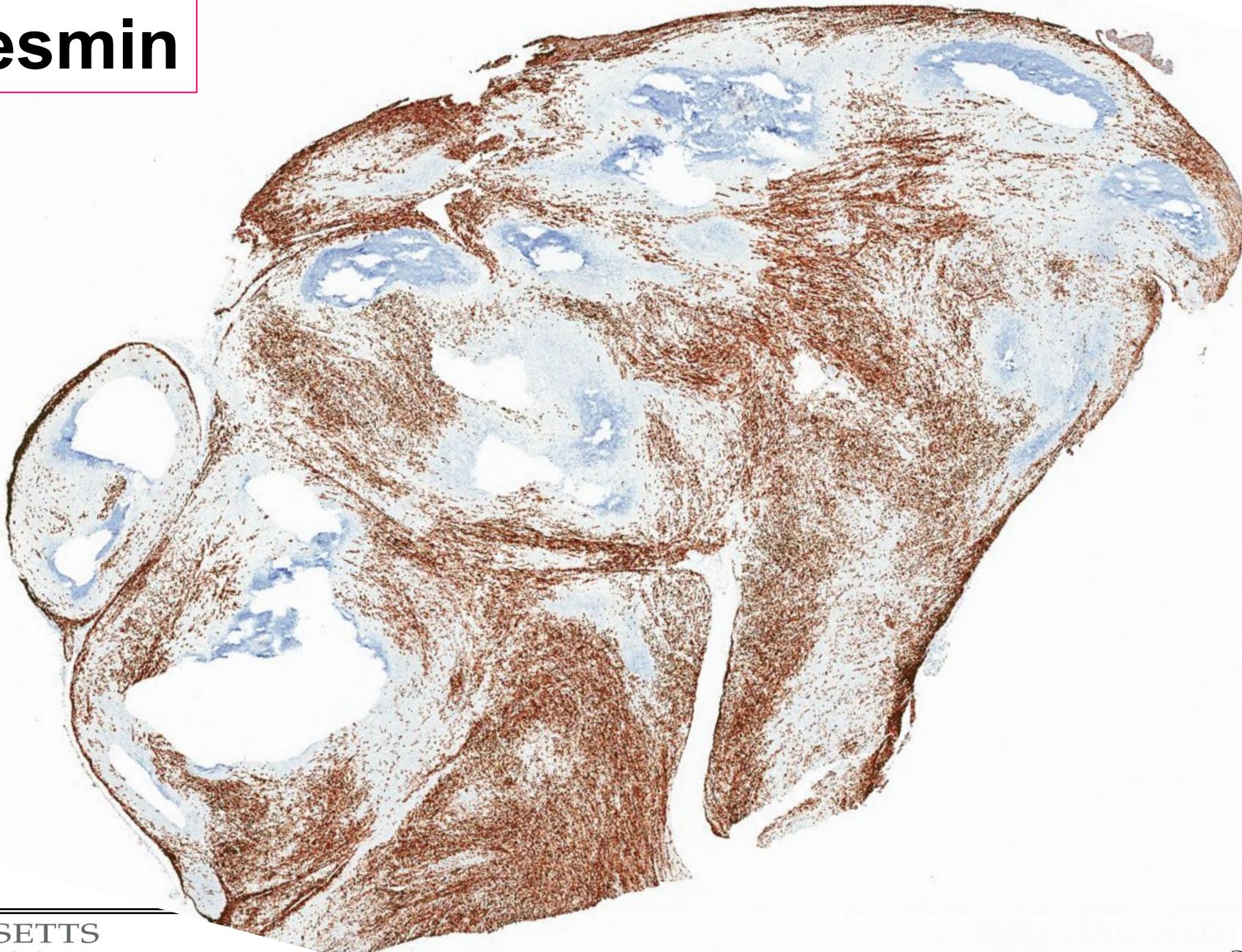
Leiomyoma







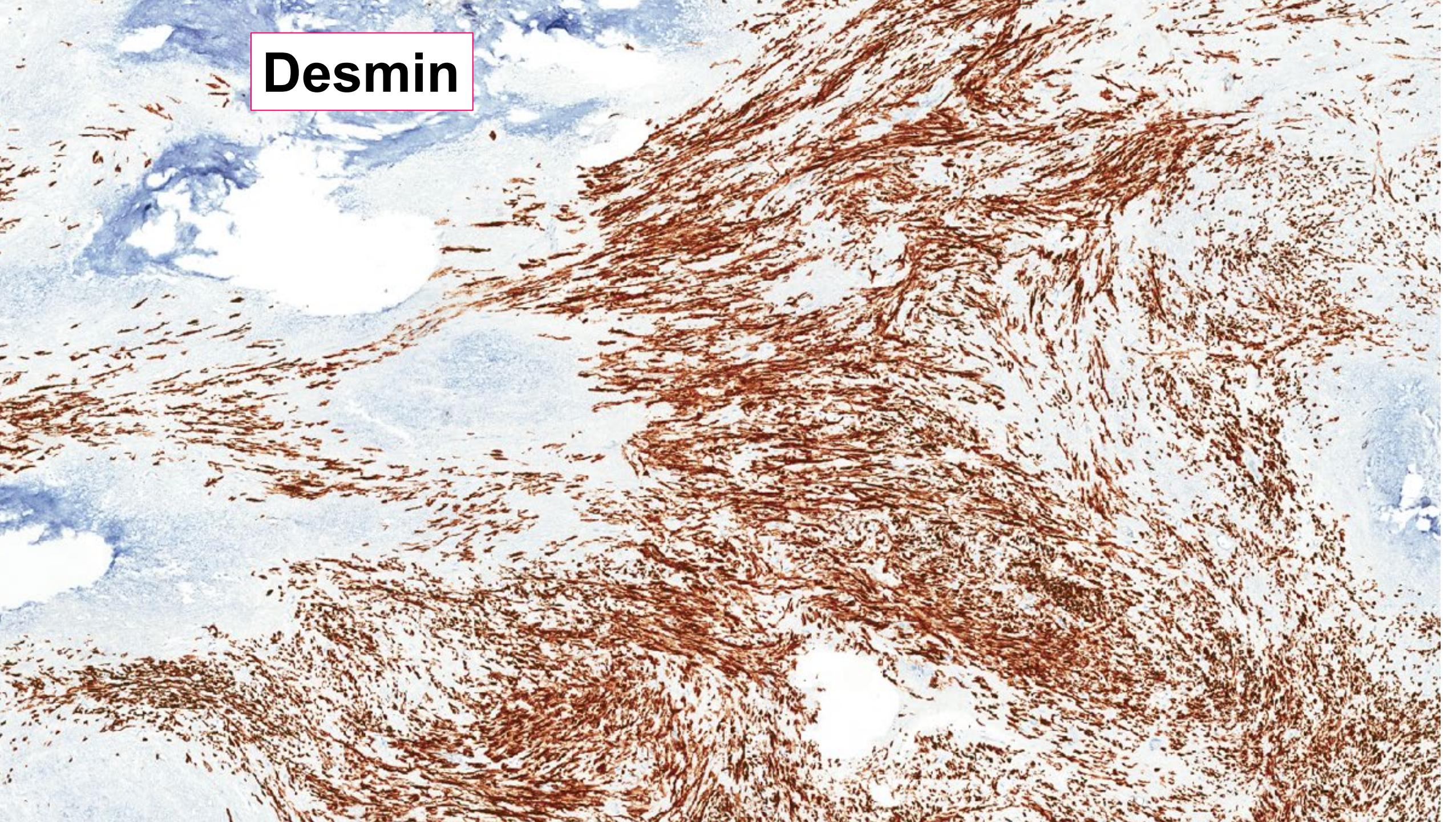
Desmin



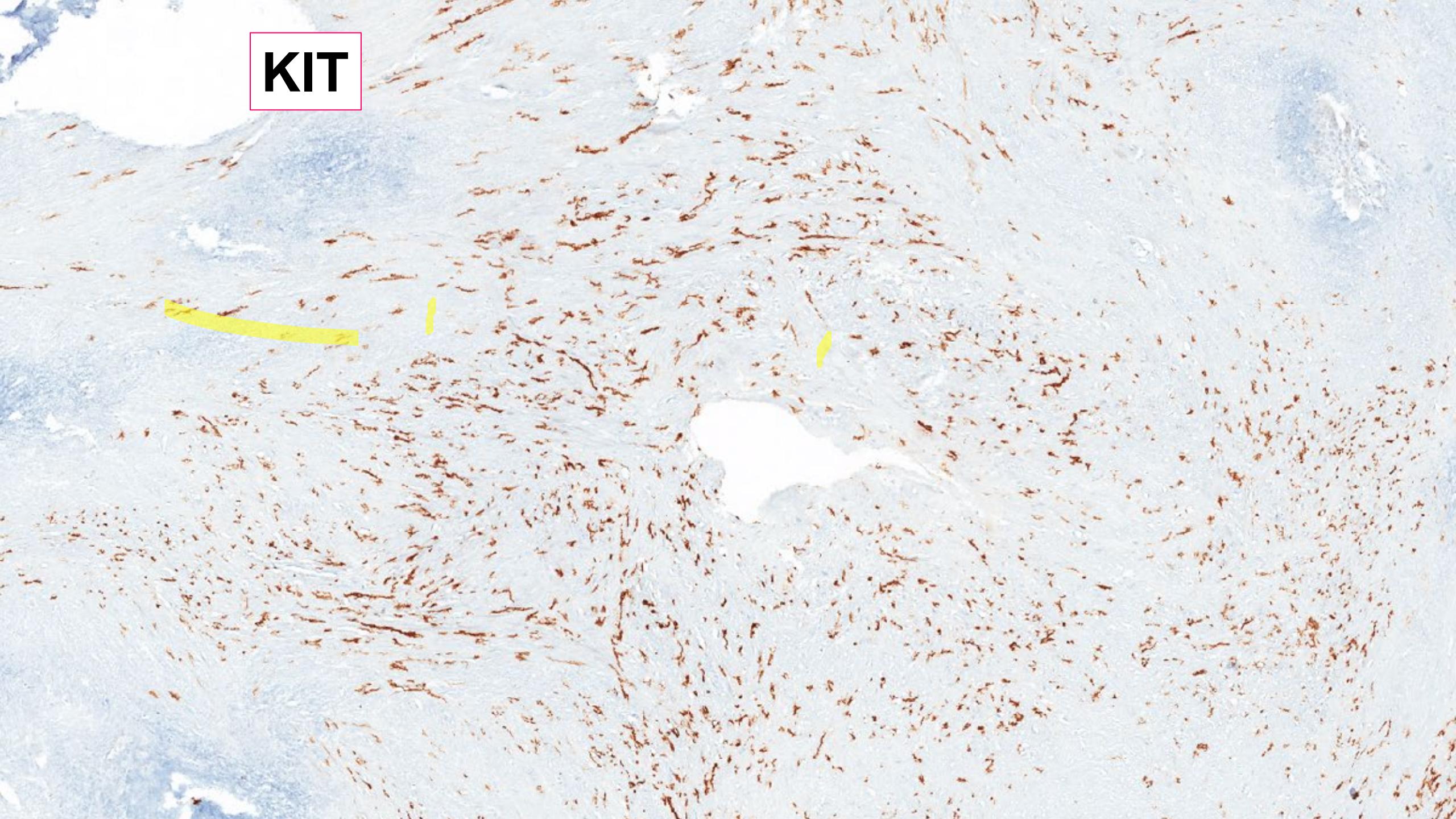
MASSACHUSETTS
GENERAL HOSPITAL

SCHOOL

Desmin



KIT



KIT



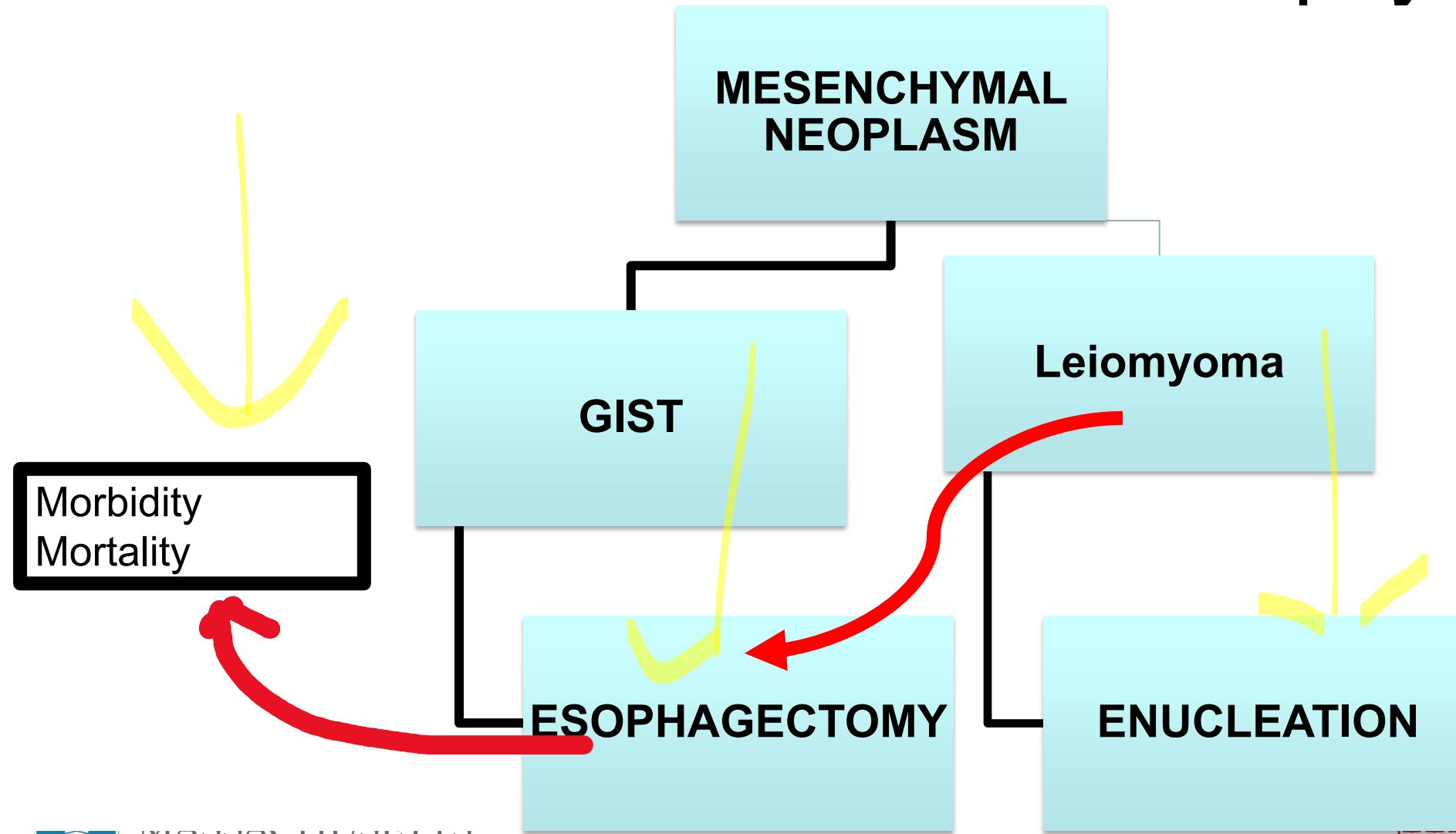


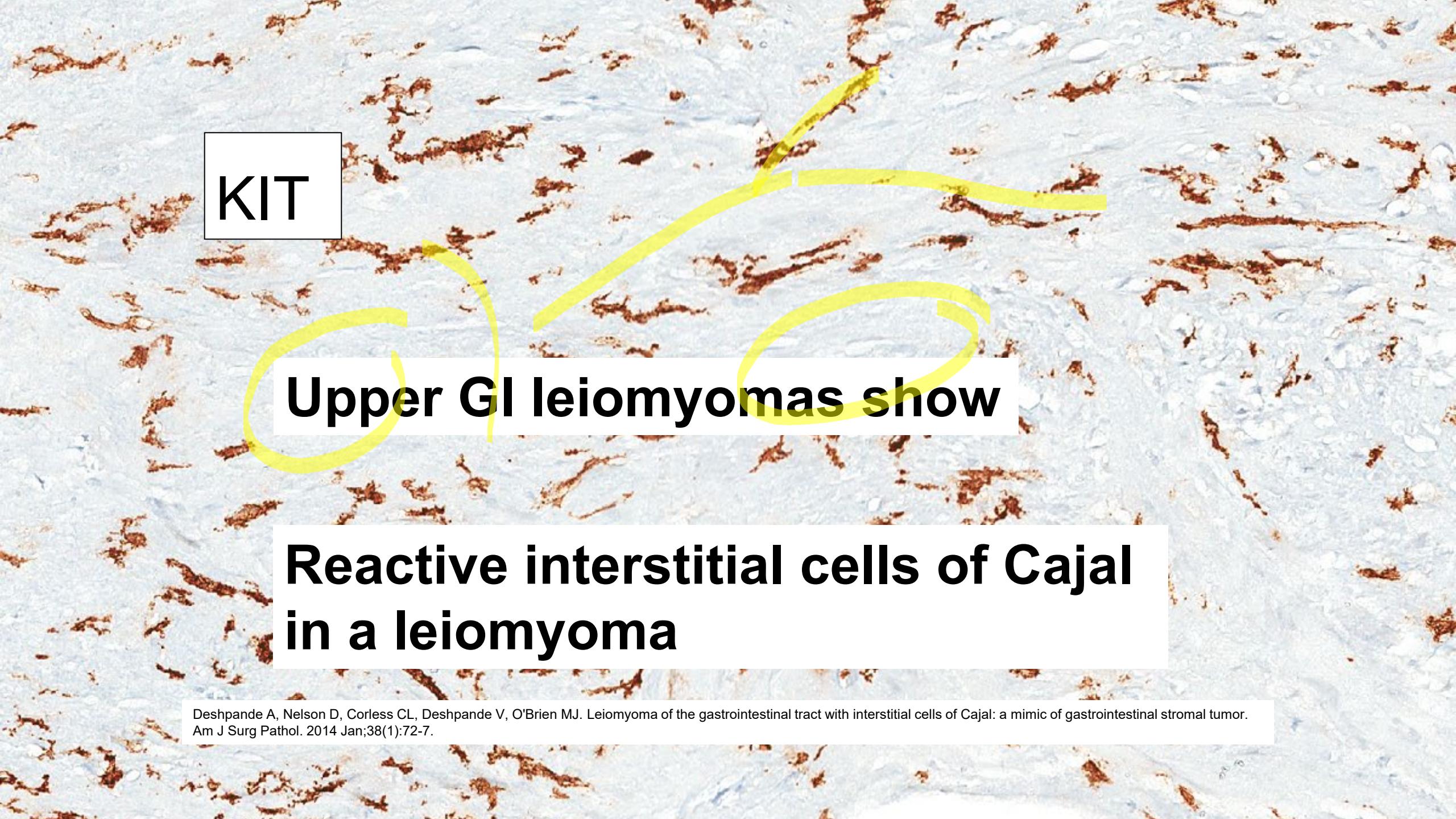
GIST with desmin?



**Leiomyoma with
interstitial cells of Cajal?**

Pay Particular Attention to Esophageal Lesions on needle biopsy





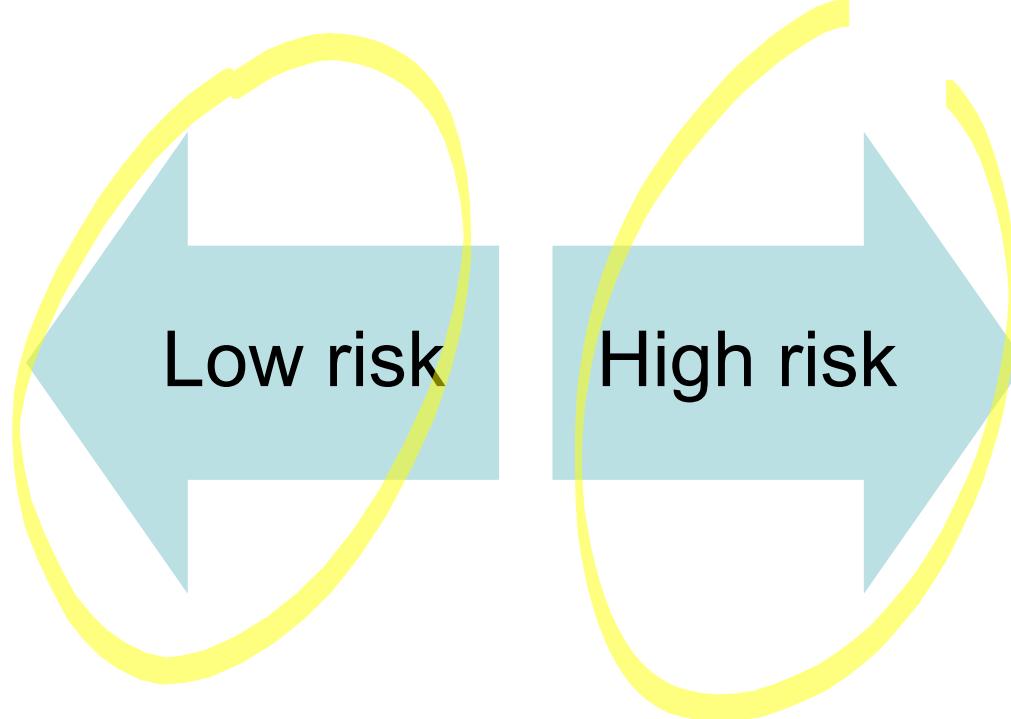
KIT

Upper GI leiomyomas show

Reactive interstitial cells of Cajal
in a leiomyoma

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):72-7.

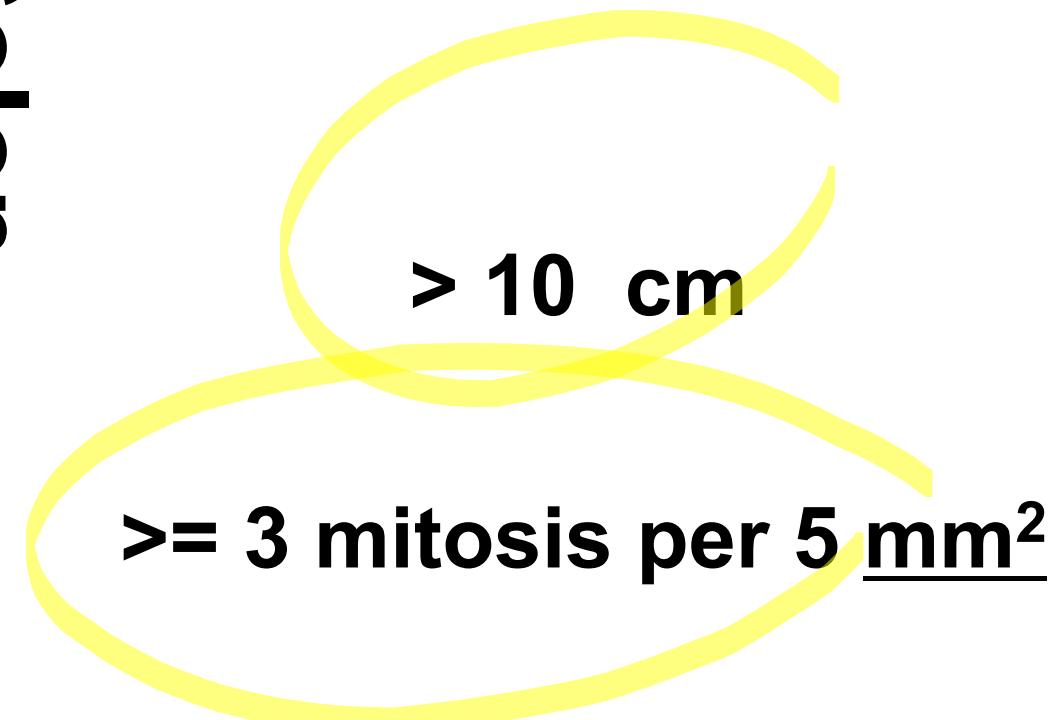
Esophagus



Mod Pathol. 2020 Jul;33(7):1410-1419

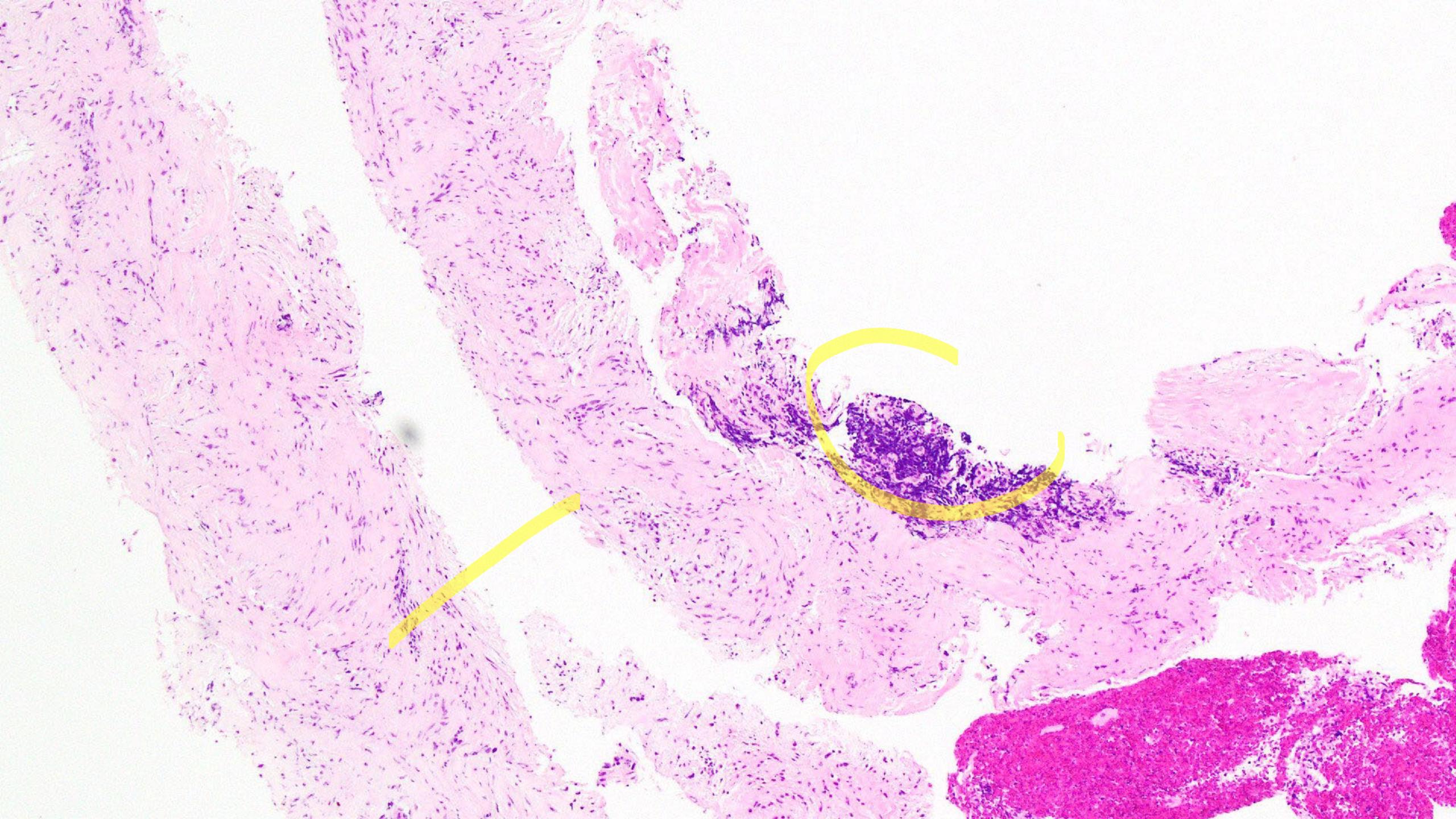
Colon

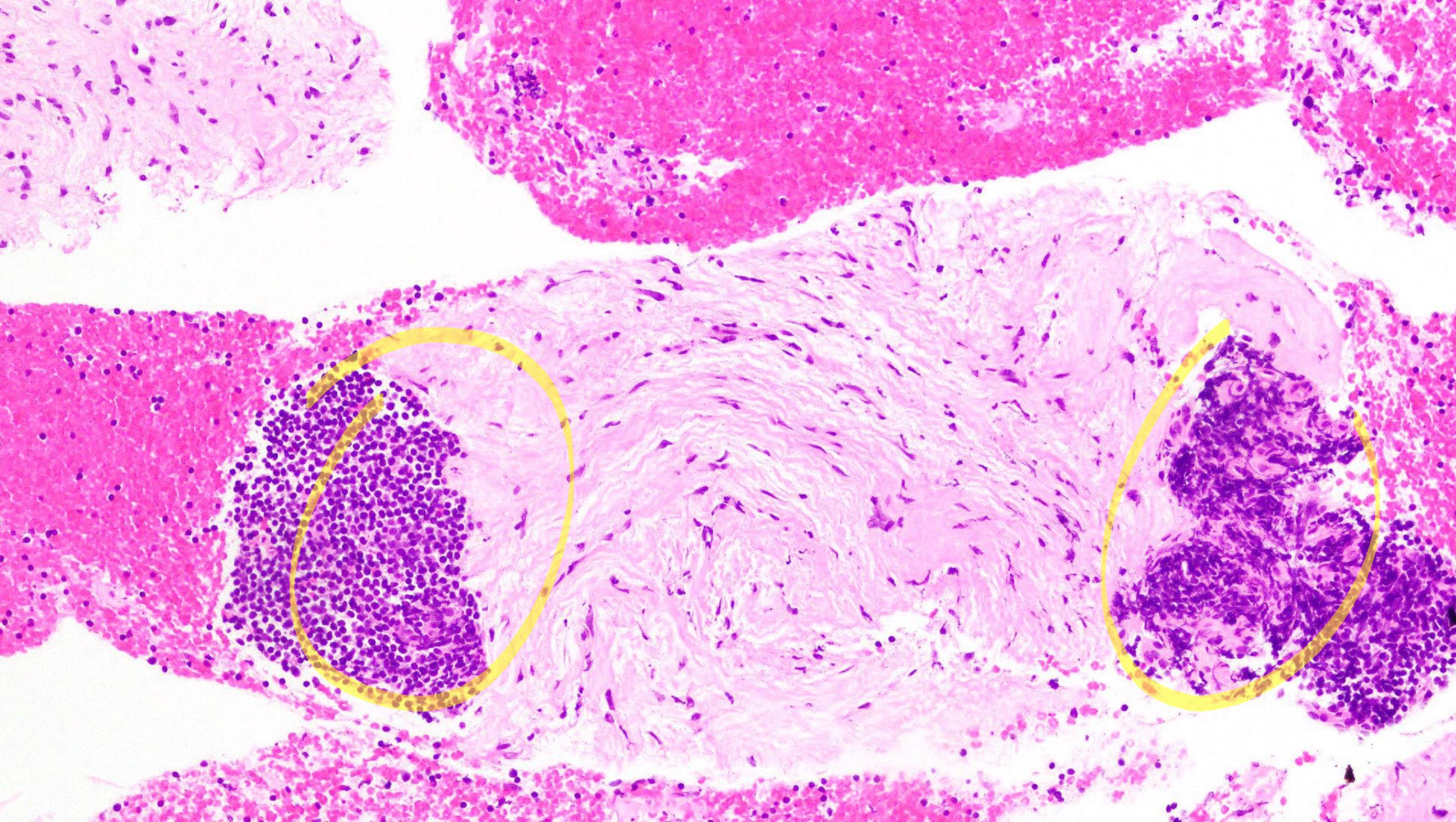
Moderate-to-severe atypia
High cellularity
Abnormal differentiation
Tumor necrosis
Mucosal ulceration
Lamina propria involvement
Serosal involvement

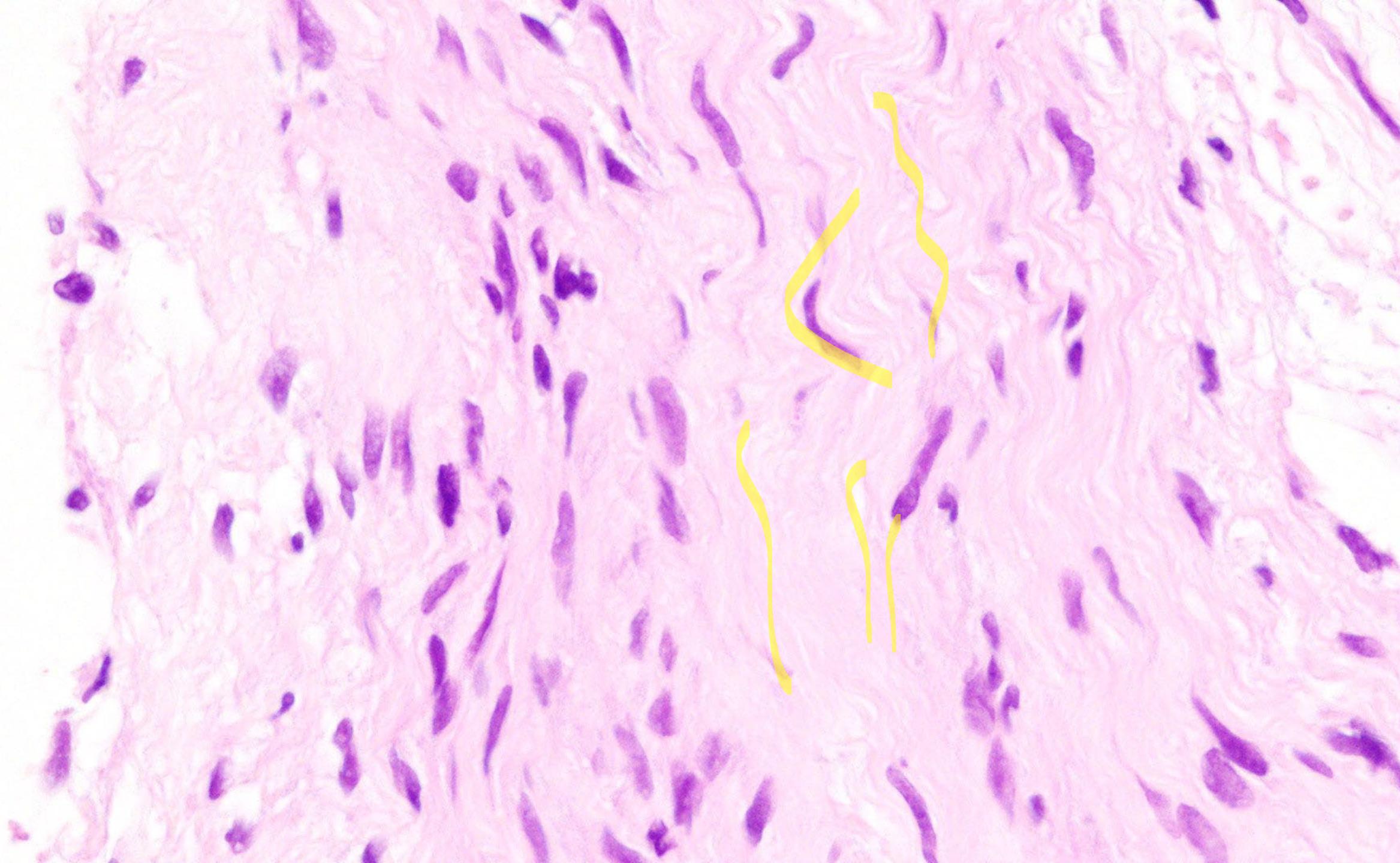


muscularis propria

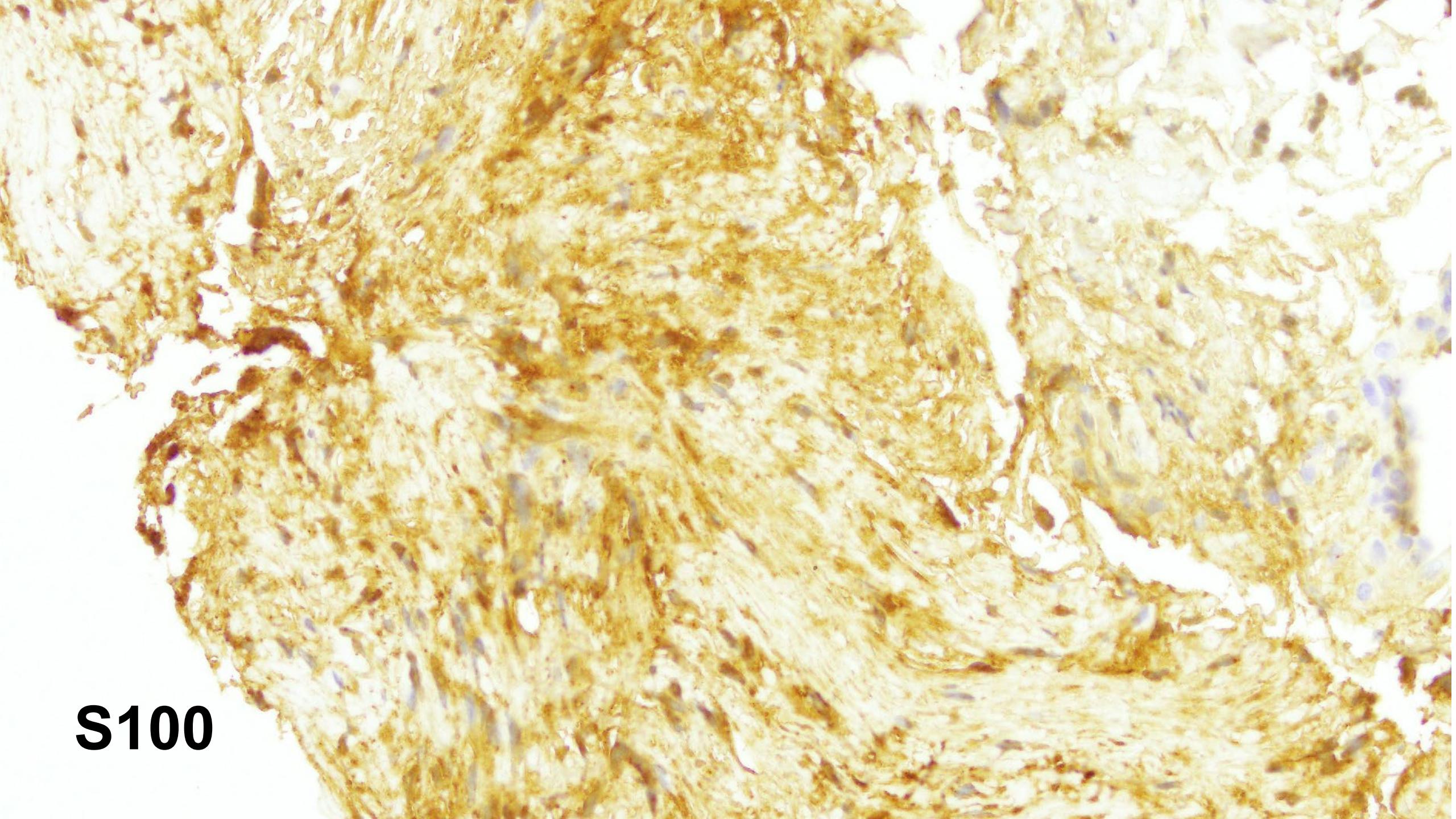




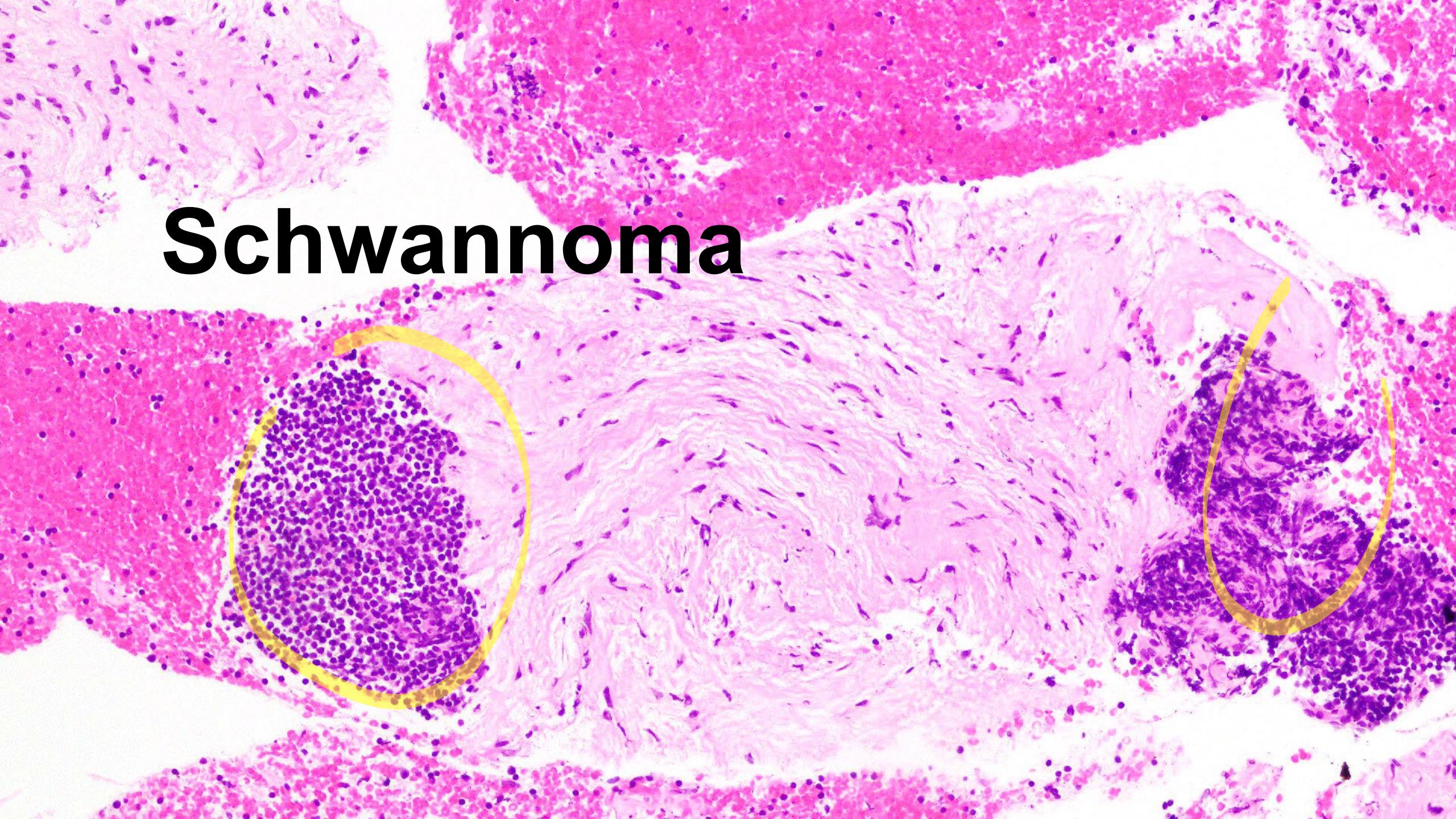




S100



Schwannoma



	Keratin	CD117	DOG1	CD34	SMA	Desmin	S100
GIST	-	+	+	70%	30-40%	Very rare	Very rare
Smooth muscle	-/+	-	-	10-15%	+	+	Very rare
Fibromatosis	-	-	-	Very rare	+	Very rare	-
Schwannoma	-	-	-	-	-	-	+



Mucosal bumps



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

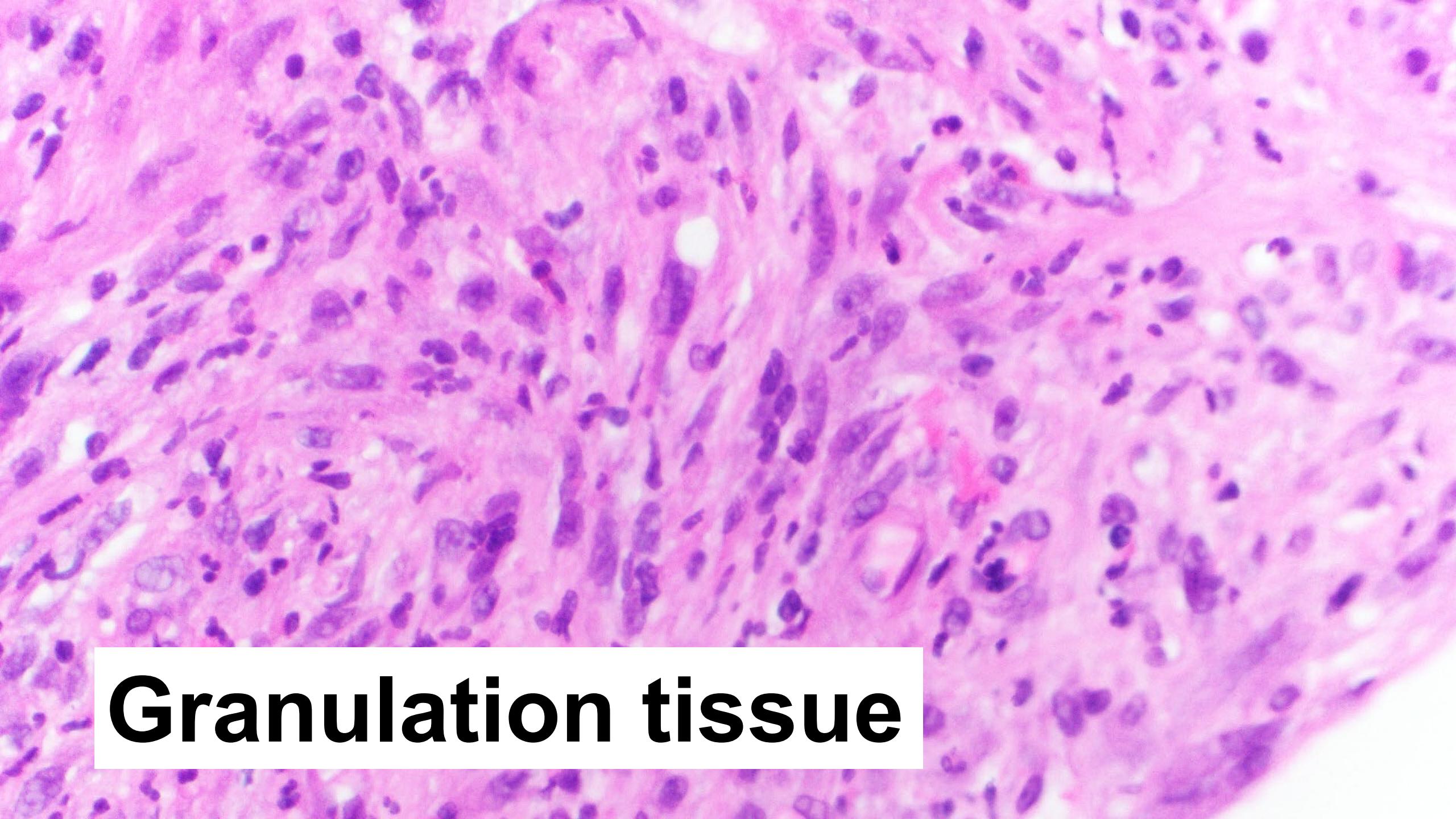
Most common bland spindle cell lesion in the mucosa?



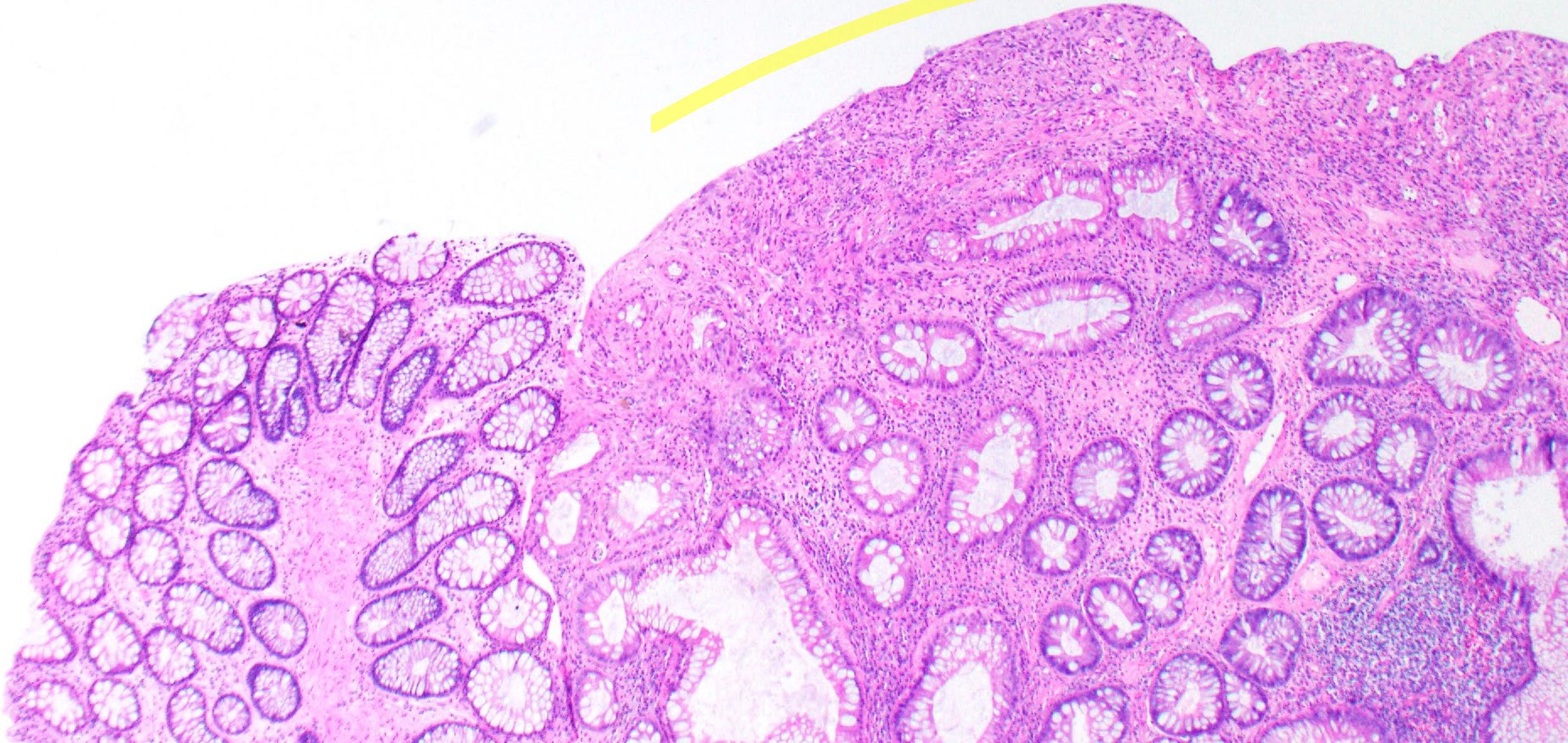
MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

A high-magnification light micrograph of granulation tissue. The tissue is composed of a dense network of pink-stained collagen fibers. Within this matrix, numerous small, dark purple-stained nuclei of fibroblasts are scattered. Several larger, more prominent blood vessels are visible, characterized by their thick, pink-stained walls and central lumens. A single, large, clear, circular area represents a vacuole or a degenerated cellular remnant.

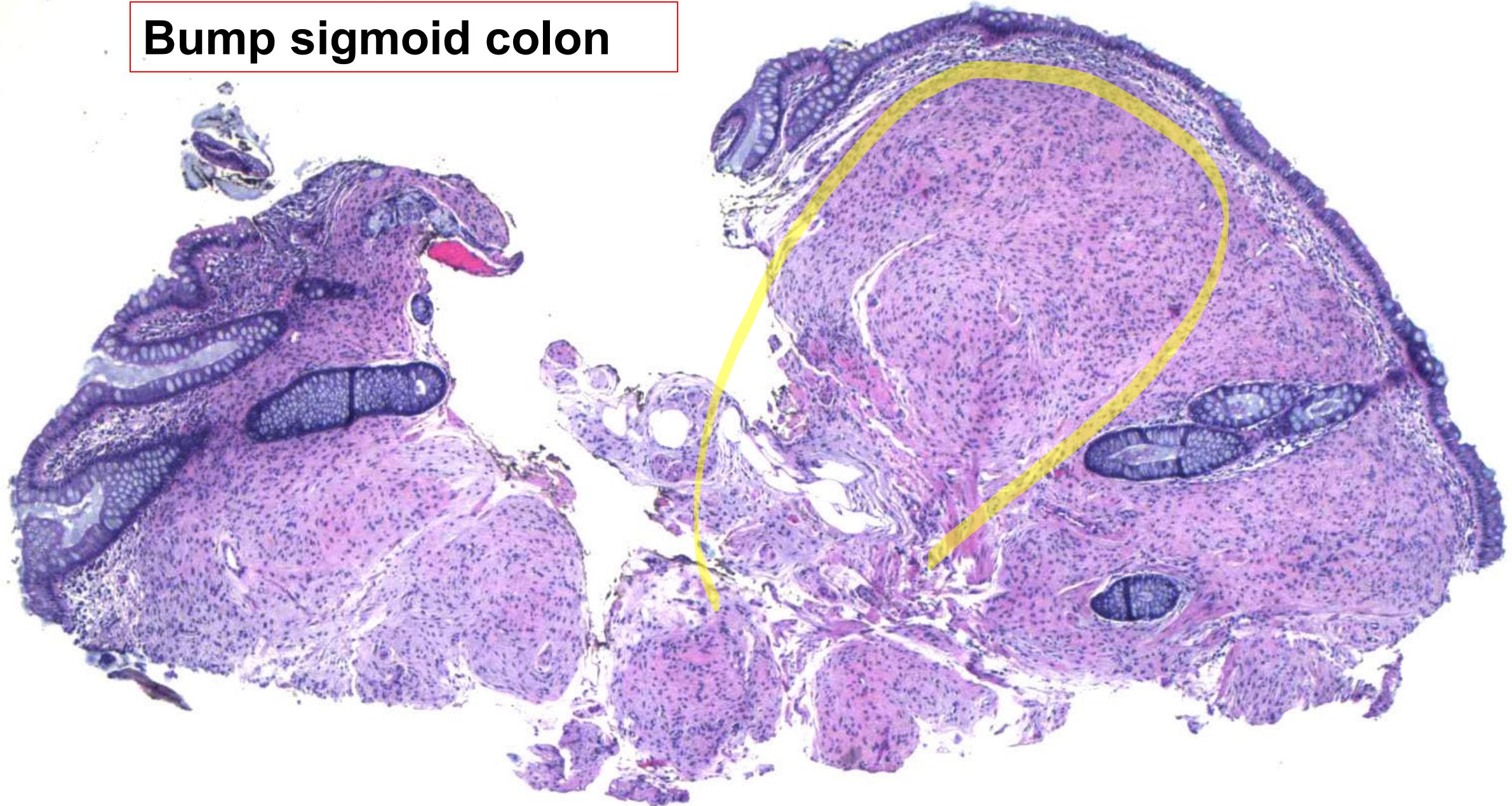
Granulation tissue



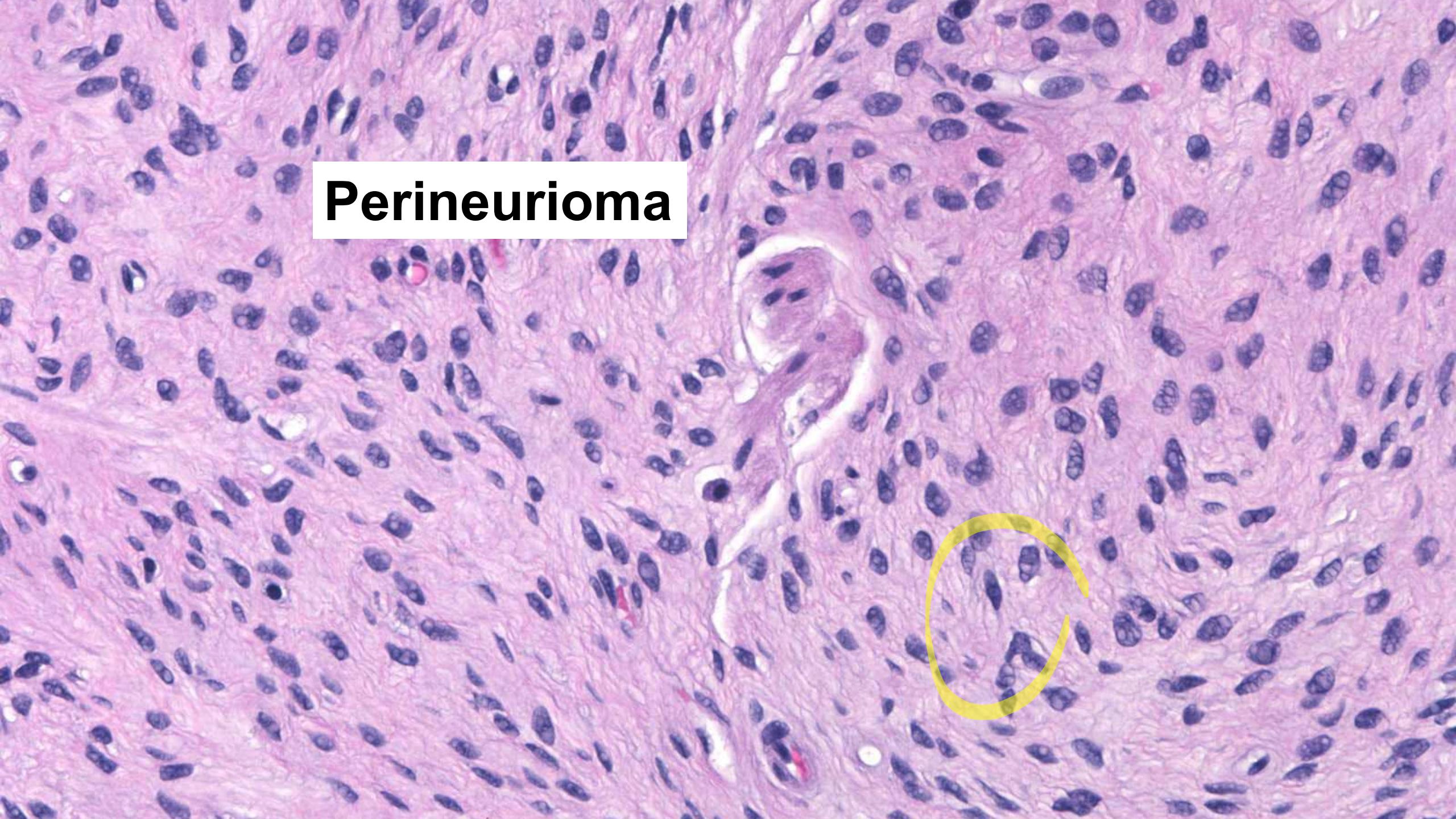
1



Bump sigmoid colon



Perineurioma



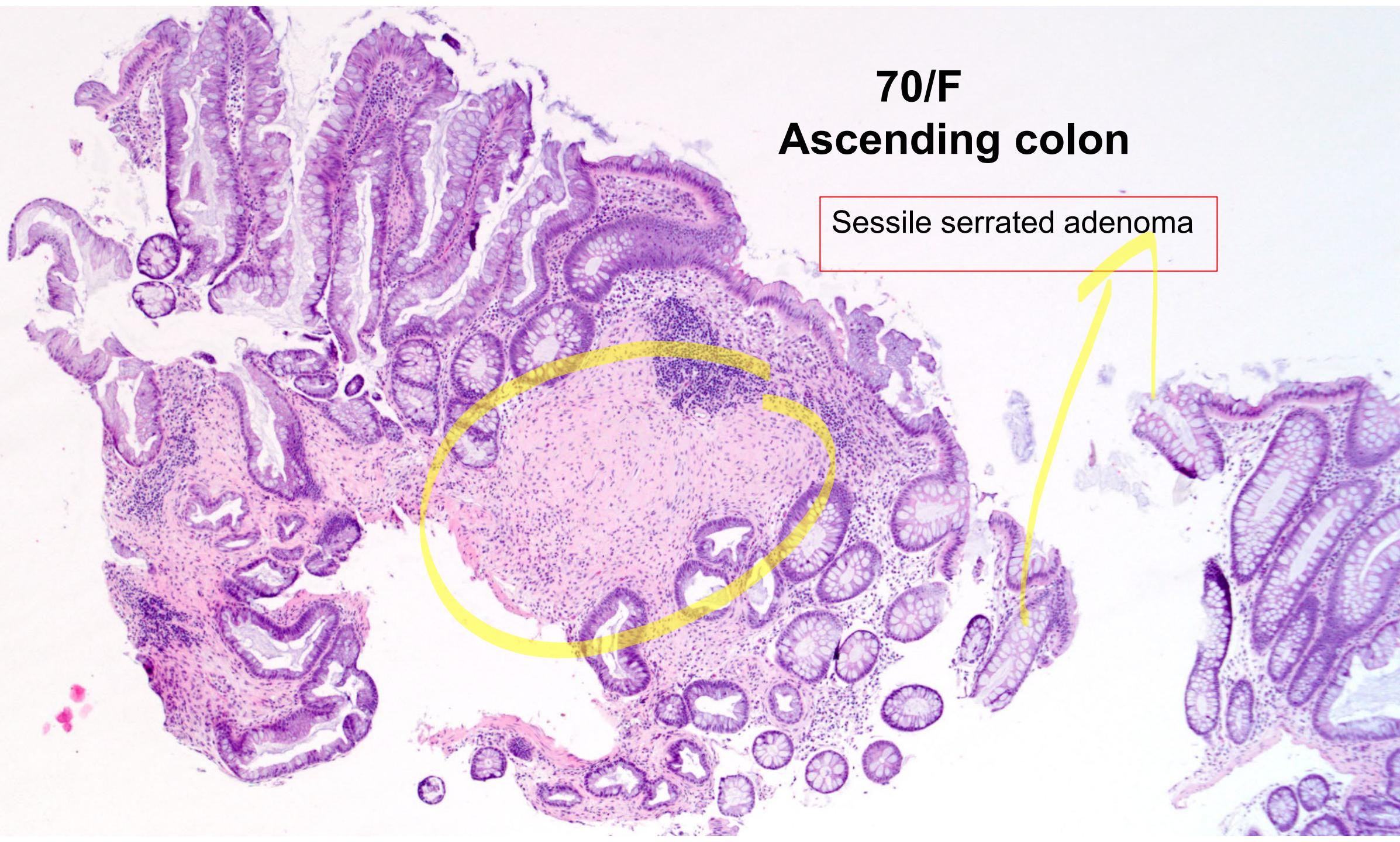
Perineurioma

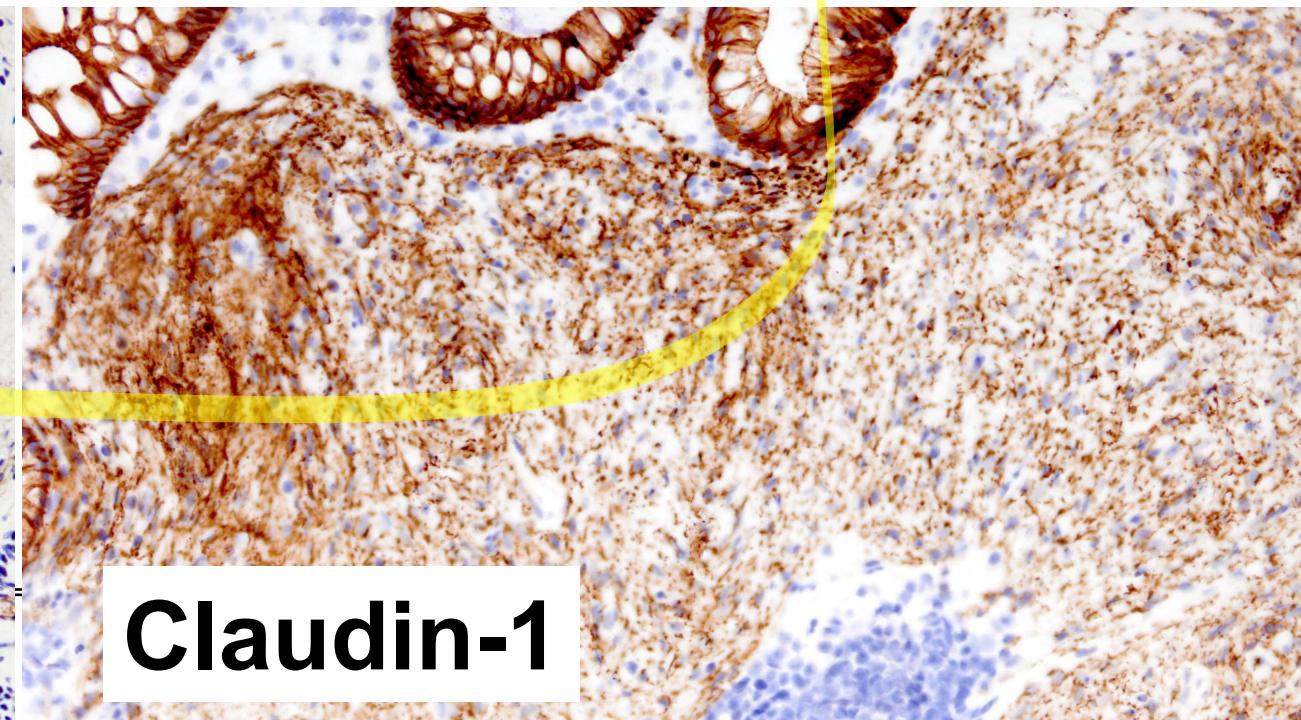
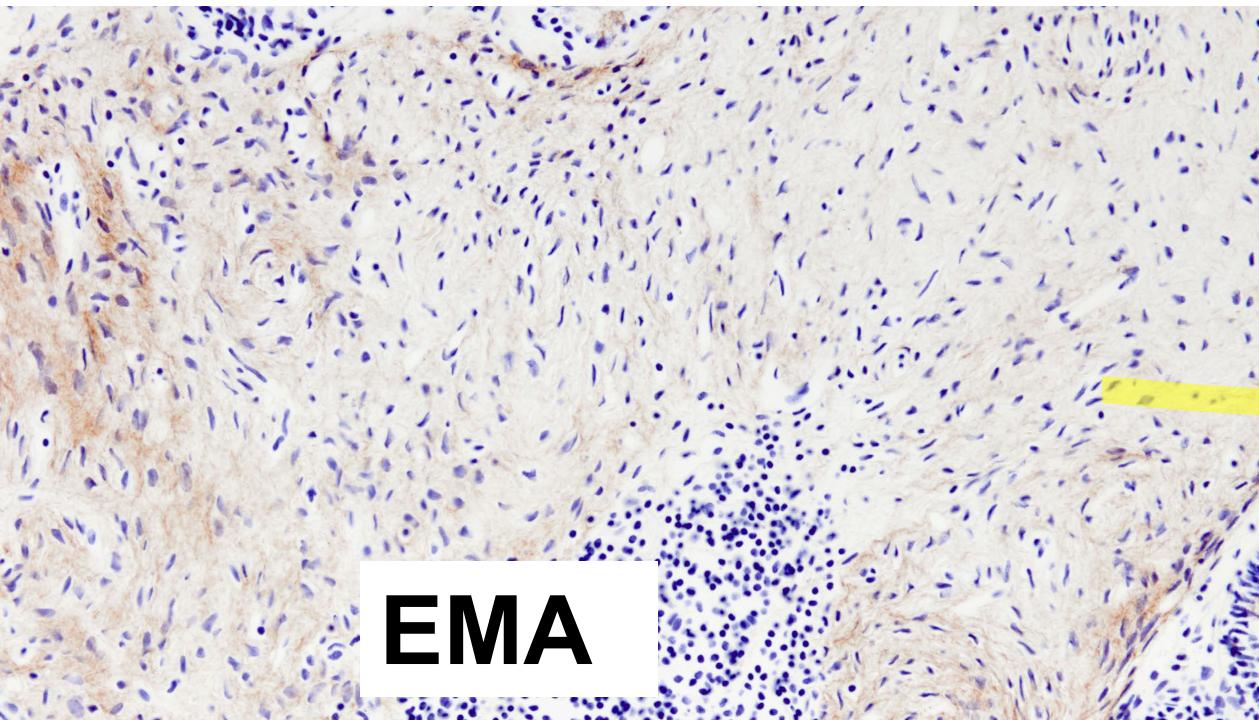
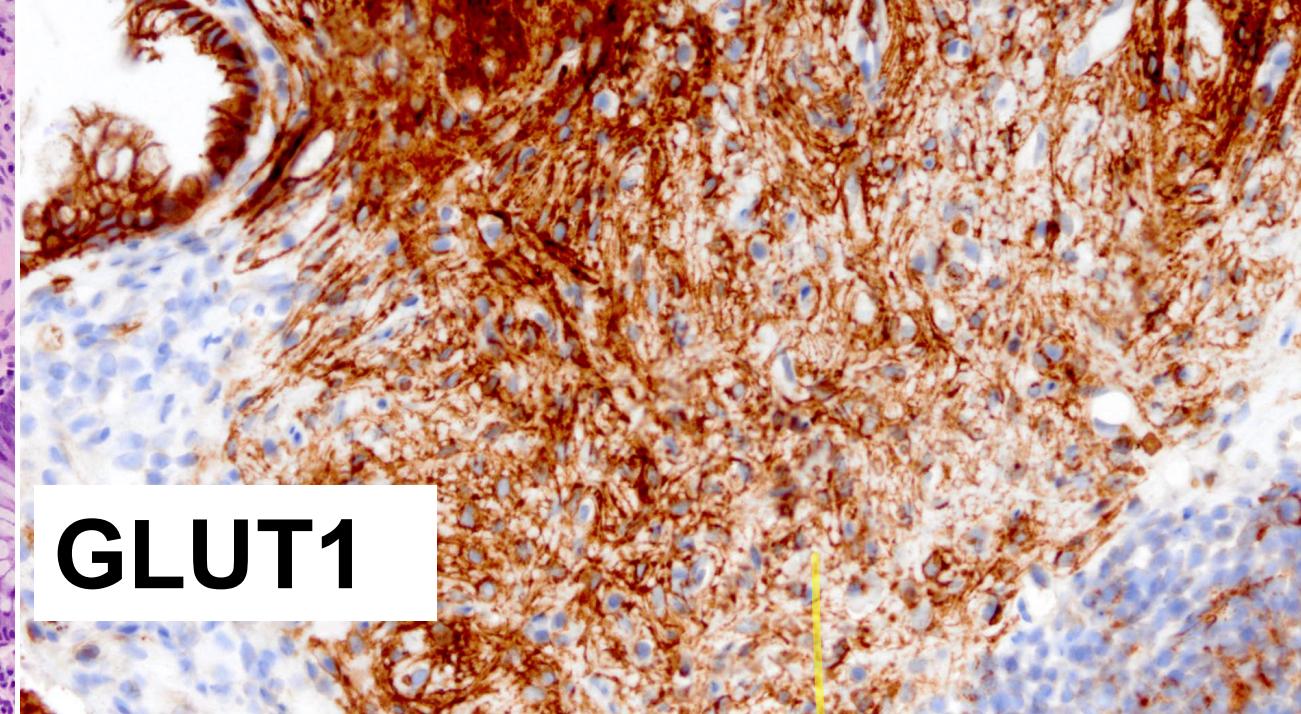
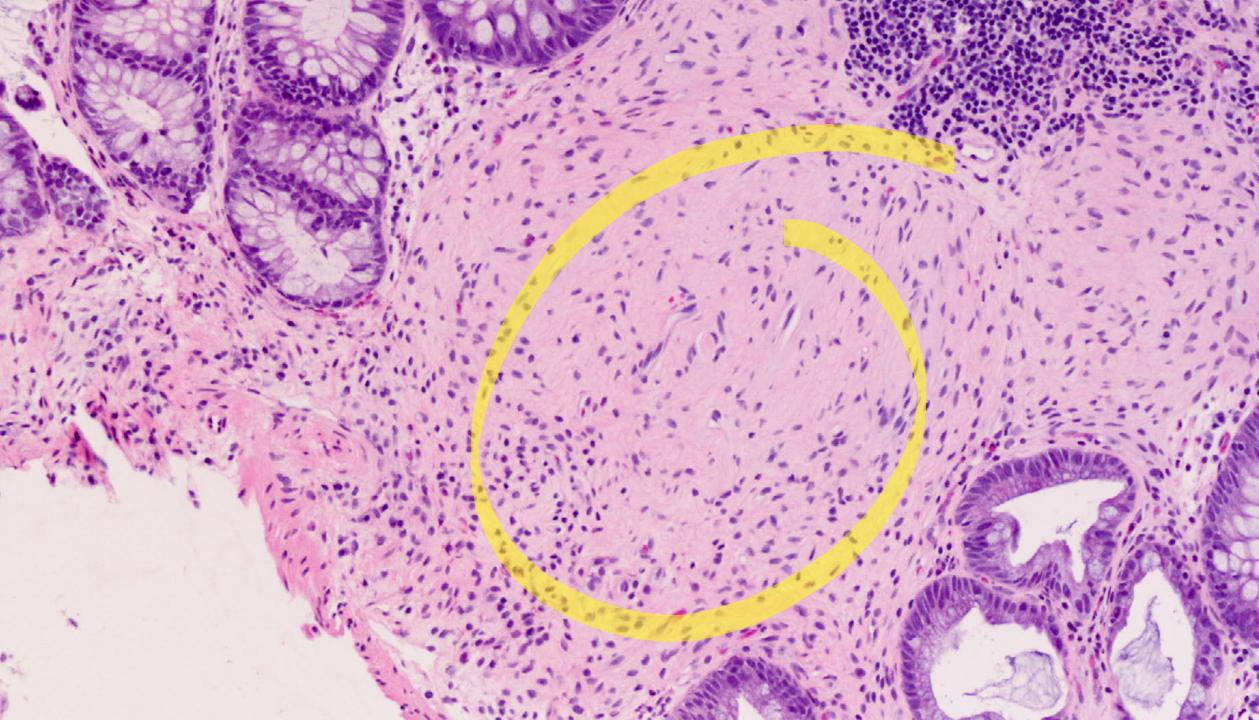
EMA

Other Perineurioma markers
Glut1 (not specific)
Claudin-1 (not sensitive)

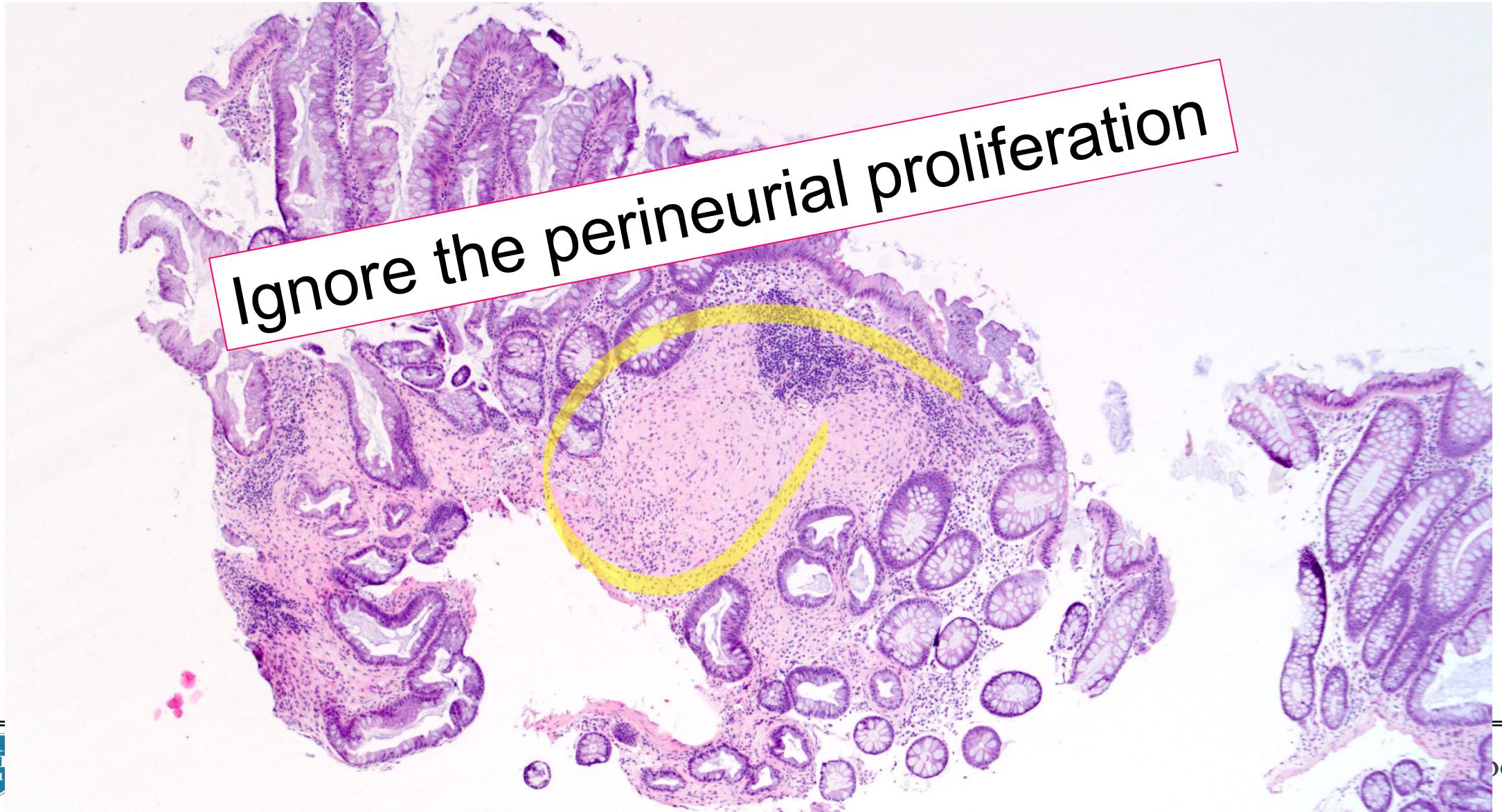
70/F
Ascending colon

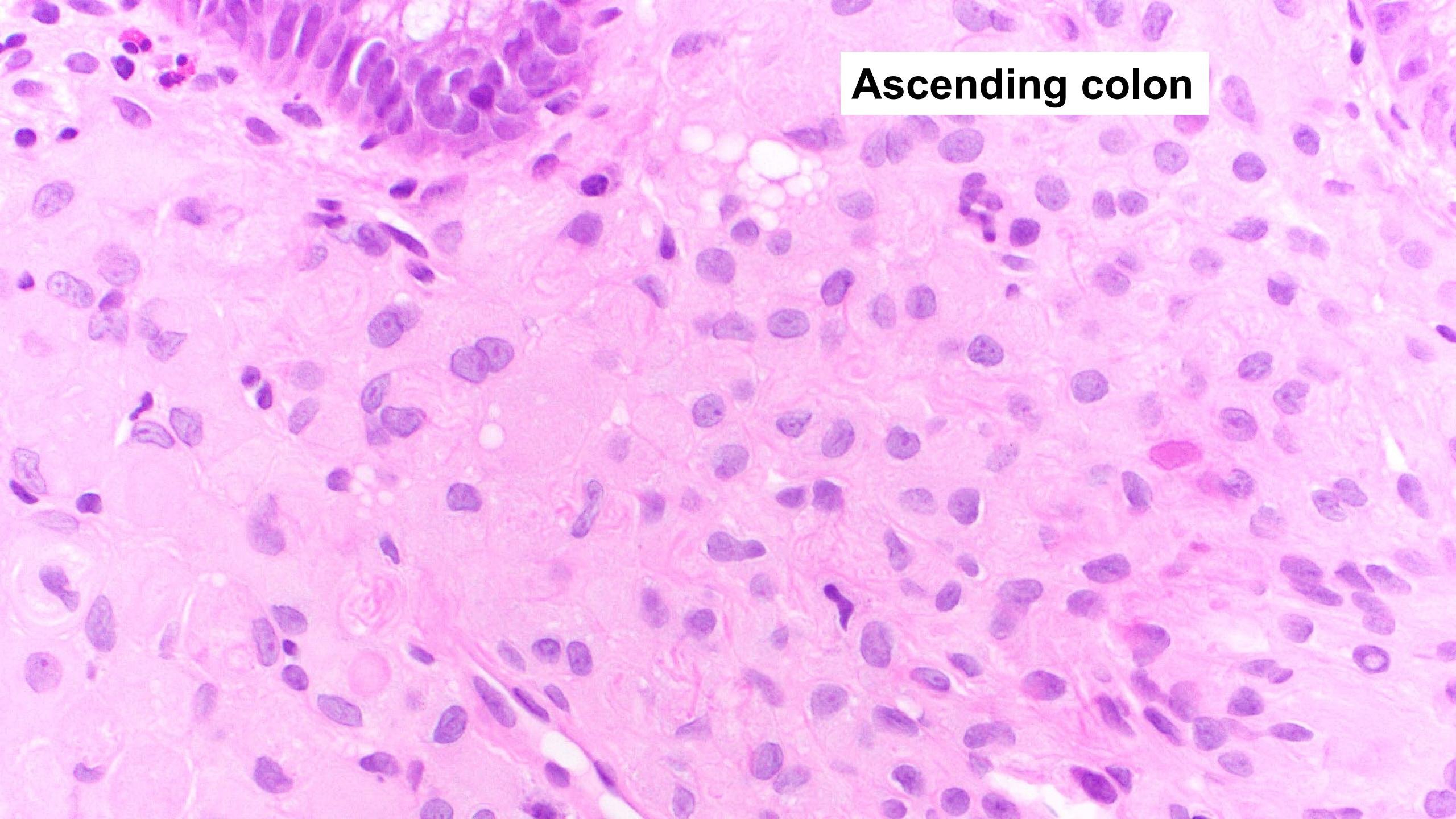
Sessile serrated adenoma





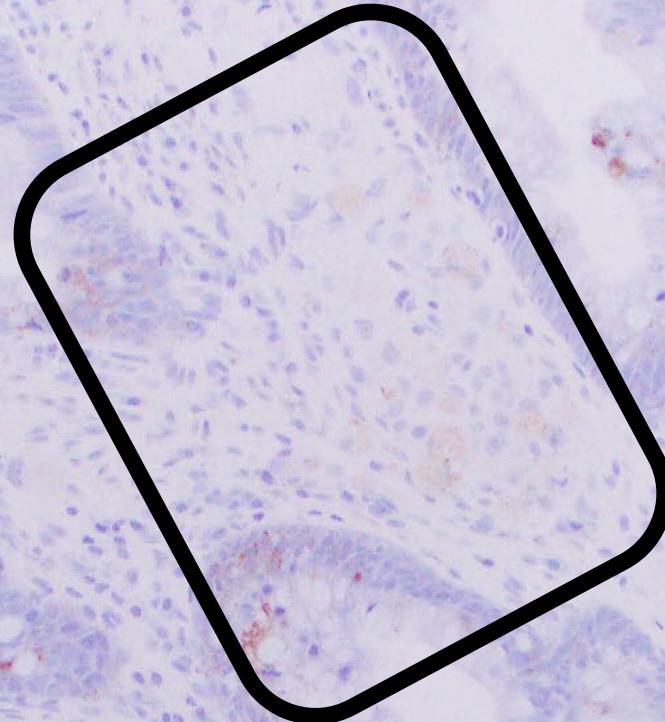
Perineurial proliferation with Serrated Lesion



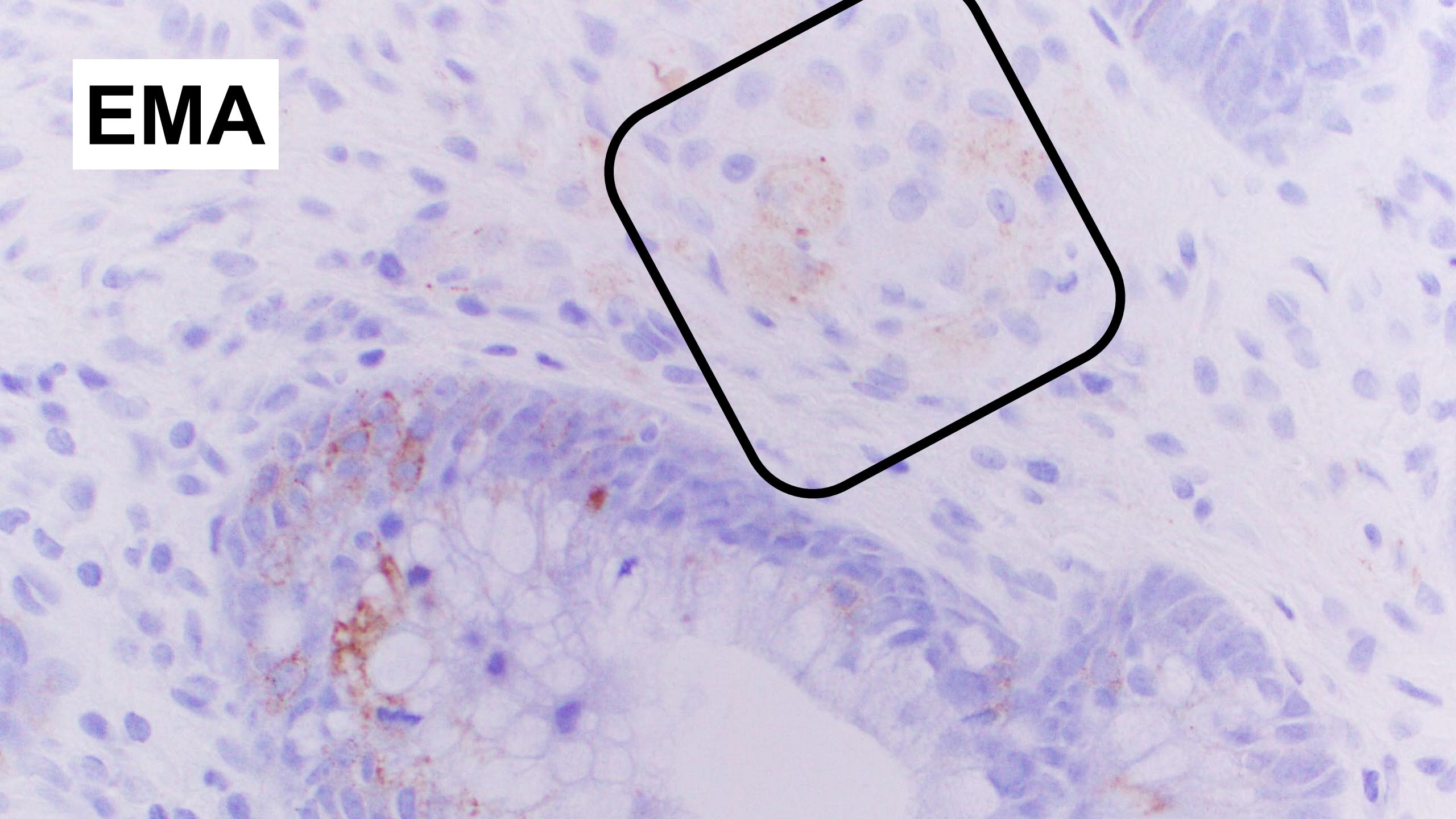


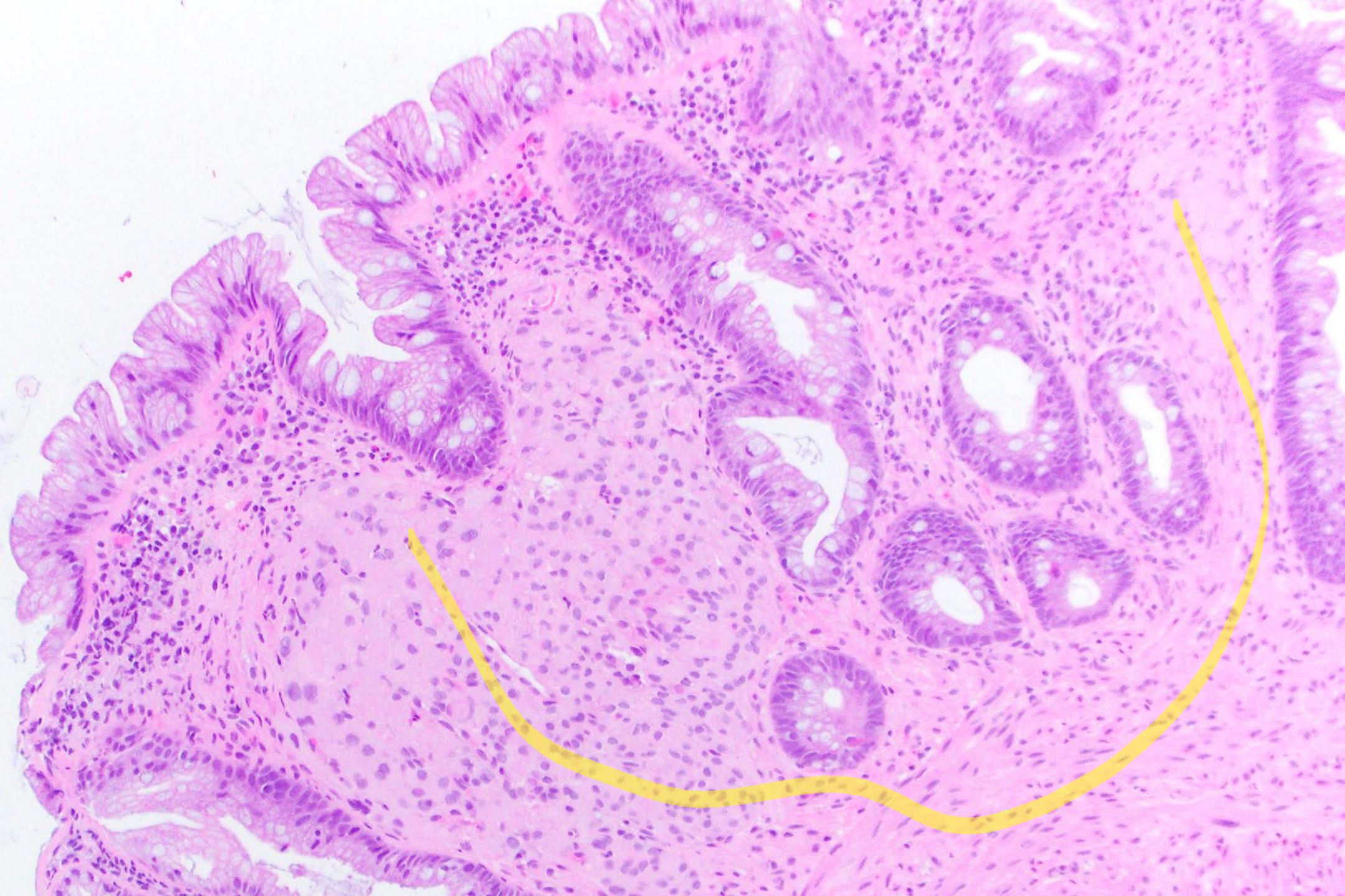
Ascending colon

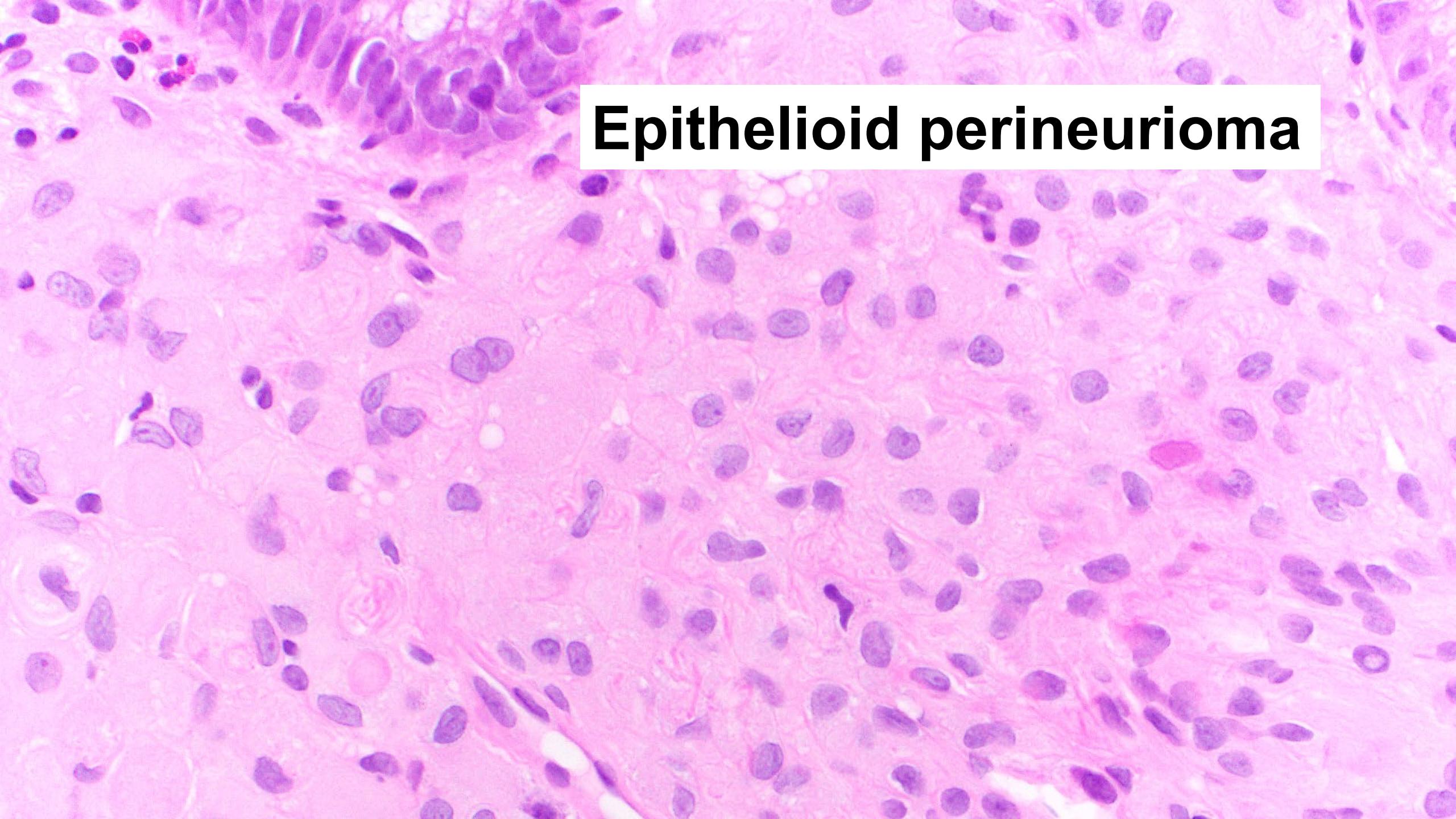
EMA



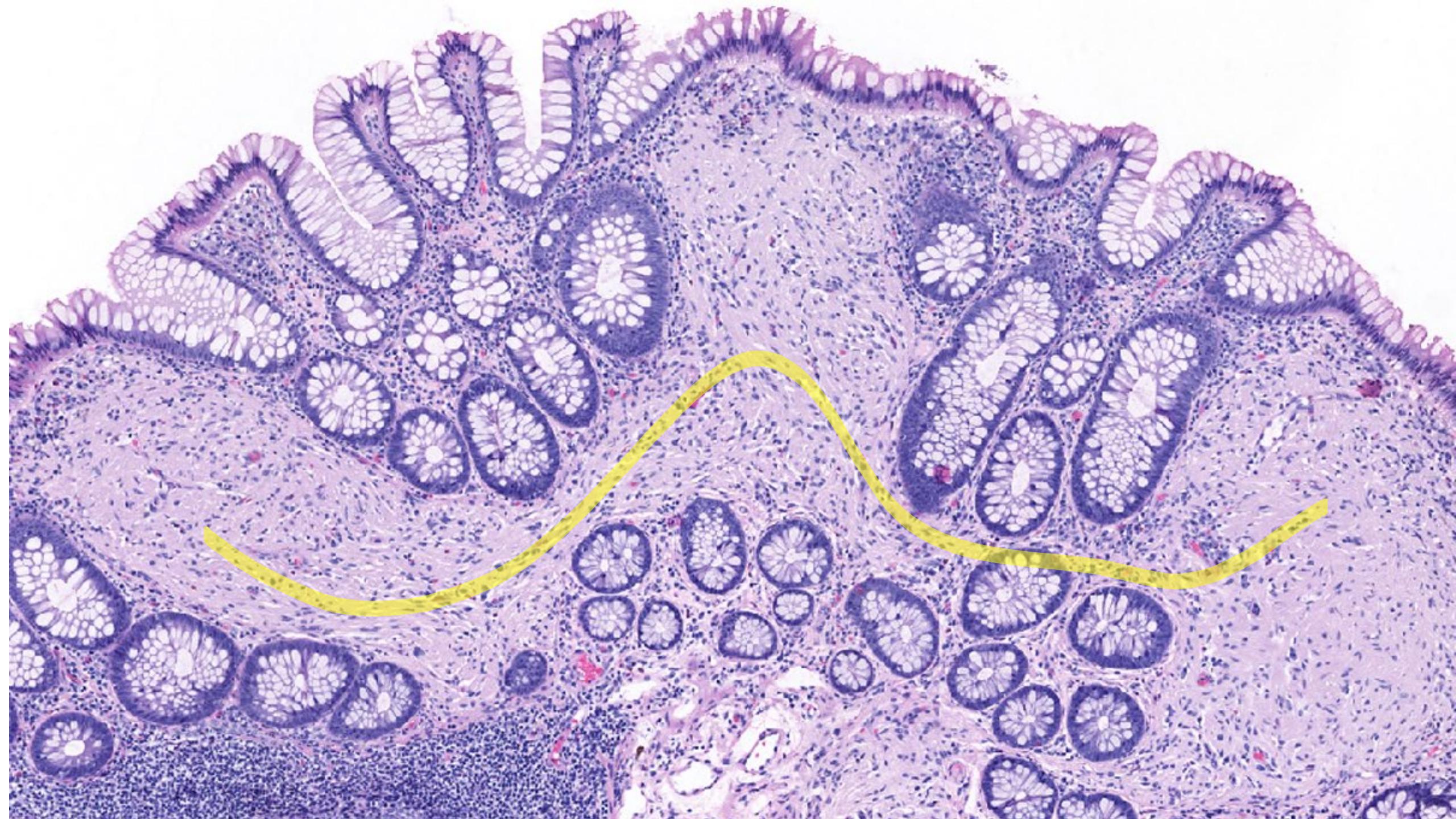
EMA



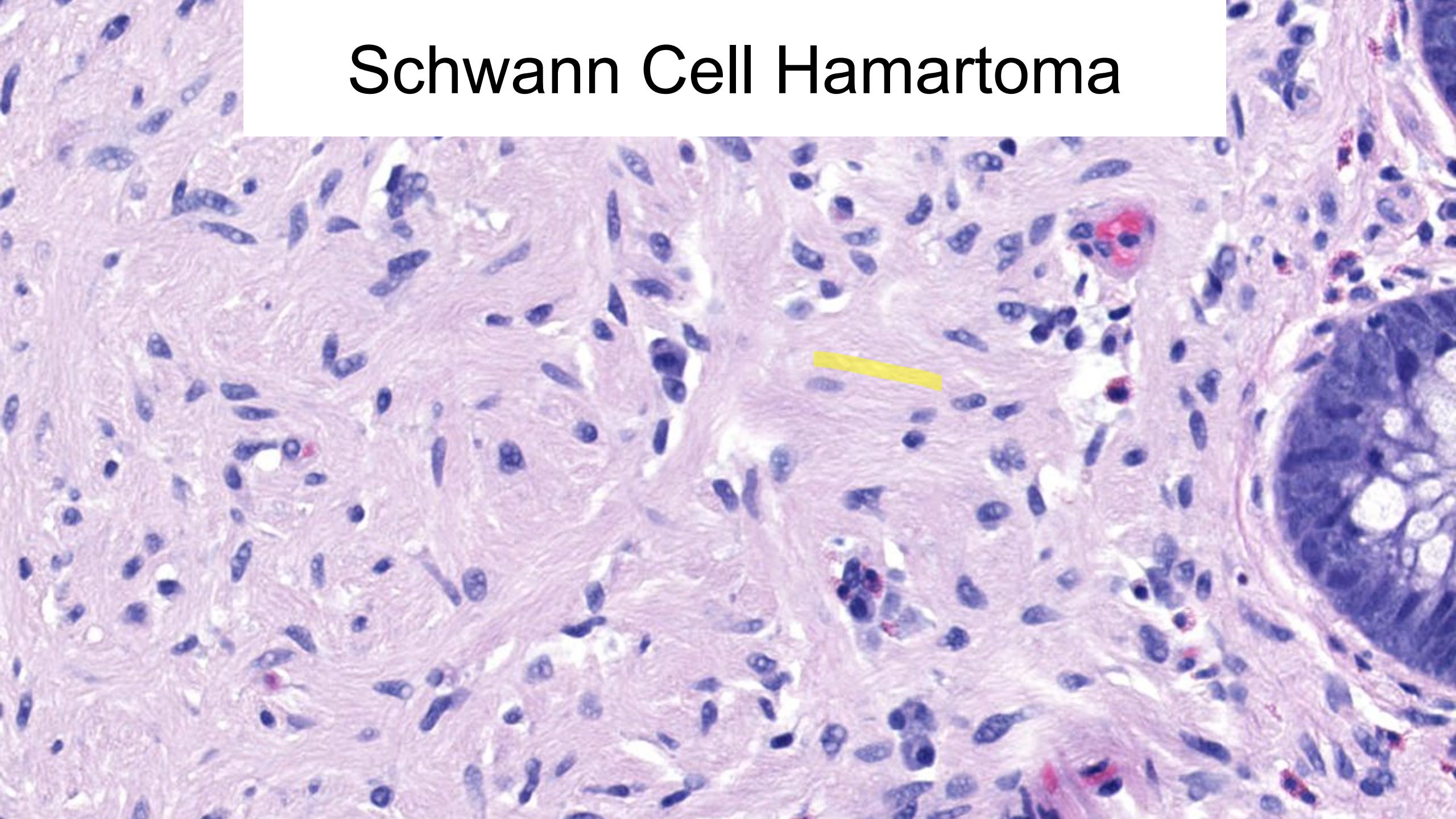


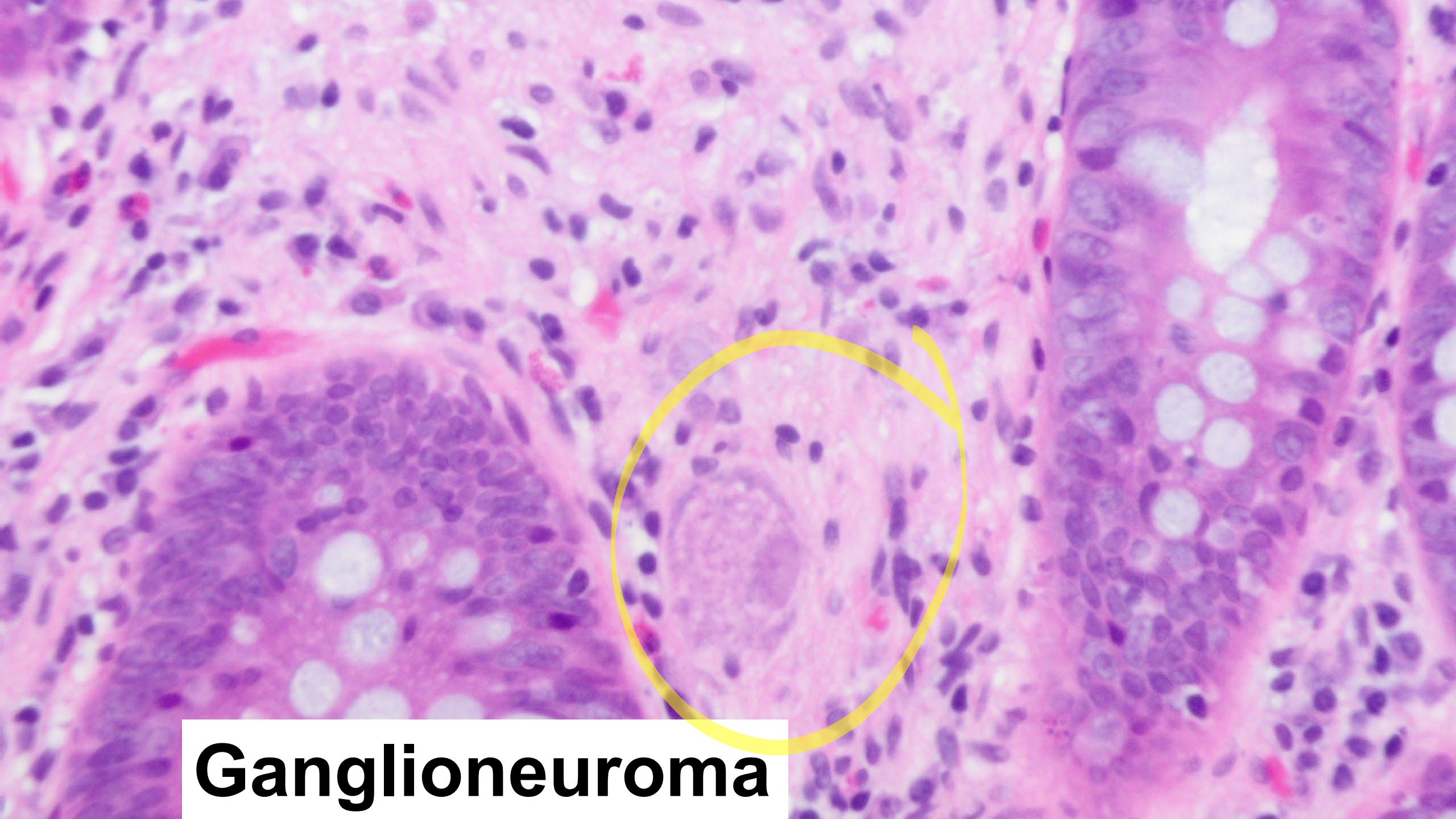
A high-magnification light micrograph showing a cellular tissue sample. The cells are polygonal with large, dark purple nuclei and pale, eosinophilic cytoplasm. They are arranged in a somewhat disorganized, infiltrative pattern. Some cells appear larger and more pleomorphic than others. A prominent feature is a dense, pink-stained area in the lower-left corner, which represents a peripheral nerve fascicle. The overall appearance is characteristic of epithelioid perineurioma.

Epithelioid perineurioma

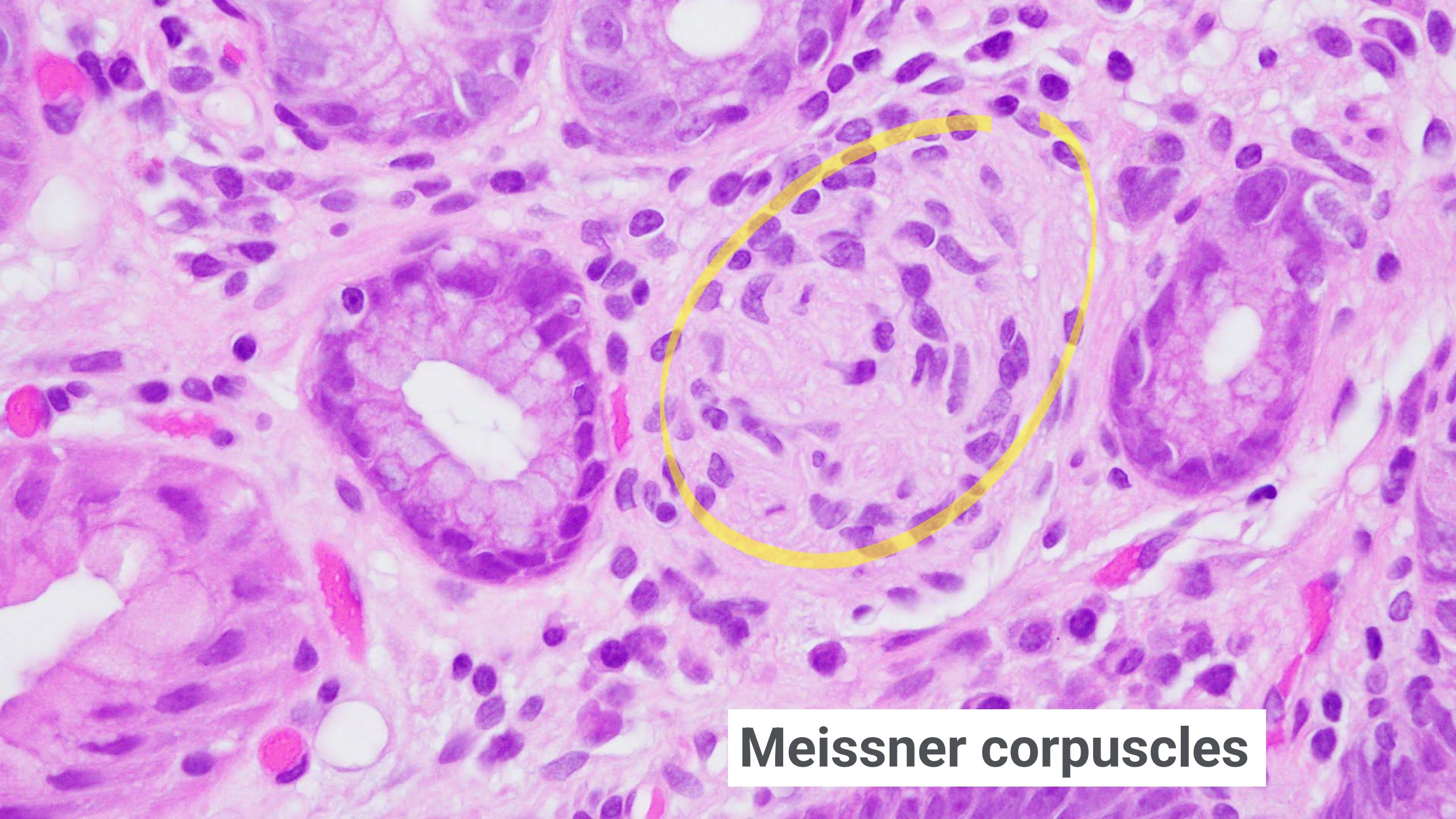


Schwann Cell Hamartoma

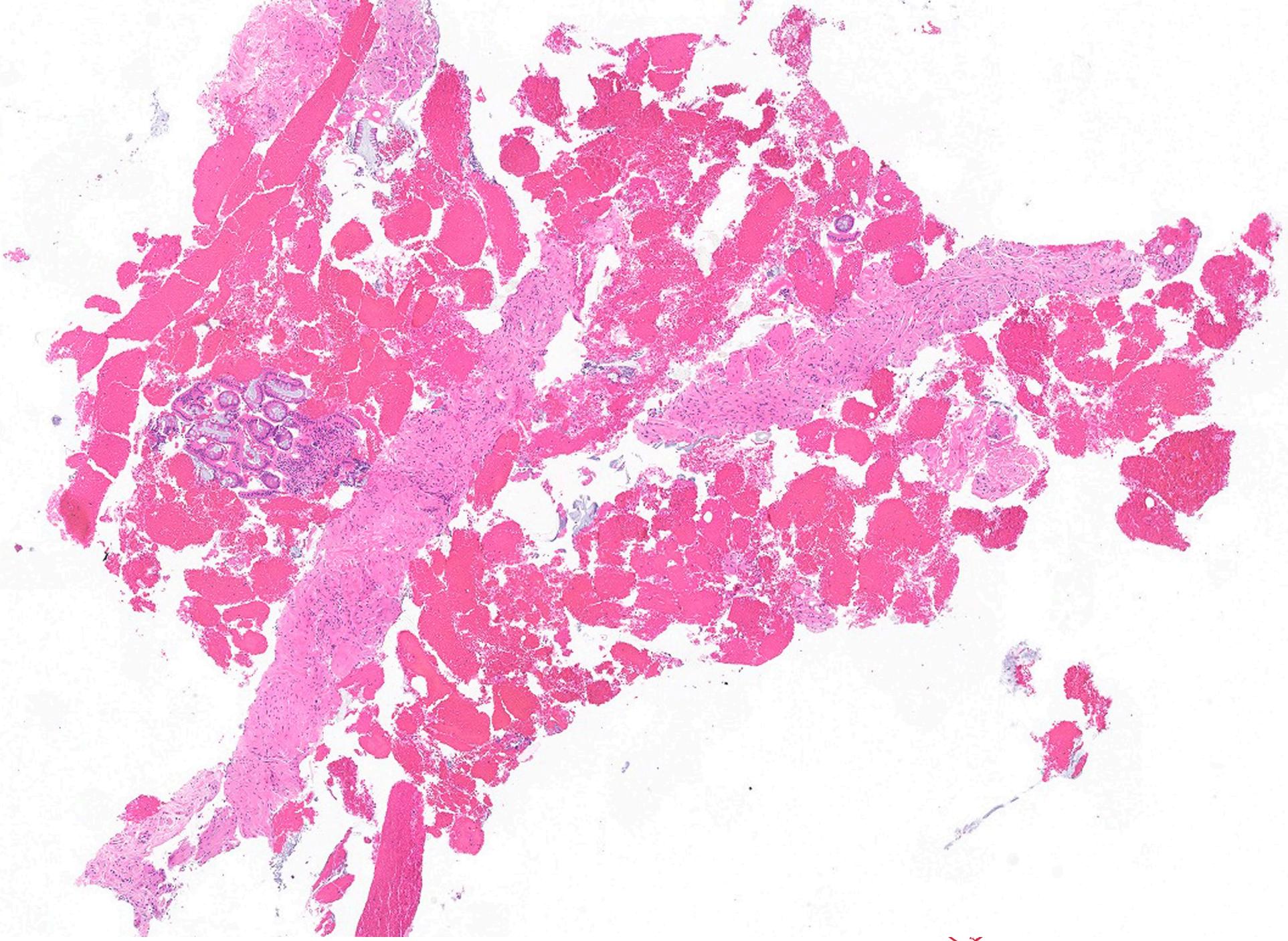


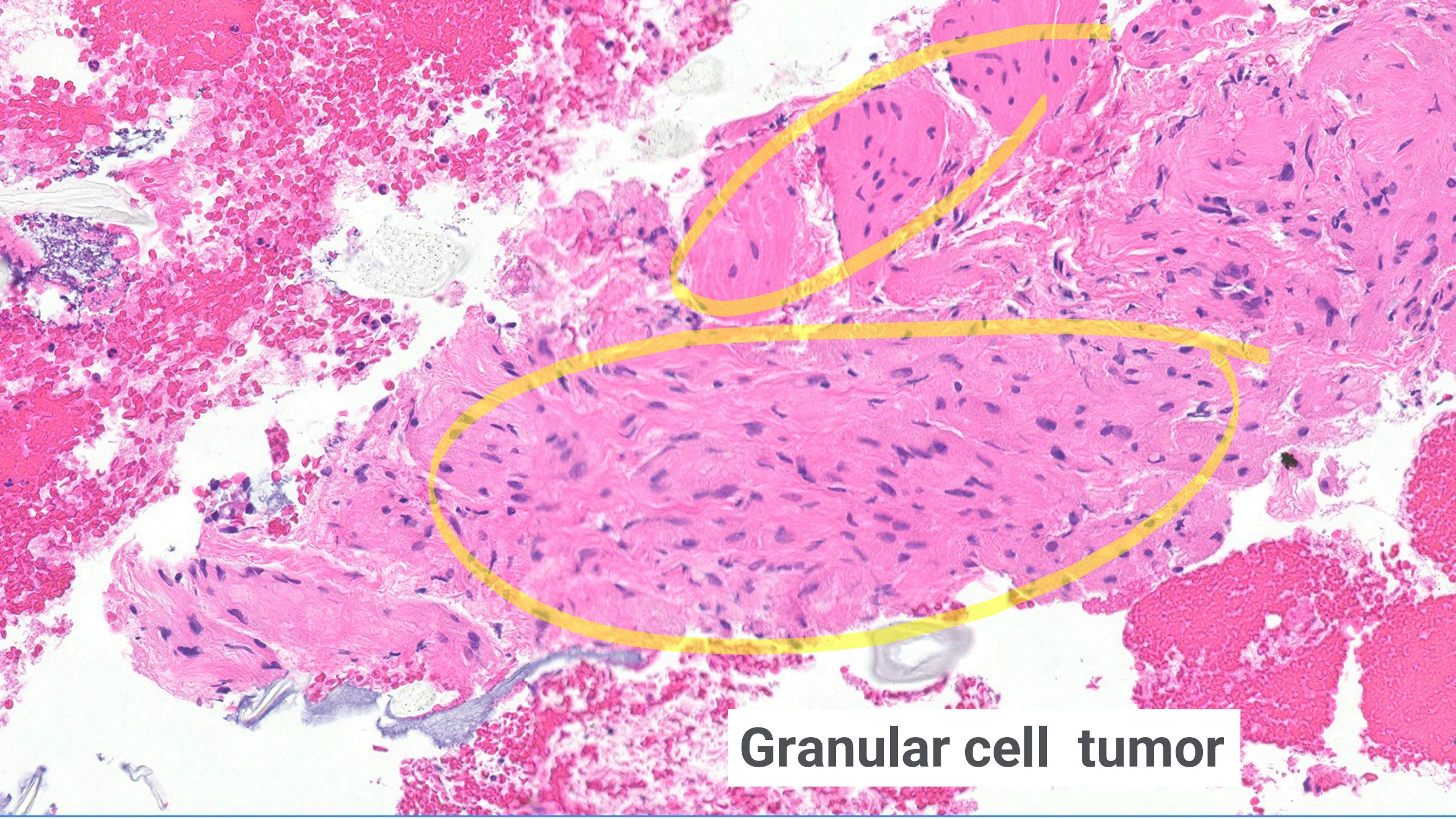


Ganglioneuroma



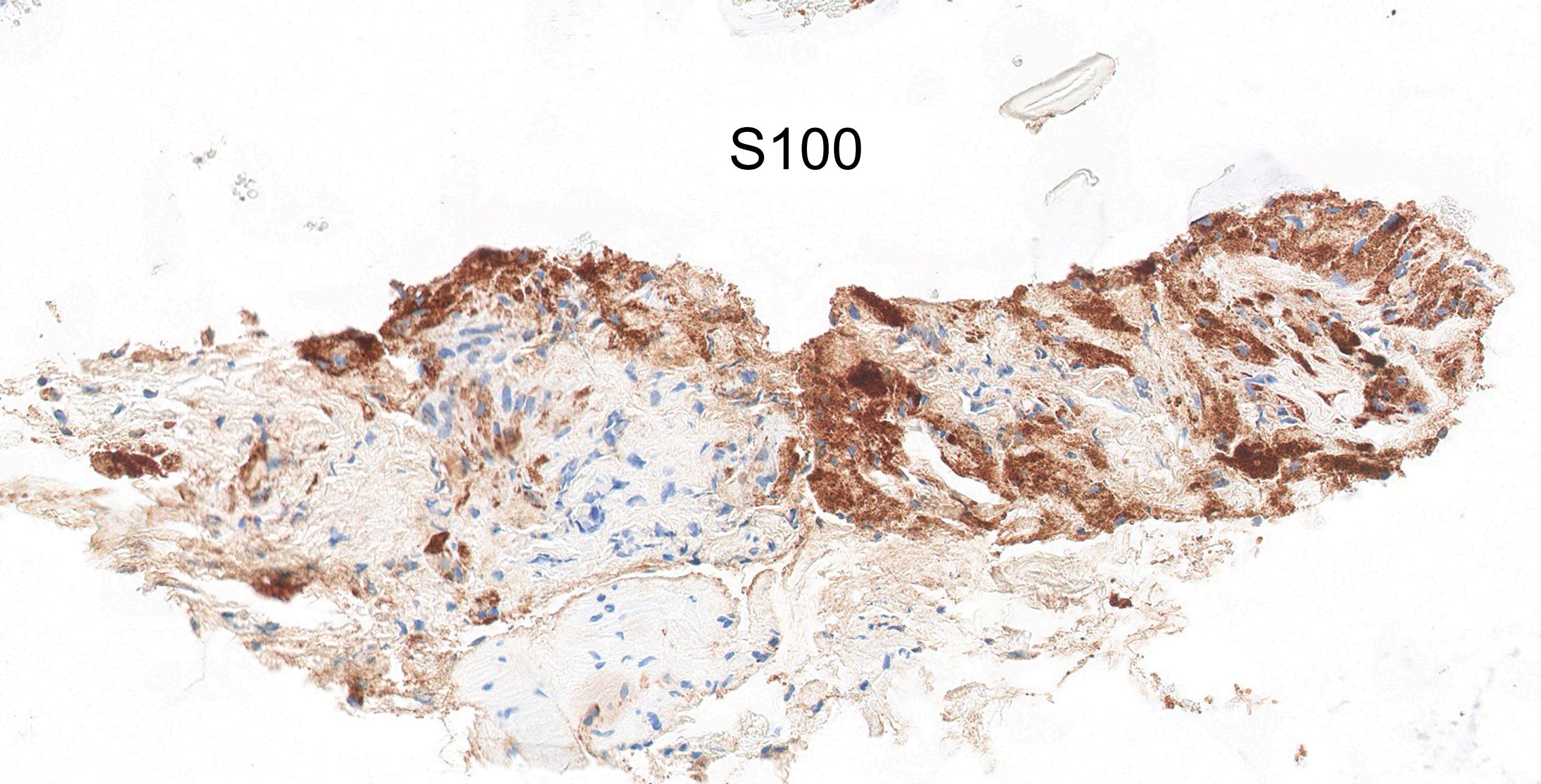
Meissner corpuscles

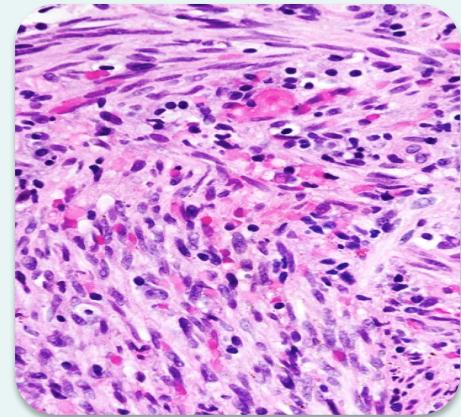
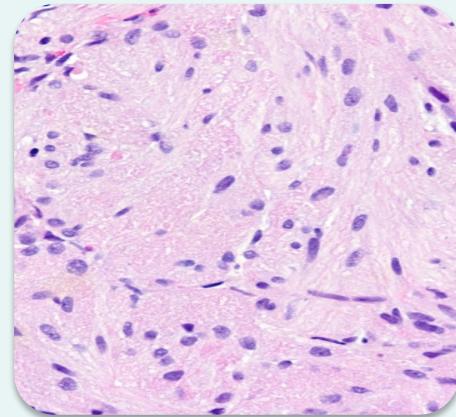
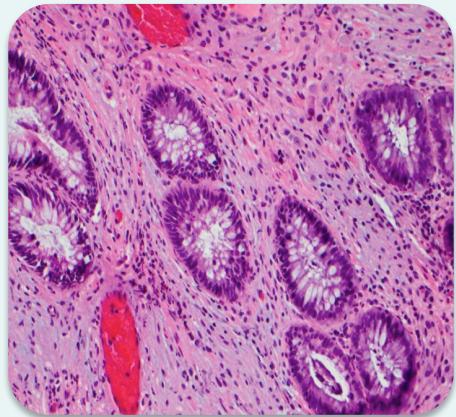
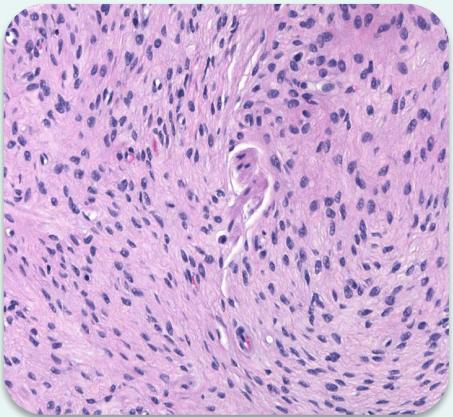




Granular cell tumor

S100





Perineurioma

S100
Negative

EMA
Positive

Schwann Cell H

S100
Positive

Ganglioneuroma

S100
Positive

Granular cell T

S100
Positive

Kaposi Sarcoma

S100
Negative

HHV8 Positive

Mucosal spindle cell lesions

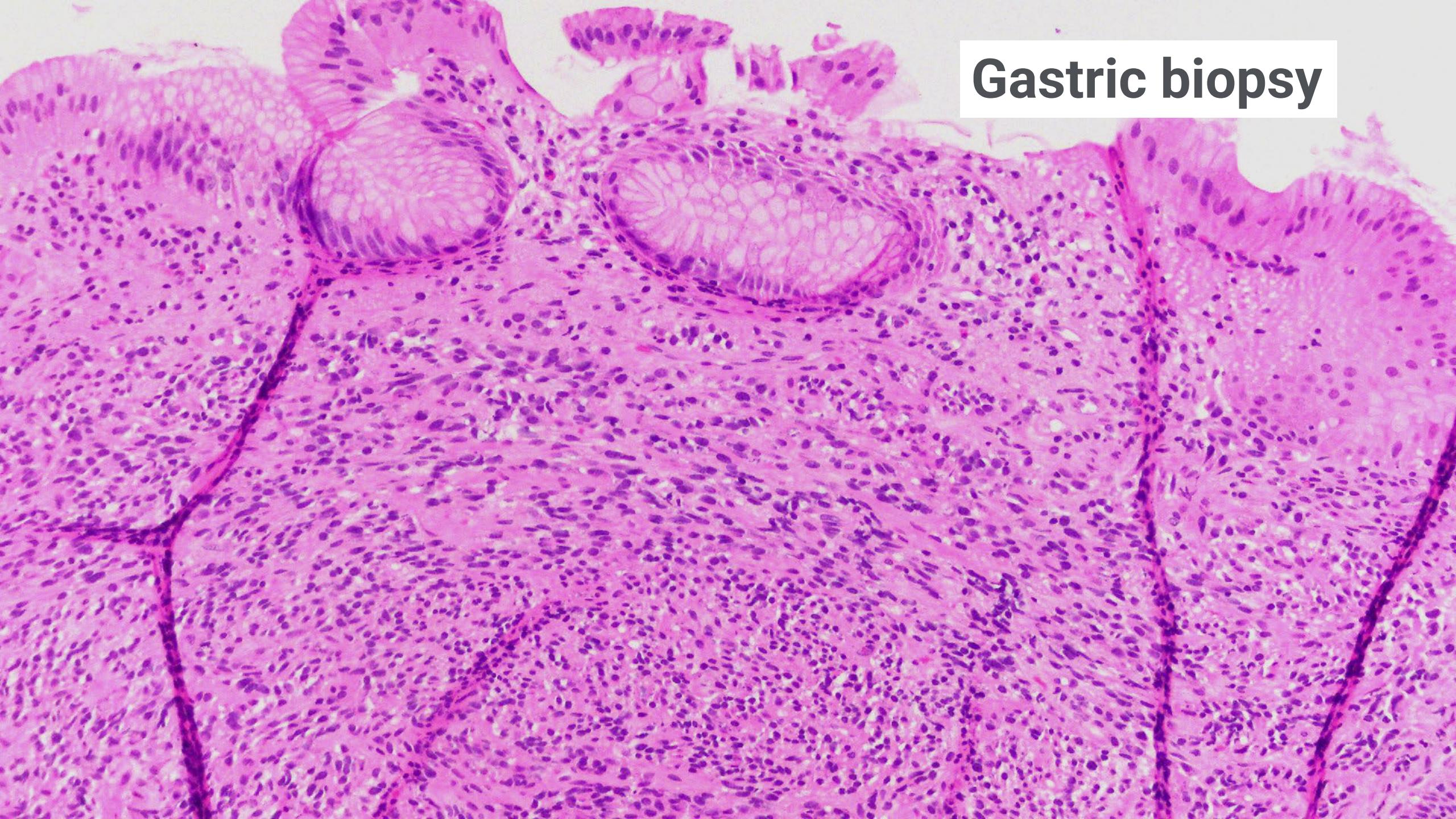


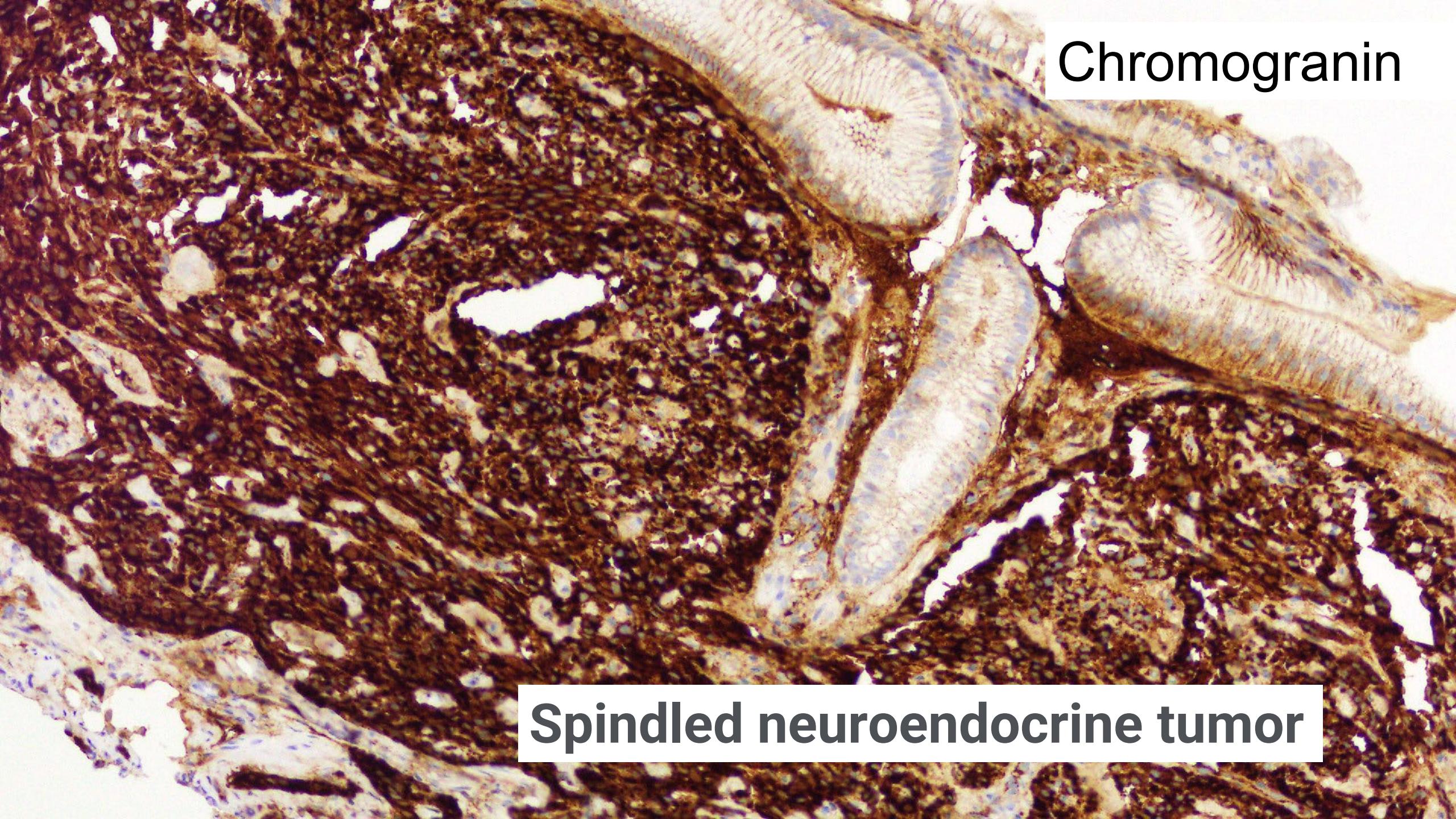
MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

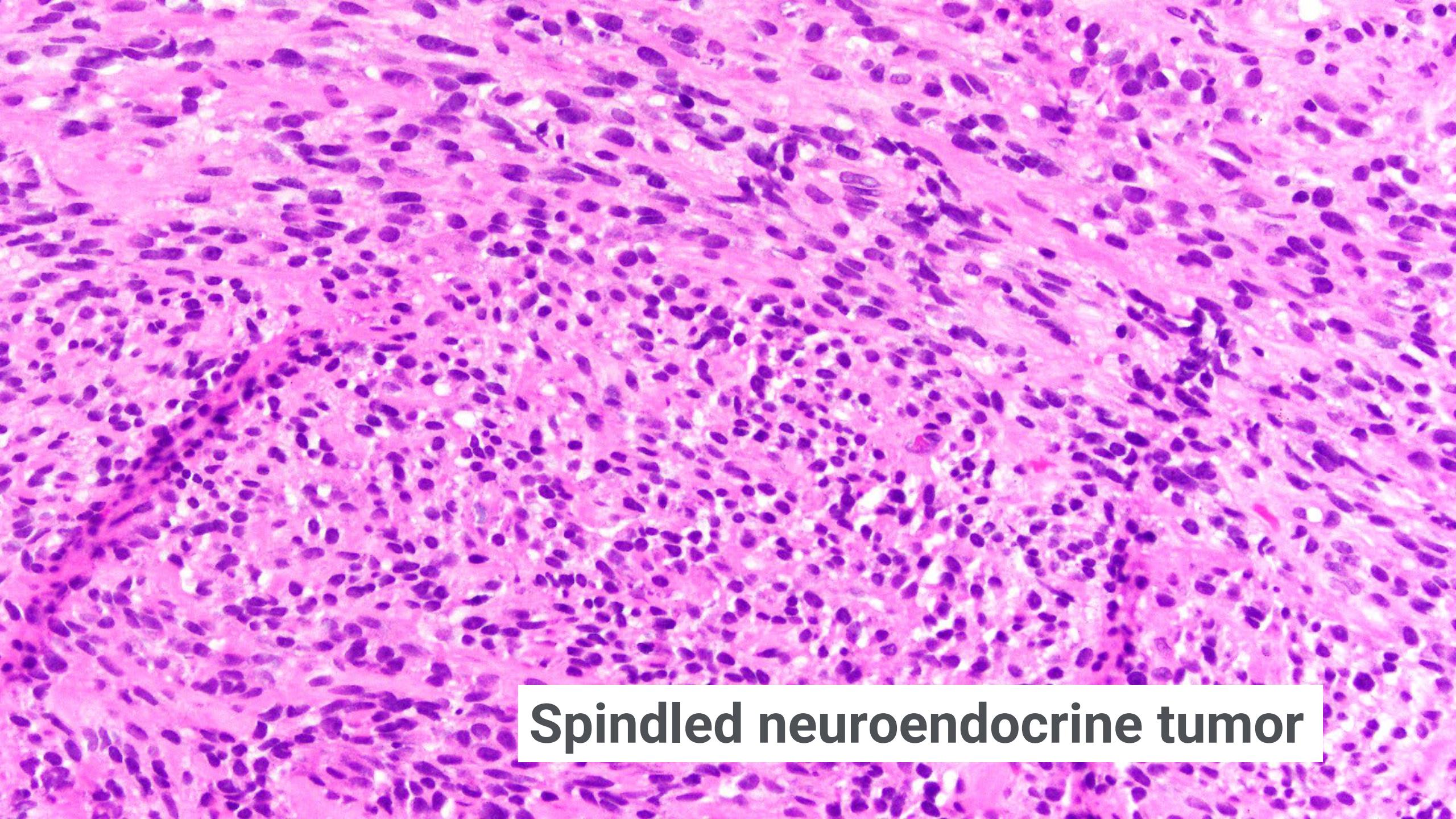
Gastric biopsy





Chromogranin

Spindled neuroendocrine tumor

A high-magnification light micrograph of a tissue sample stained with hematoxylin. The image shows a dense population of spindle-shaped cells. These cells have elongated, somewhat wavy nuclei, which are dark purple in color. There is significant nuclear pleomorphism, with some nuclei appearing larger and more irregular than others. The cytoplasm is pale pink and appears relatively uniform. The overall arrangement of the cells suggests a infiltrative growth pattern typical of a malignant tumor. A small, white rectangular box is overlaid on the bottom right corner of the image.

Spindled neuroendocrine tumor

Submucosal Tumors



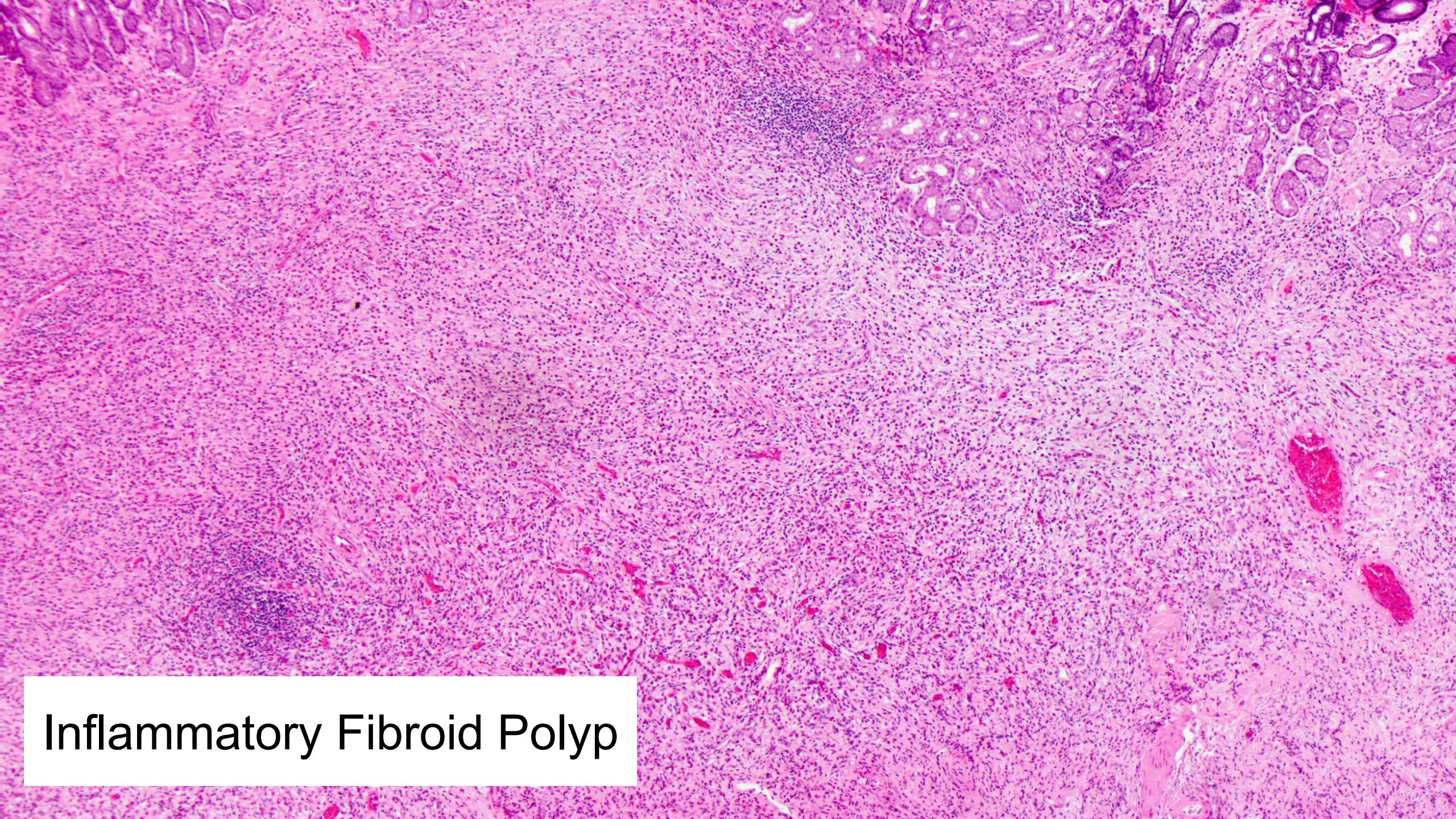
MASSACHUSETTS
GENERAL HOSPITAL



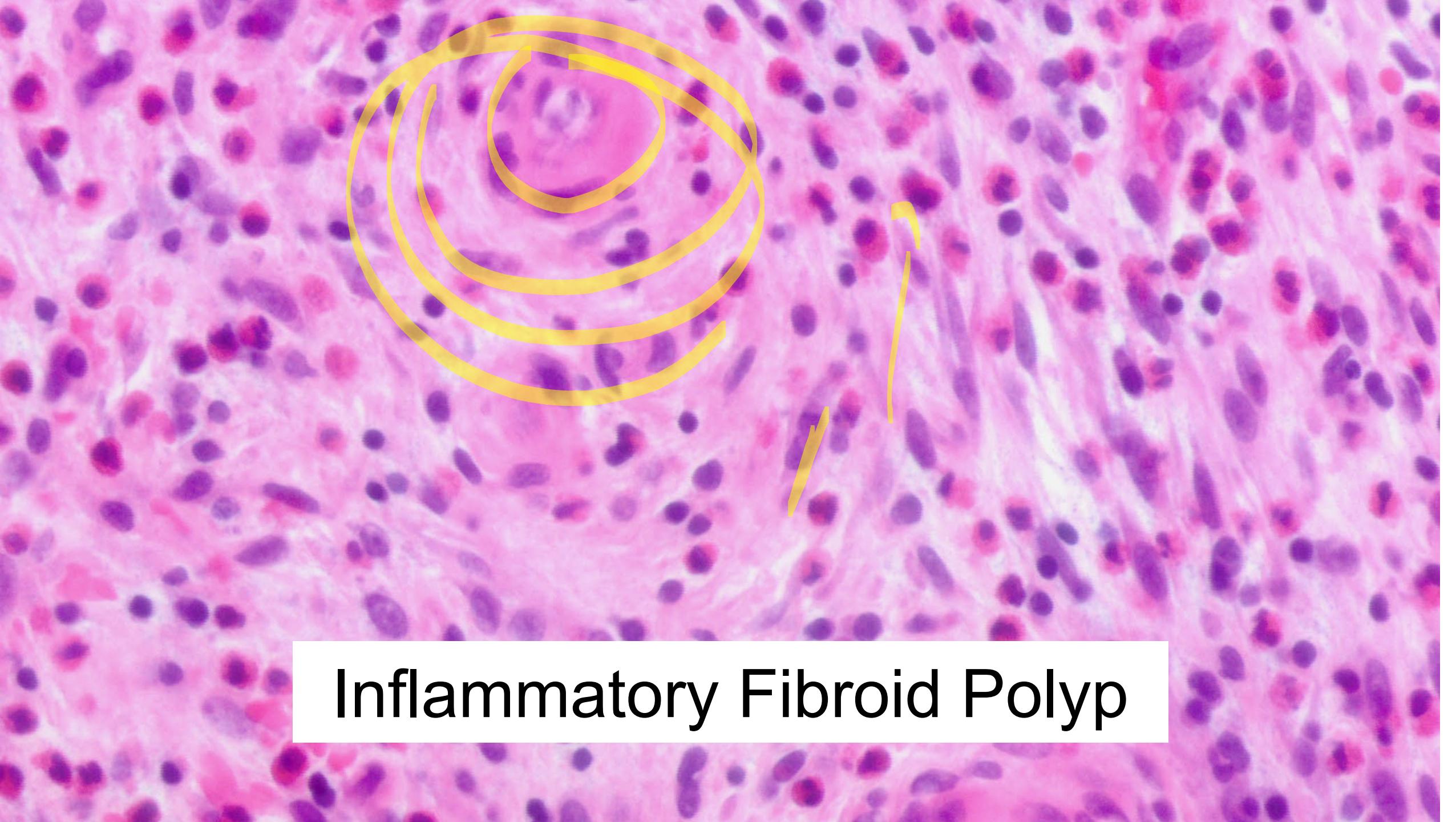
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Inflammatory Fibroid Polyp

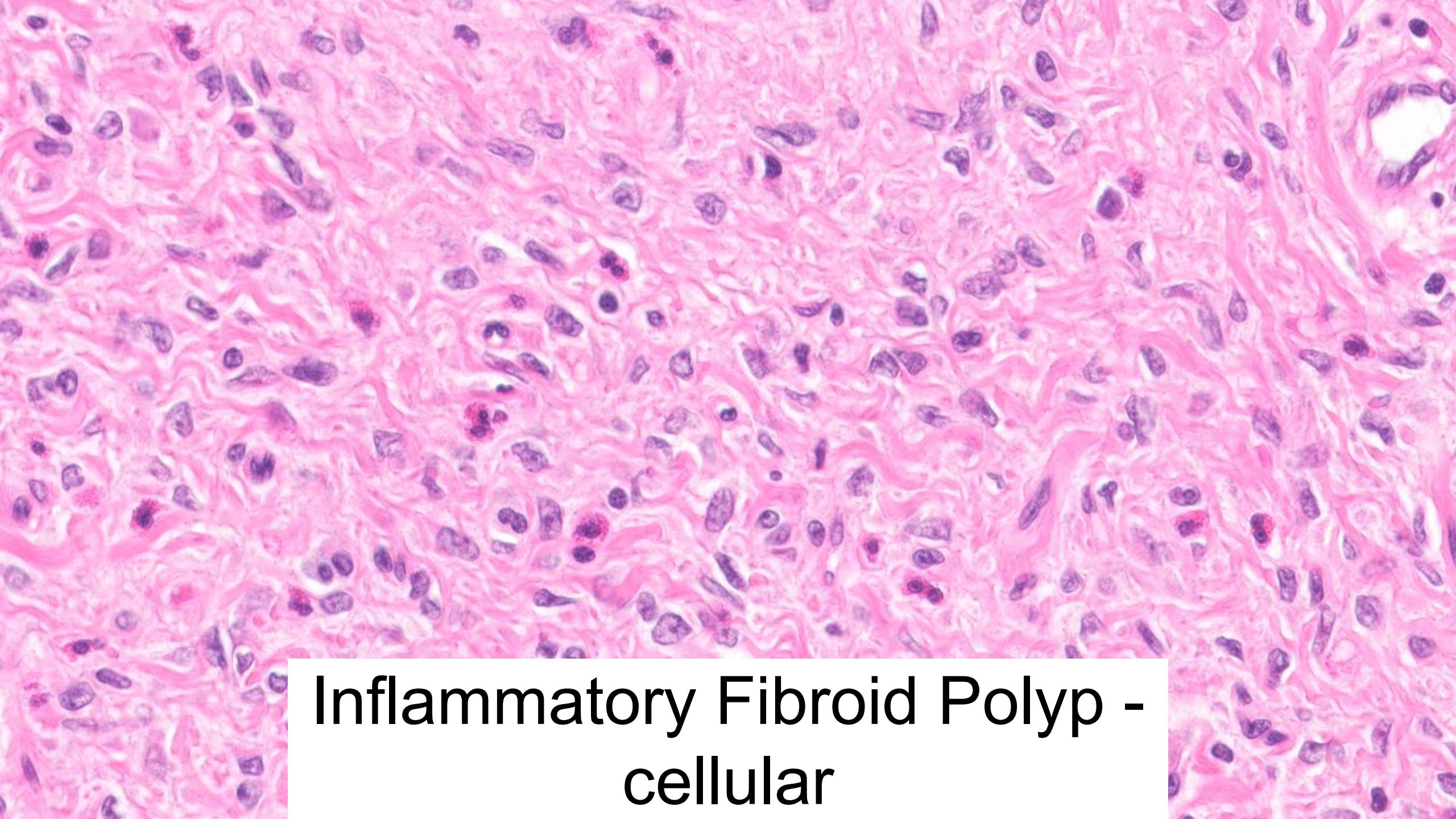
- Benign stromal tumor
- Gastric antrum>distal ileum>>esophagus, colon, proximal small bowel
- Activating PDGFRA mutations in over half cases

A high-magnification light micrograph showing a dense, cellular tissue sample. The majority of the field is occupied by a dense infiltrate of small, uniform, pink-stained cells, characteristic of lymphocytes. Interspersed among these lymphocytes are larger, more pleomorphic cells with darker, more eosinophilic cytoplasm, likely plasma cells or histiocytes. In the upper right corner, there are several distinct, rounded structures with a clear, pale center and a thick, dark-staining outer border, which are typical features of a fibroid polyp. The overall pattern is one of a reactive, inflammatory infiltrate with focal areas of neoplastic transformation.

Inflammatory Fibroid Polyp



Inflammatory Fibroid Polyp

A high-magnification light micrograph showing a cellular infiltrate. The tissue is densely packed with small, polygonal cells, many of which contain prominent, dark purple, pleomorphic nuclei. Interspersed among these are larger, more rounded cells with pale, eosinophilic cytoplasm. The overall pattern is somewhat disorganized and infiltrative, characteristic of an inflammatory process.

Inflammatory Fibroid Polyp -
cellular

Inflammatory Fibroid Polyp

PDGFRA

The World of Fusions



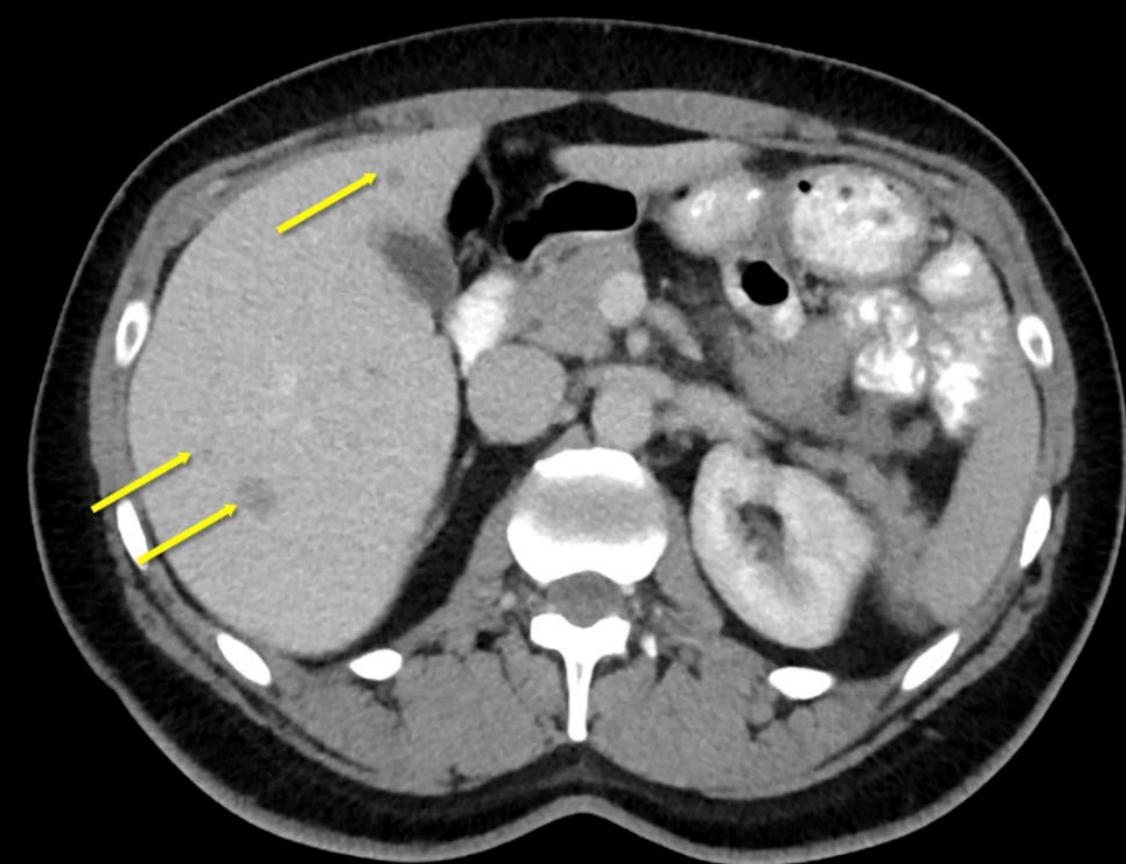
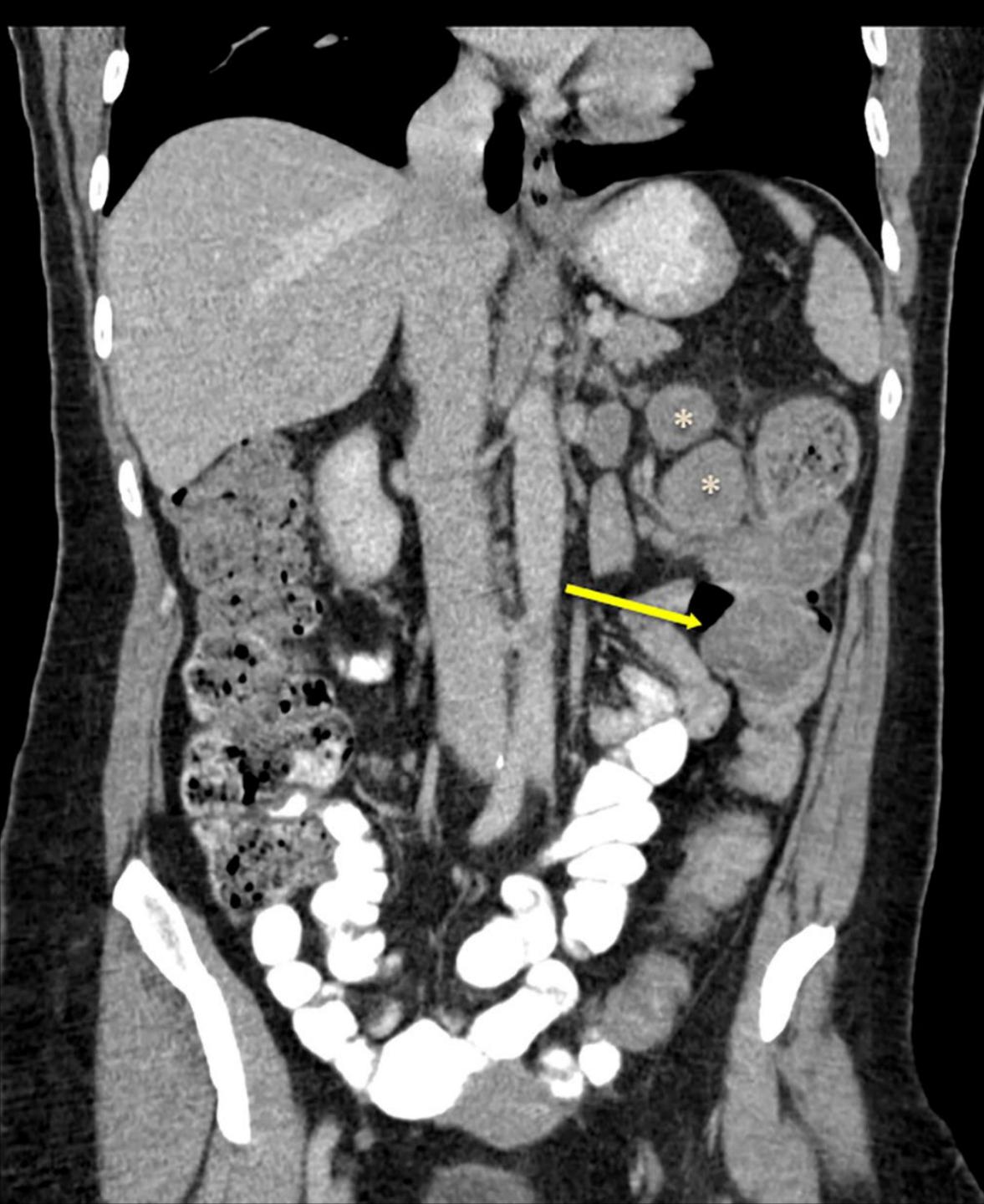
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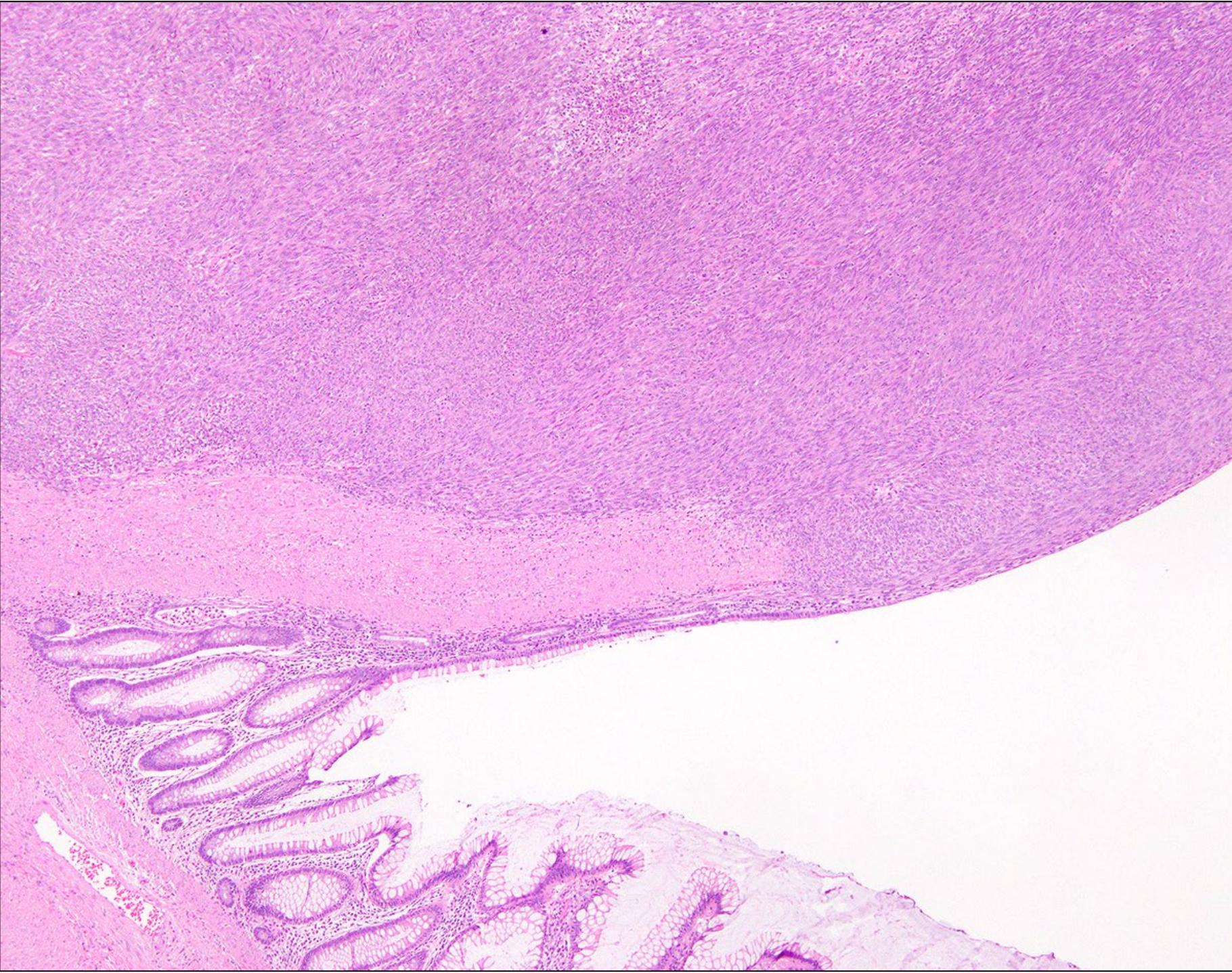
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NUTM1-Rearranged Sarcoma

- Extremely rare
- No age or sex predilection
- Spindled, epithelioid/rhabdoid and hyalinized/nested patterns
- Express keratins (weak, patchy) and NUTM1 protein
- Negative for other tested markers; SMARCB1-retained
- *MDX4-NUTM1*
- *summuoxa*
- Aggressive sarcomas with locoregional/distant metastases and poor outcome



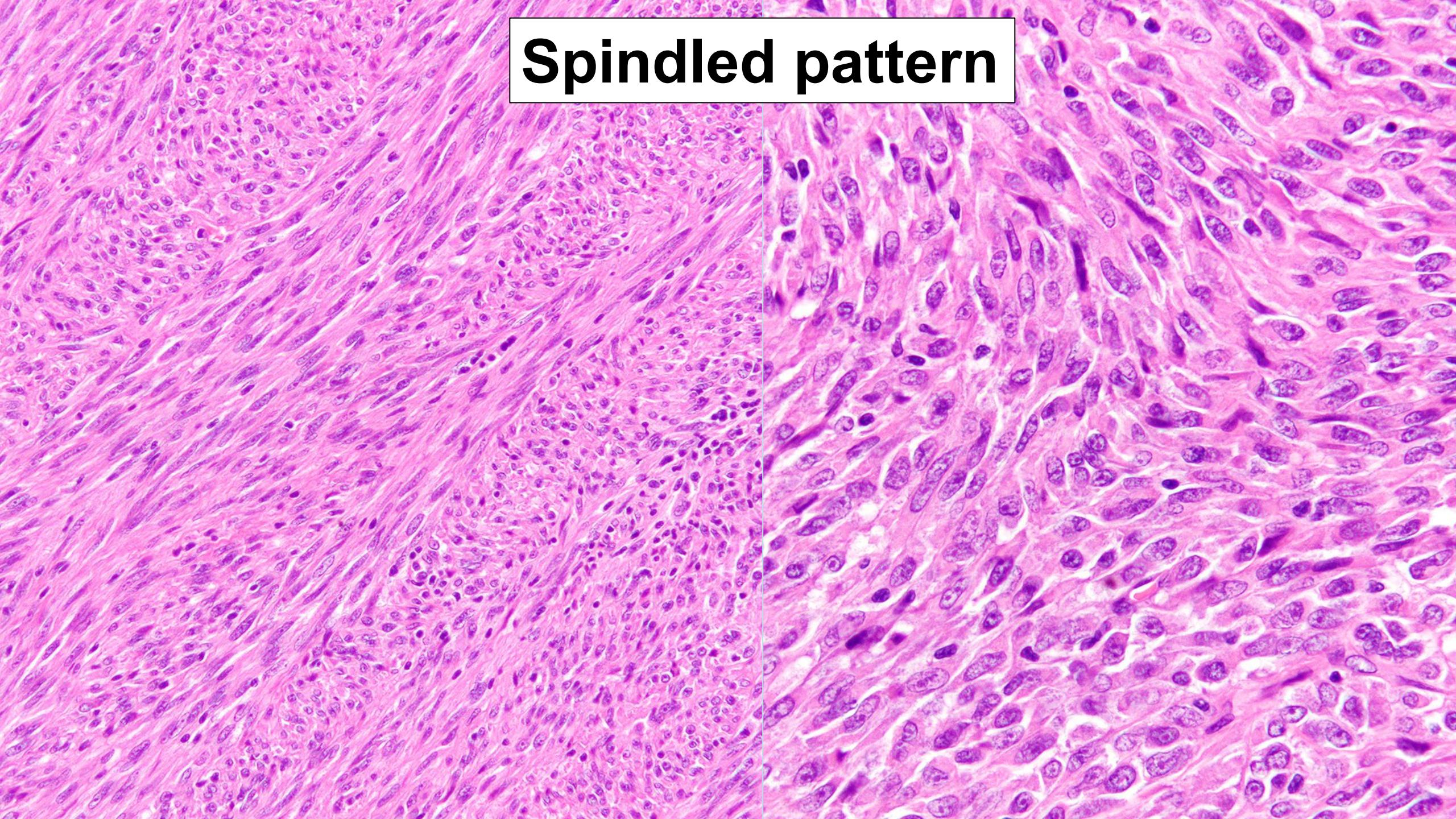
Andrew Folpe



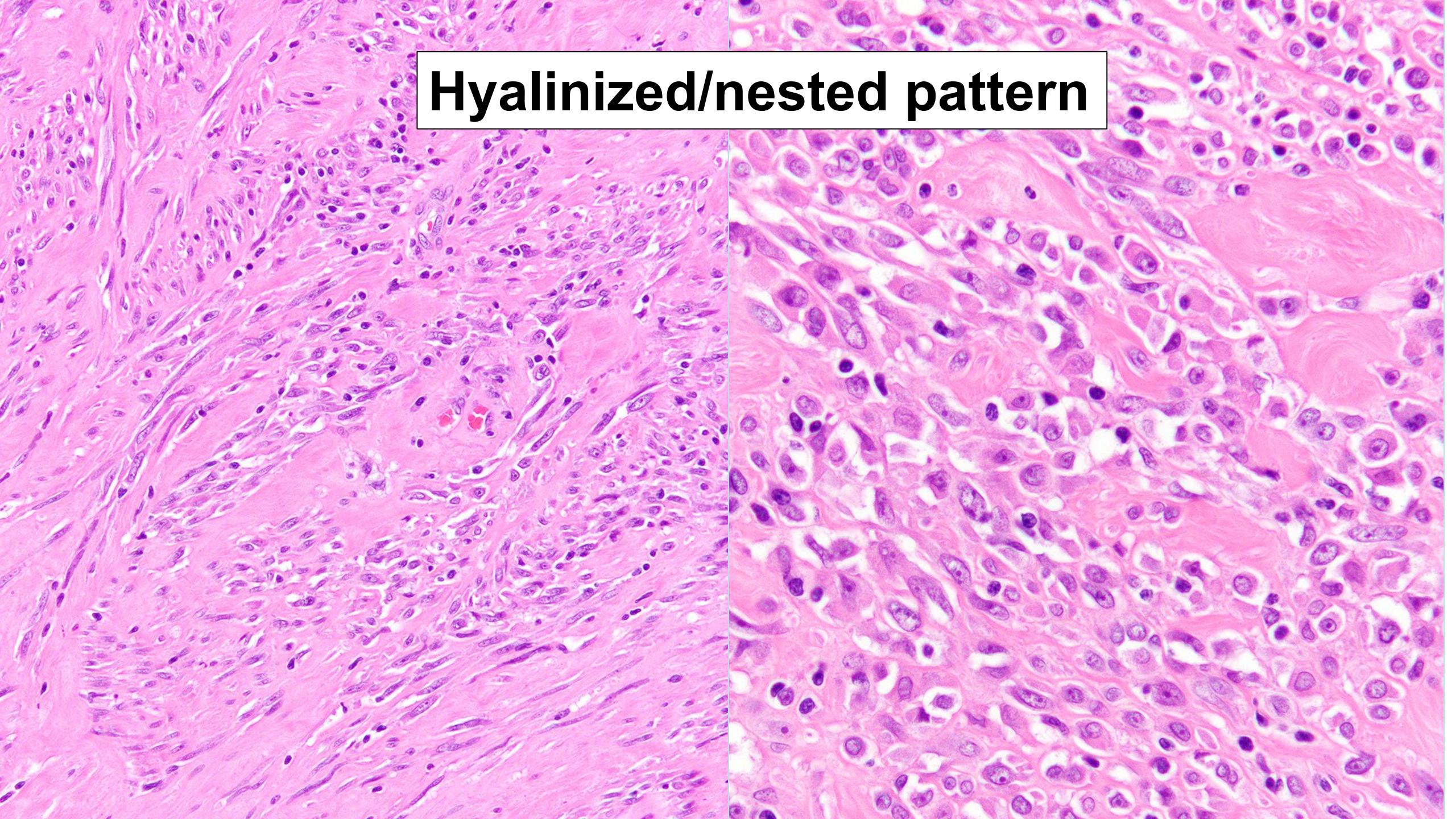
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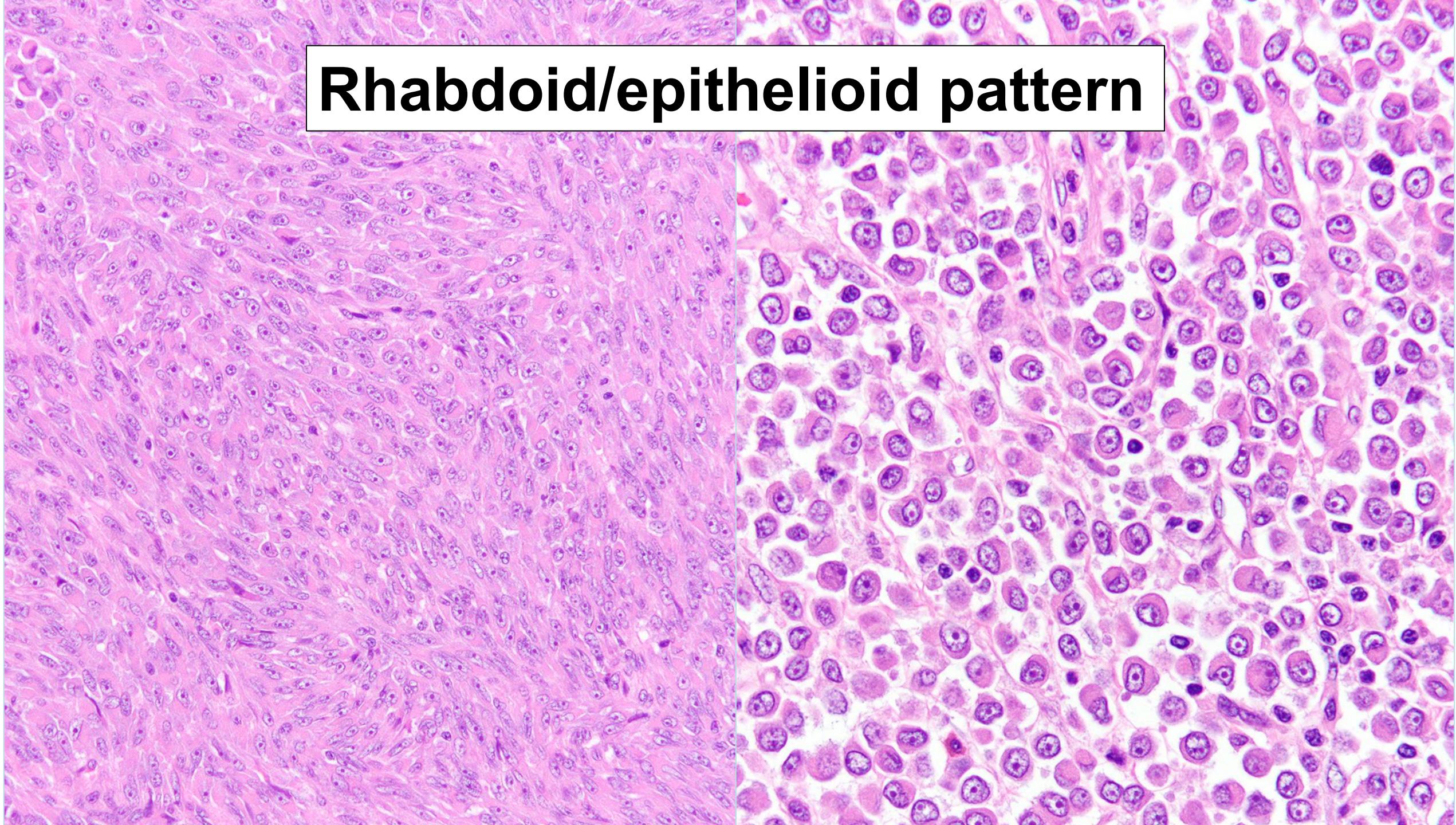
Spindled pattern

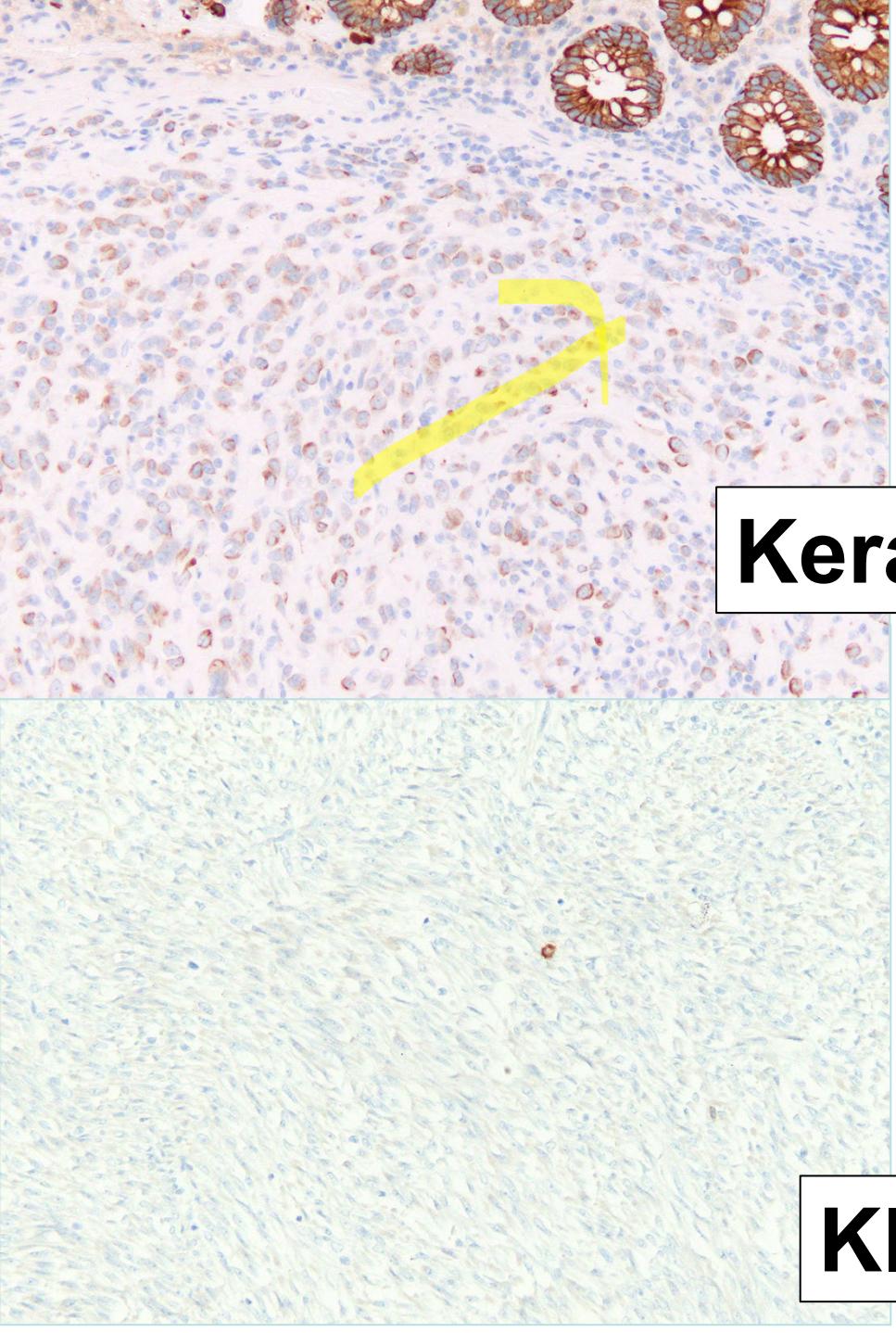


Hyalinized/nested pattern



Rhabdoid/epithelioid pattern





Keratin

KIT

SMARCB1

NUTM1

NUTM1-Rearranged Sarcoma

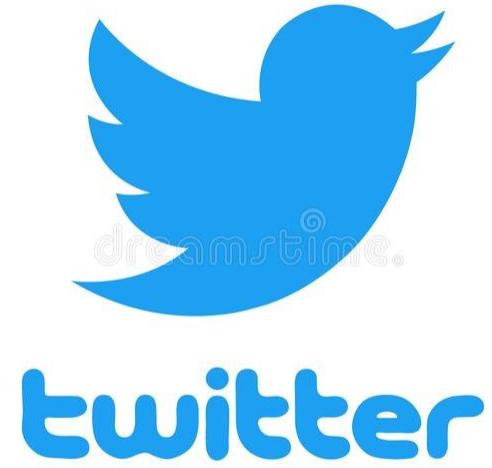
NUTM1



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<https://www.youtube.com/c/vikramdeshpandePathology>

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