Royal Cornwall Hospitals NHS Trust

University Hospitals Plymouth NHS Trust

Getting the gist of GIST

and submucosal mimics in the oesophagus and stomach

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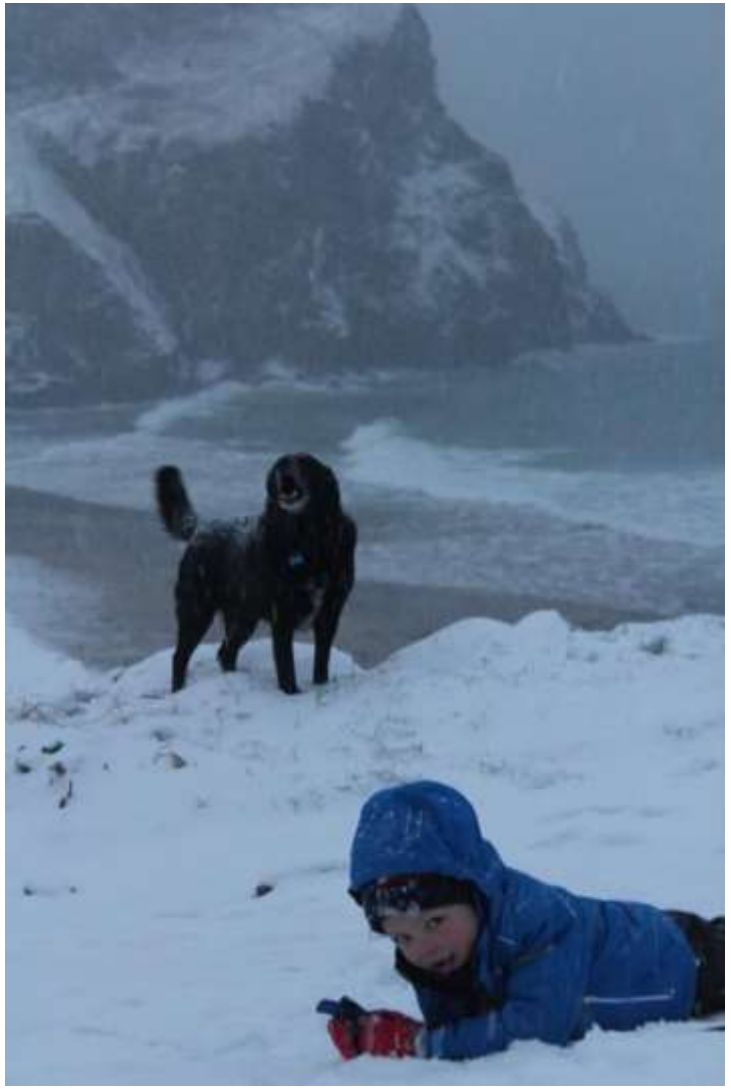
Pathkids.com
@pathkids Follows you

March 2018. relocation to Cornwall.

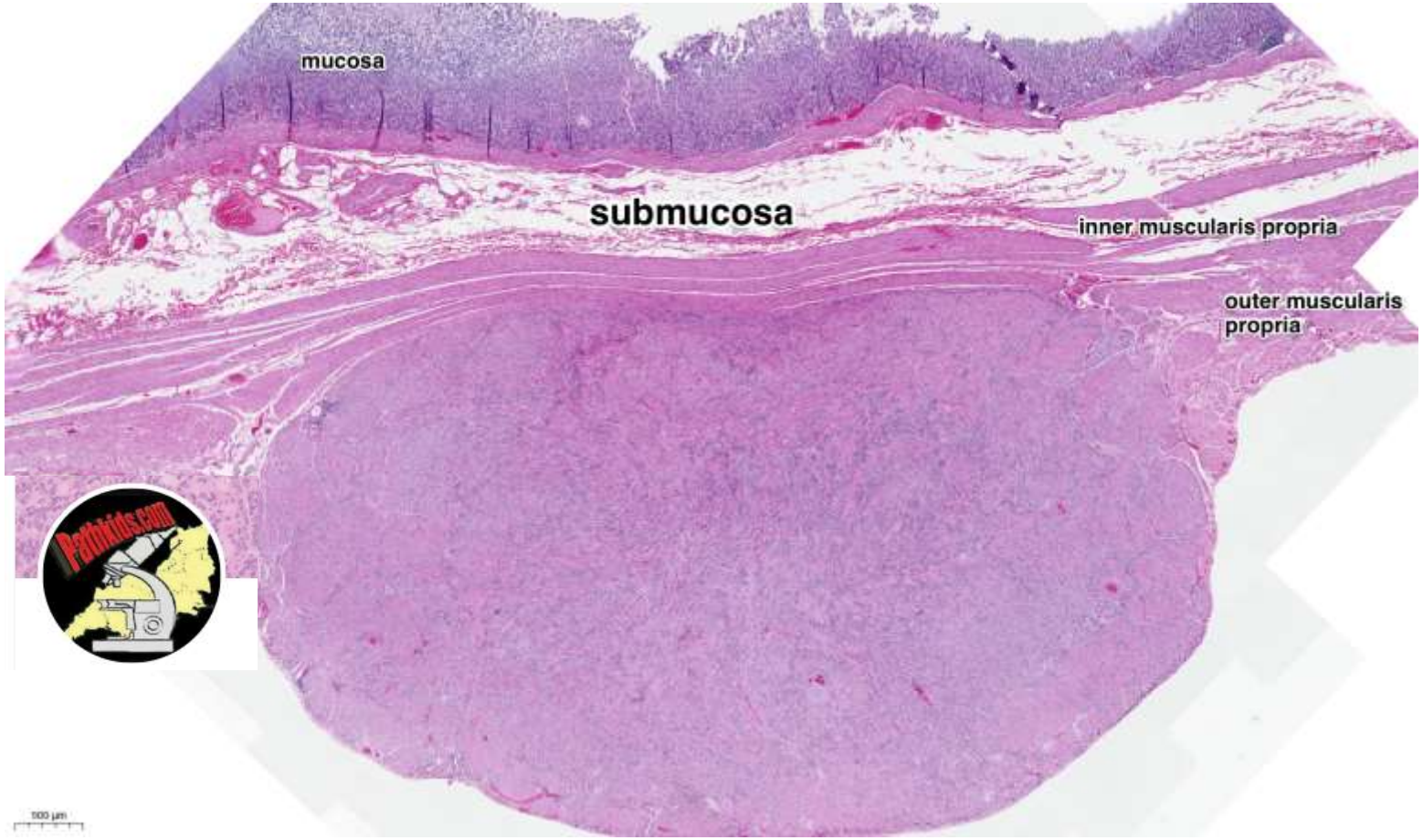
The beast from the east and the pest from the west



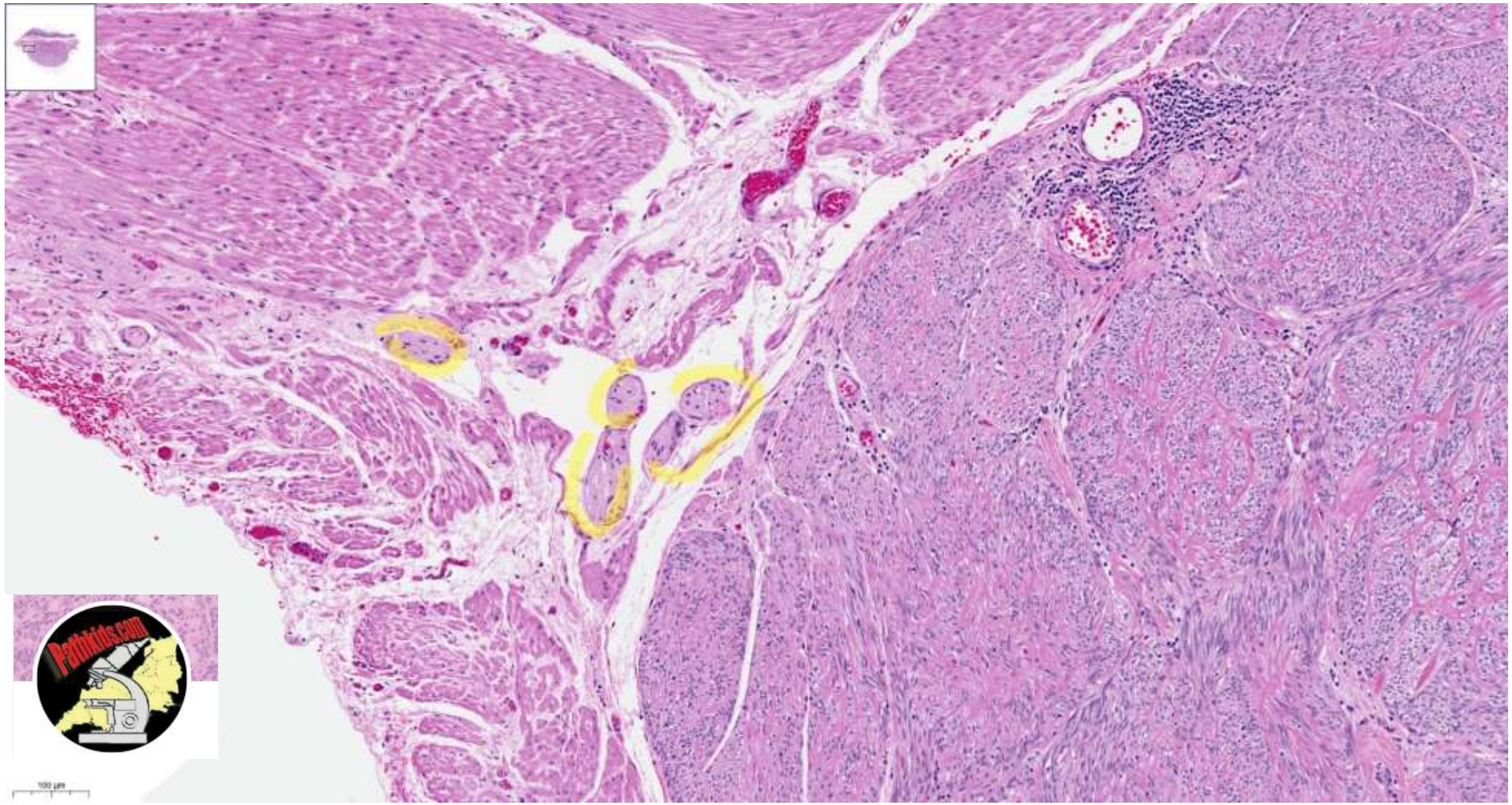
Introduction

- 16 “real cases” with slides at this link on Pathkids.com/wp blog page
- All are “under the surface” submucosal or mural
- Not exhaustive but includes histological as well as clinical GIST mimics
- Please ask questions by hand up, into the chat, or email/private chat to Elinor.george@nhs.net or Adam.Douglas@nhs.net who have both kindly agreed to read out any questions of you want to be anonymous
- No such thing as a silly question. If I don’t know the answer now I will get back to you! Tim.bracey@nhs.net

Our clinical colleagues tend to call anything "beneath" the mucosal surface "a GIST"



GIST arises from Cajal cells in the muscularis myenteric plexus



GIST prognosis depends on 3 Histopathology factors

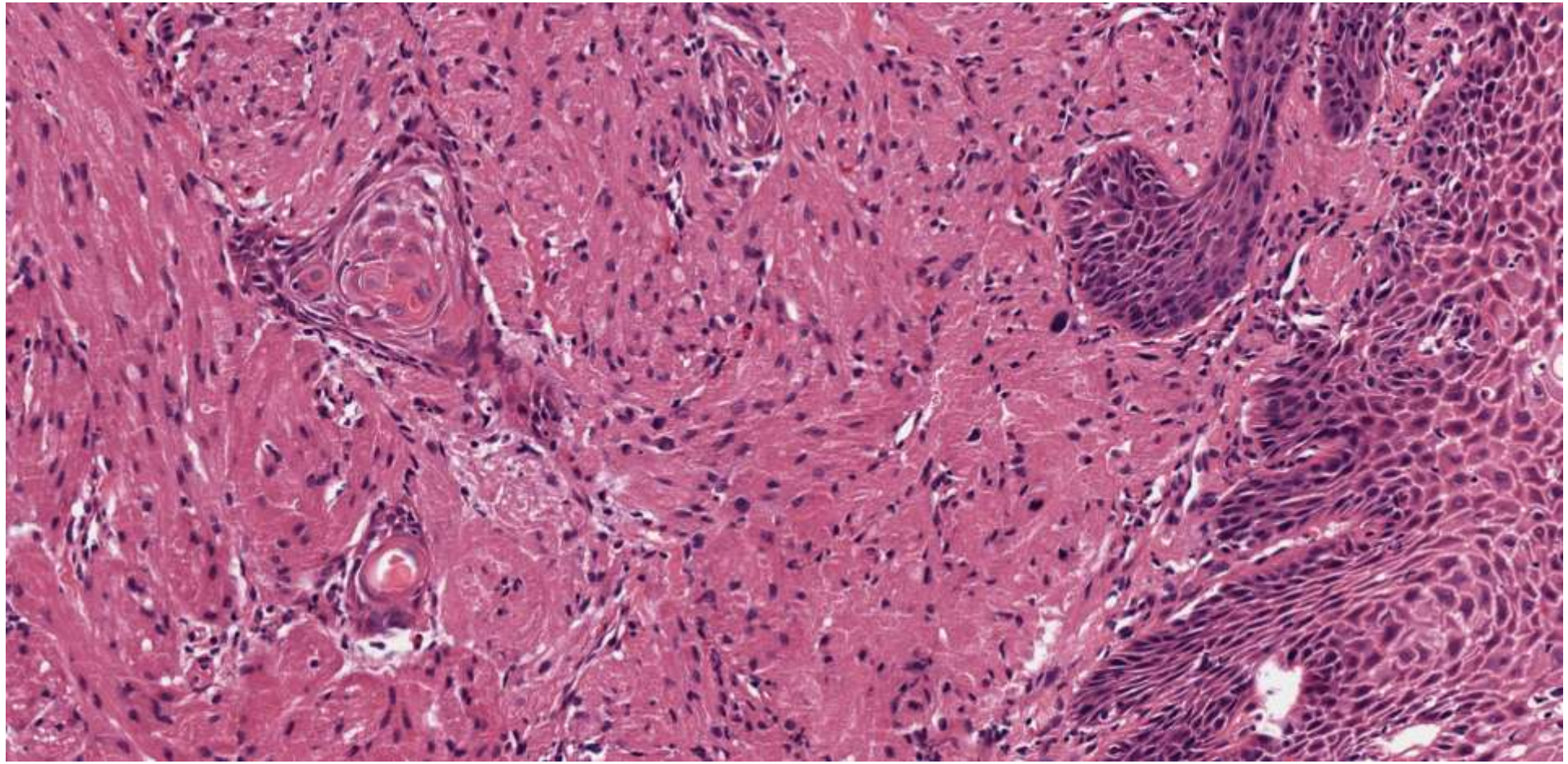
- Location
- Size
- Mitotic rate

- Job 1 is to confirm its definitely a GIST with morphology and appropriate immunohistochemistry.
- CD117, DOG1, CD34 (plus other markers if alternatives suspected)

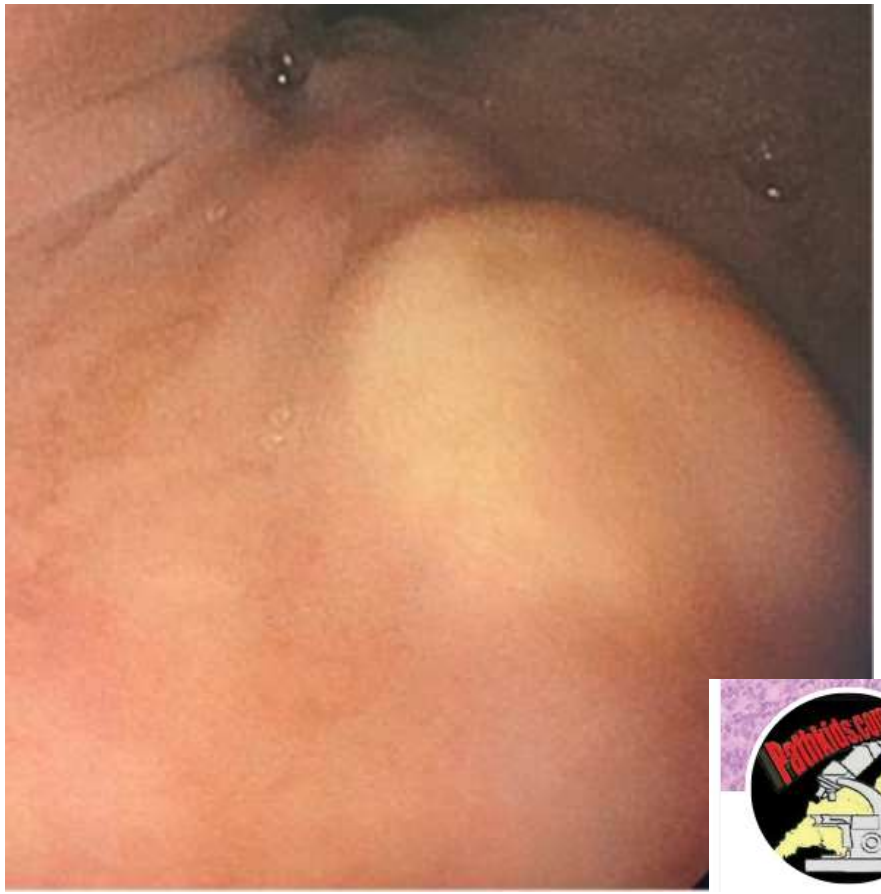
Case 1

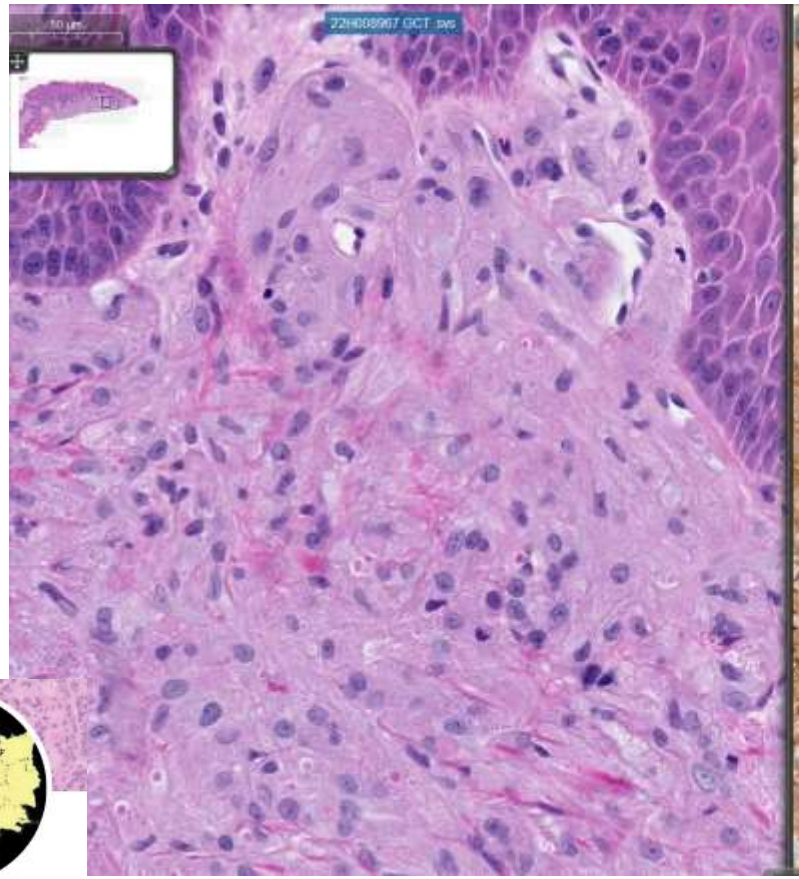
- ?GIST distal oesophagus EMR
- Whole slide image link from Leeds , another one from me with S100.

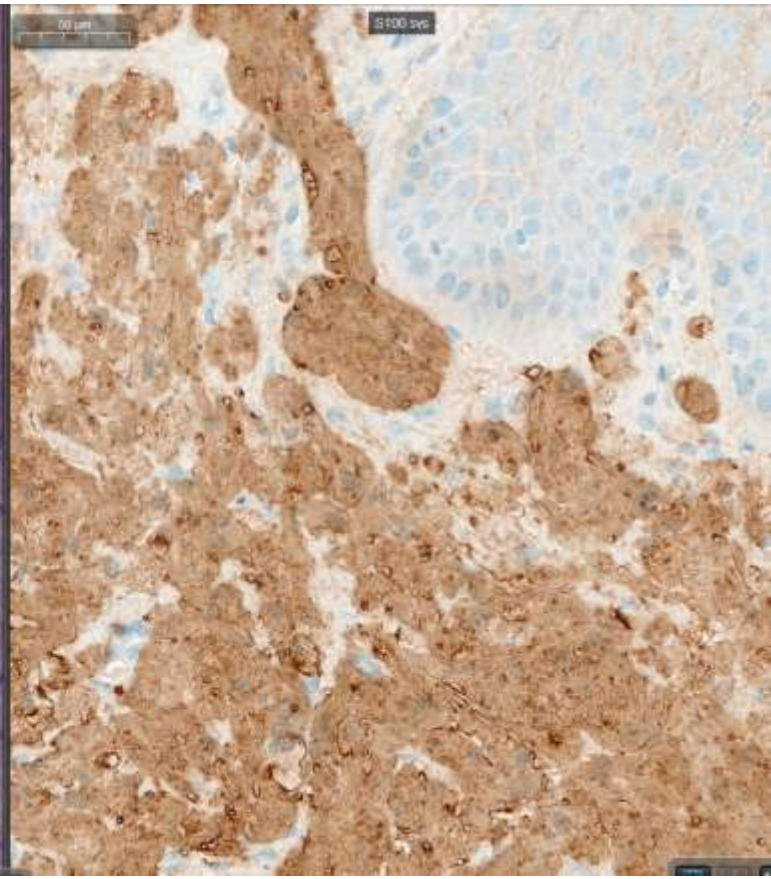
Case 1



Case 1: Oesophageal granular cell tumour







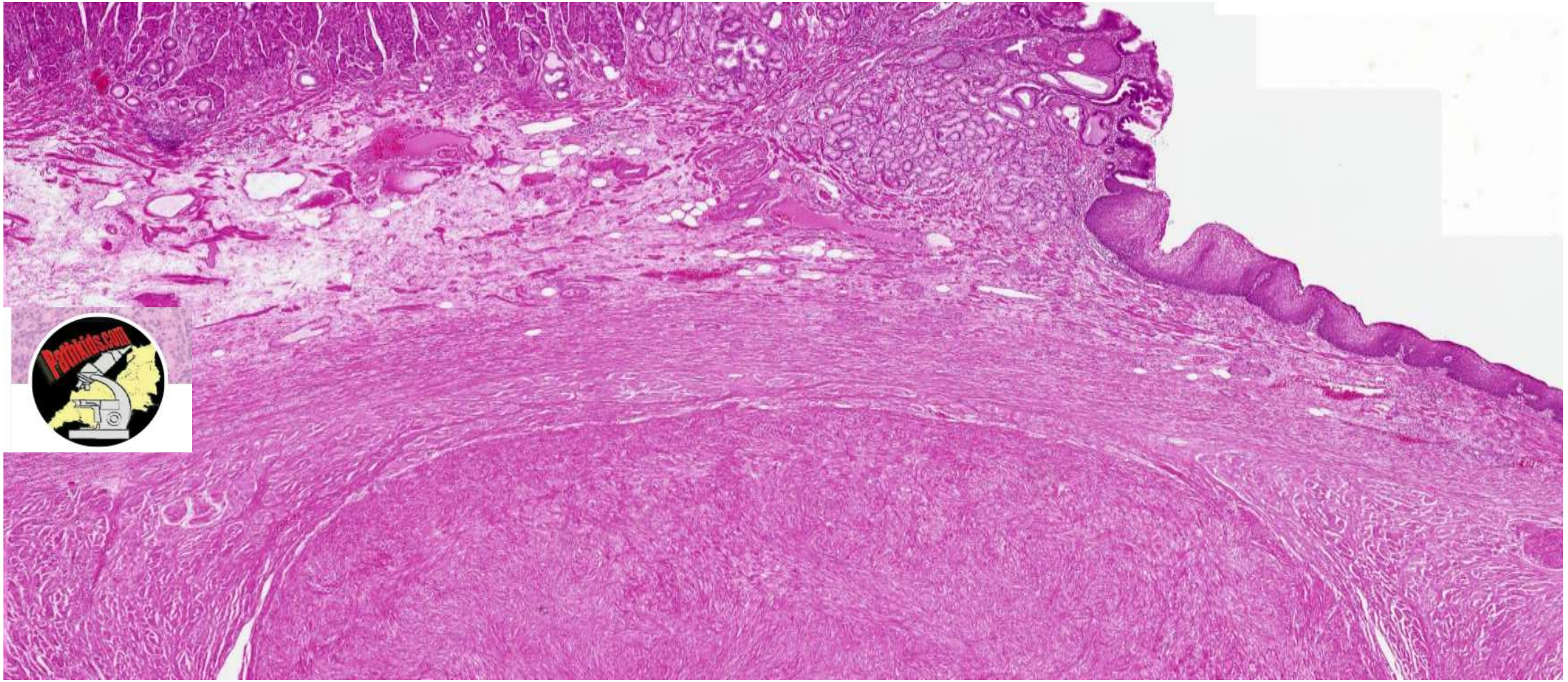
Case 1: oesophageal granular cell tumour

- 2nd most common stromal tumour of oesophagus
- Subepithelial but can require EMR to diagnose
- Yellowish "molar tooth" appearance on endoscopy
- Pseudoepithelial hyperplasia can mimic SCC on small biopsy
- Benign but *atypical forms* may behave aggressively
  - *(rapid growth, > 4 cm, tumor necrosis, increased cellularity, atypia, > 2 mitotic figures/HPF)*

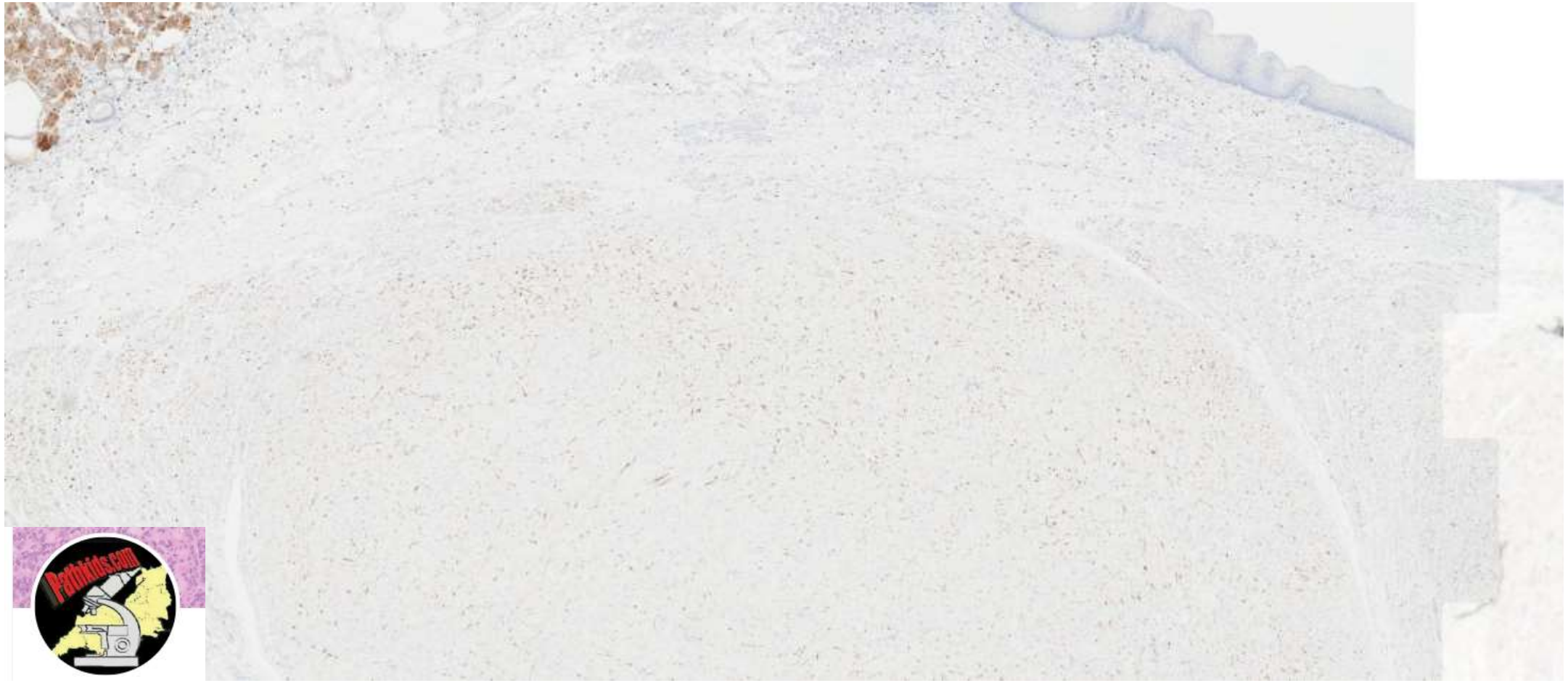
Case 2:

- Submucosal oesophageal mass suspected GIST
- . H&E slide.CD117. SMA.

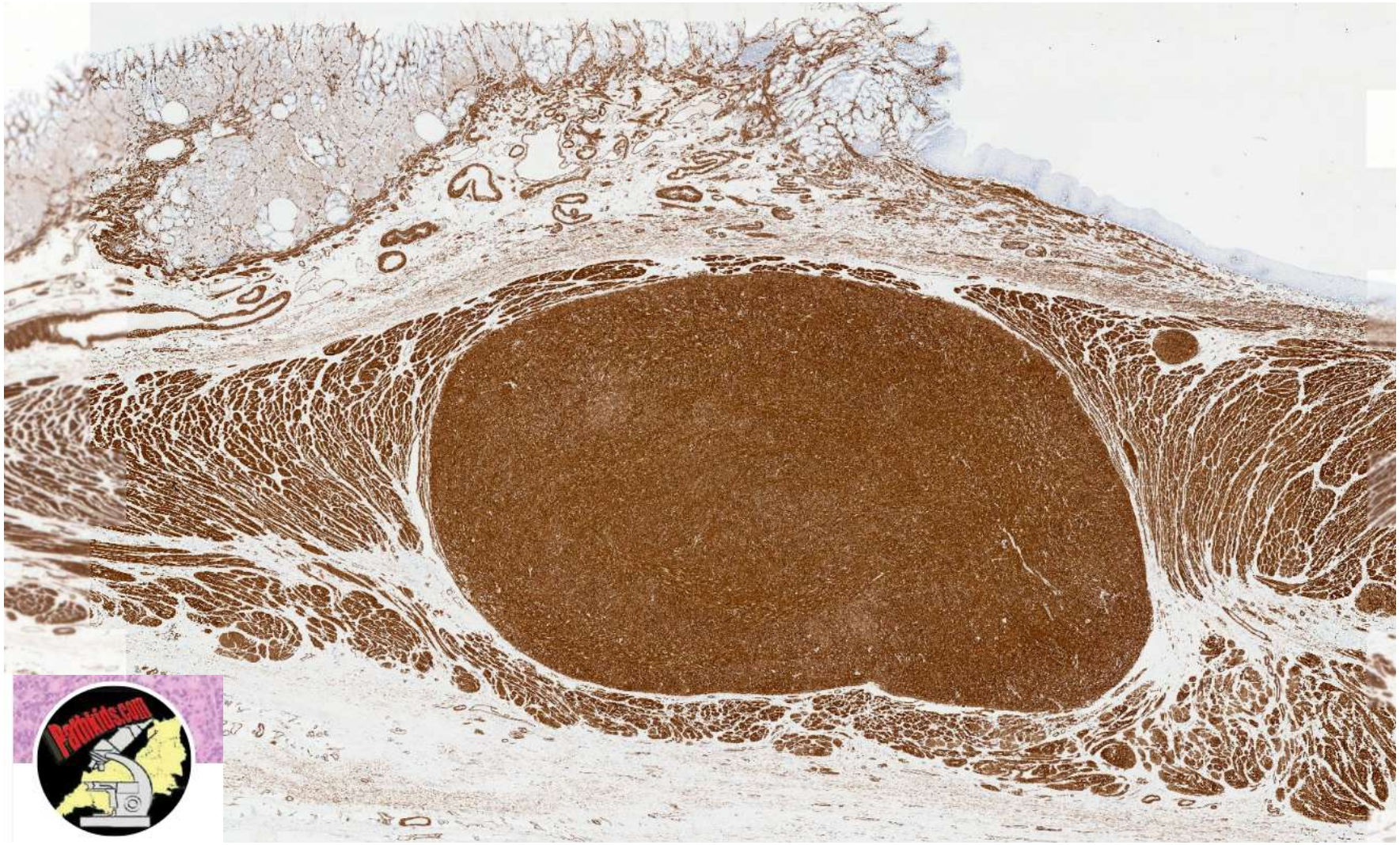
Case 2:



Case 2: CD117



Case 2: SMA



Case 2: oesophageal leiomyoma

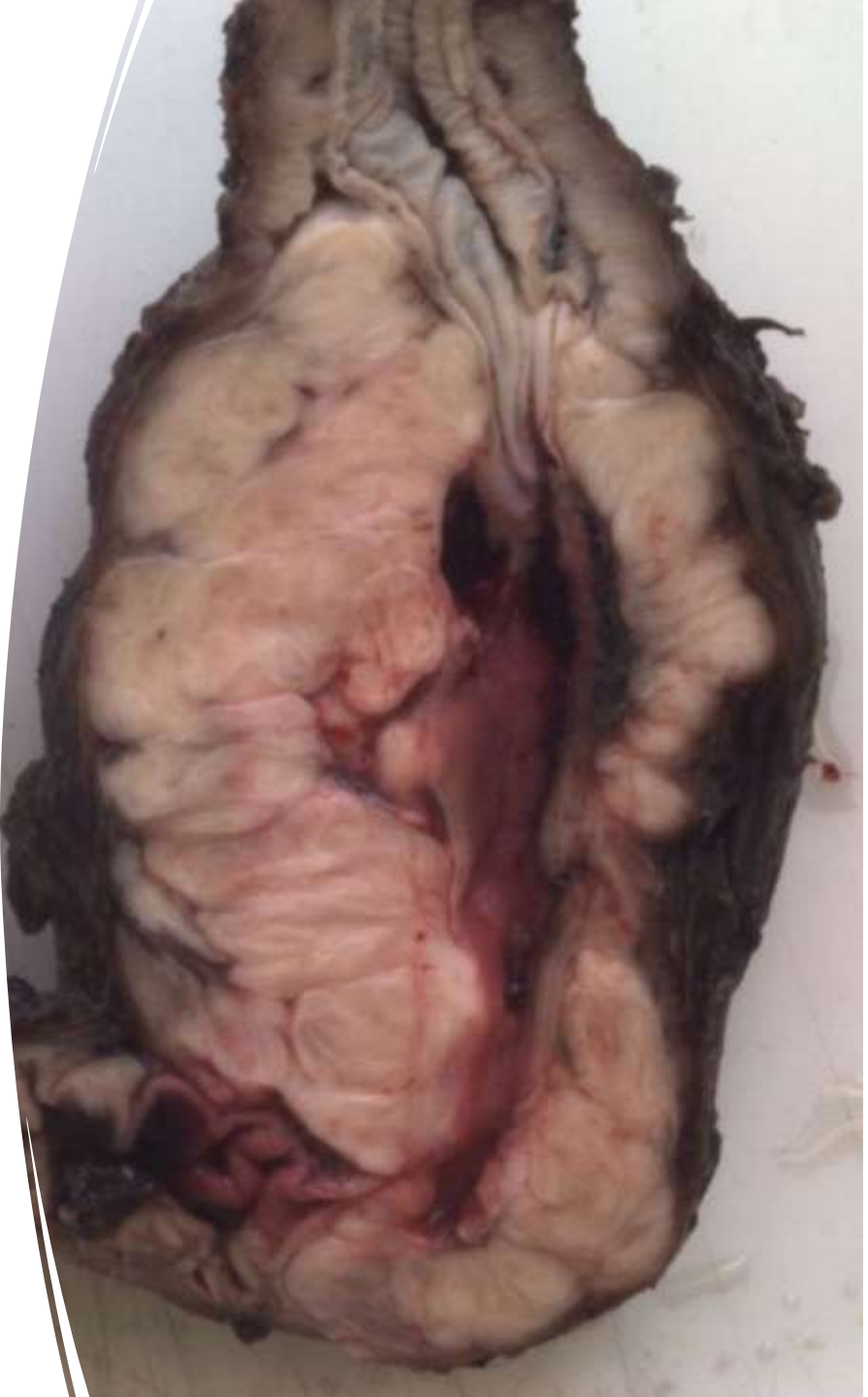
- Most common oesophageal stromal tumour
- Benign
- Submucosal from mm, or mural, usually distal, can be multiple
- Usually diminutive and incidental but can be large and symptomatic
- SMA and desmin positive
- Can have hyperplastic cajal cells so don’t misdiagnose as GIST

Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: a mimic of gastrointestinal stromal tumor

Anita Deshpande et al. Am J Surg Pathol. 2014 Jan.

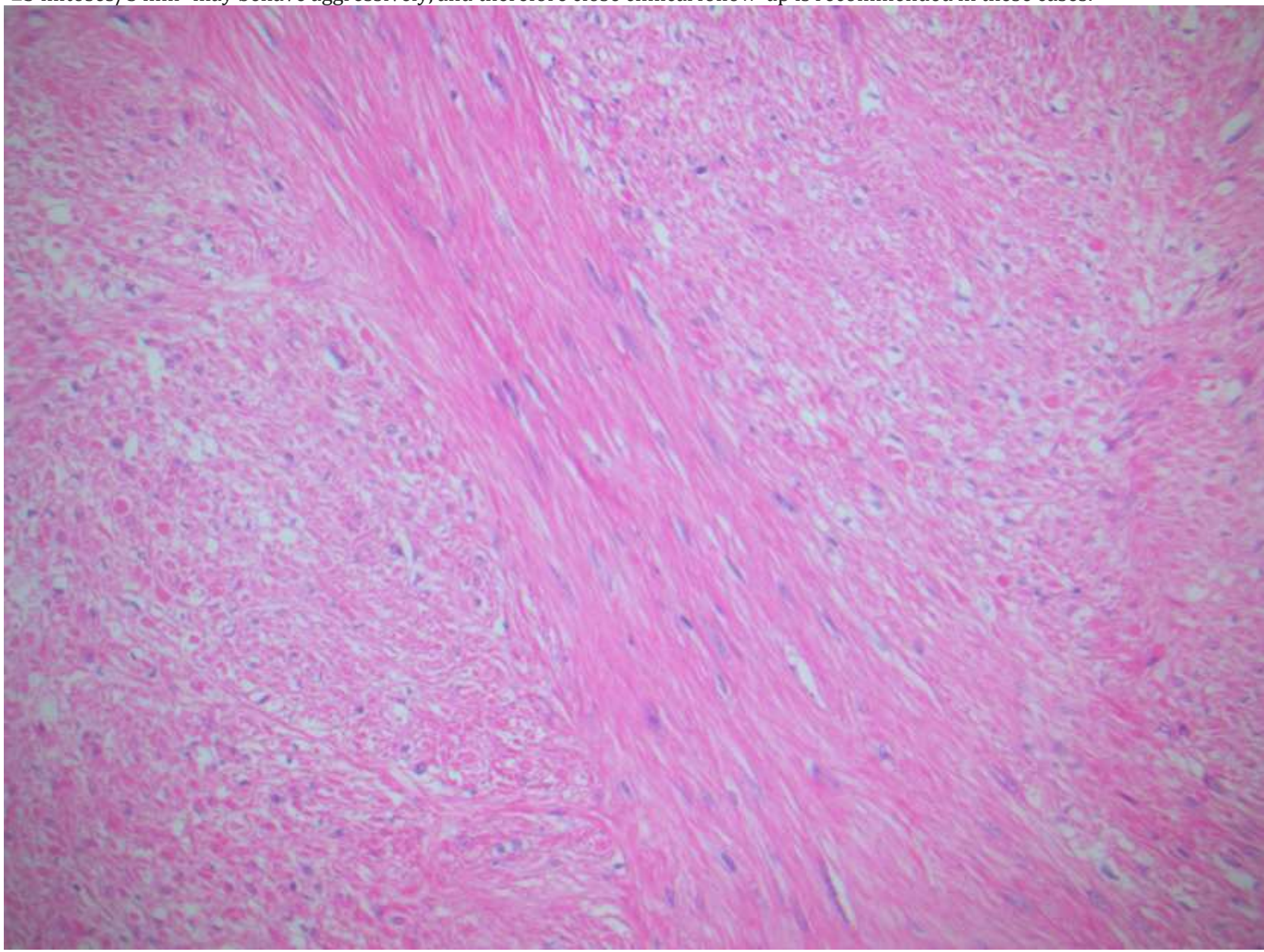
NB. Mast cells are also CD117 Positive.

Cajal cell hyperplasia is sometimes useful to distinguish leiomyoma from muscularis propria sampling.



Mod Pathol. 2020 Jul; 33(7): 1410–1419.
Published online 2020 Feb 12. doi: 10.1038/s41379-020-0492-5 **Smooth Muscle Tumors of the Gastrointestinal Tract: An Analysis of Prognostic Features in 407 Cases.** Lindsay Alpert,[1] et al.

Based on our findings, it appears that non-esophageal gastrointestinal smooth muscle tumors measuring >10 cm and/or showing ≥3 mitoses/5 mm^2 may behave aggressively, and therefore close clinical follow-up is recommended in these cases.




HI034431/18-3 B
H&E
Snowcoat
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SMA
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DOG 1
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16/01/2019 08
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CD117
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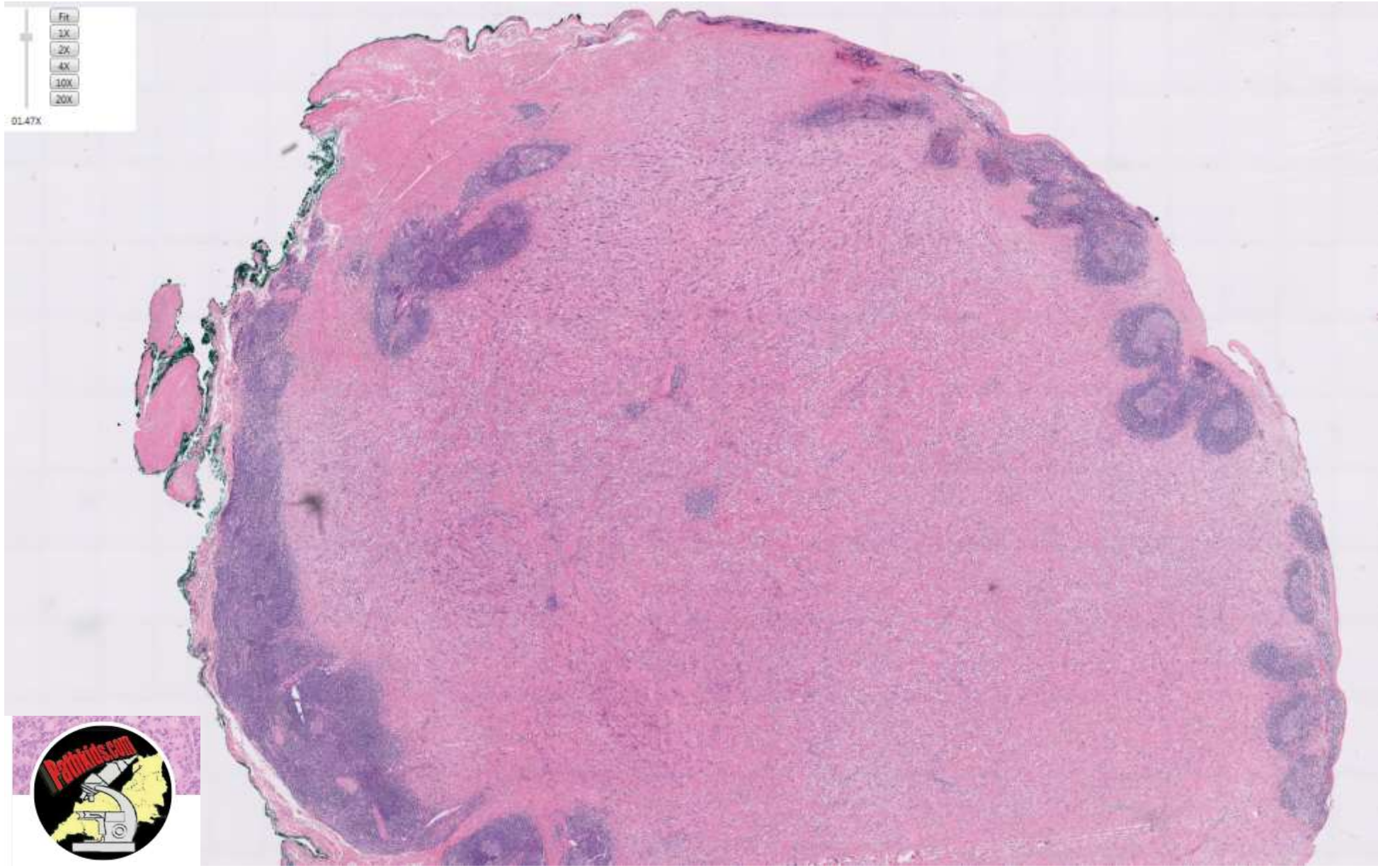
Pathkids.com

Case 3:

- Patient with SCC oesophagus. Incidental gastric lesion found in preoperative staging. Frozen section clinically presumed GIST
- Slides.


Fit
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2X
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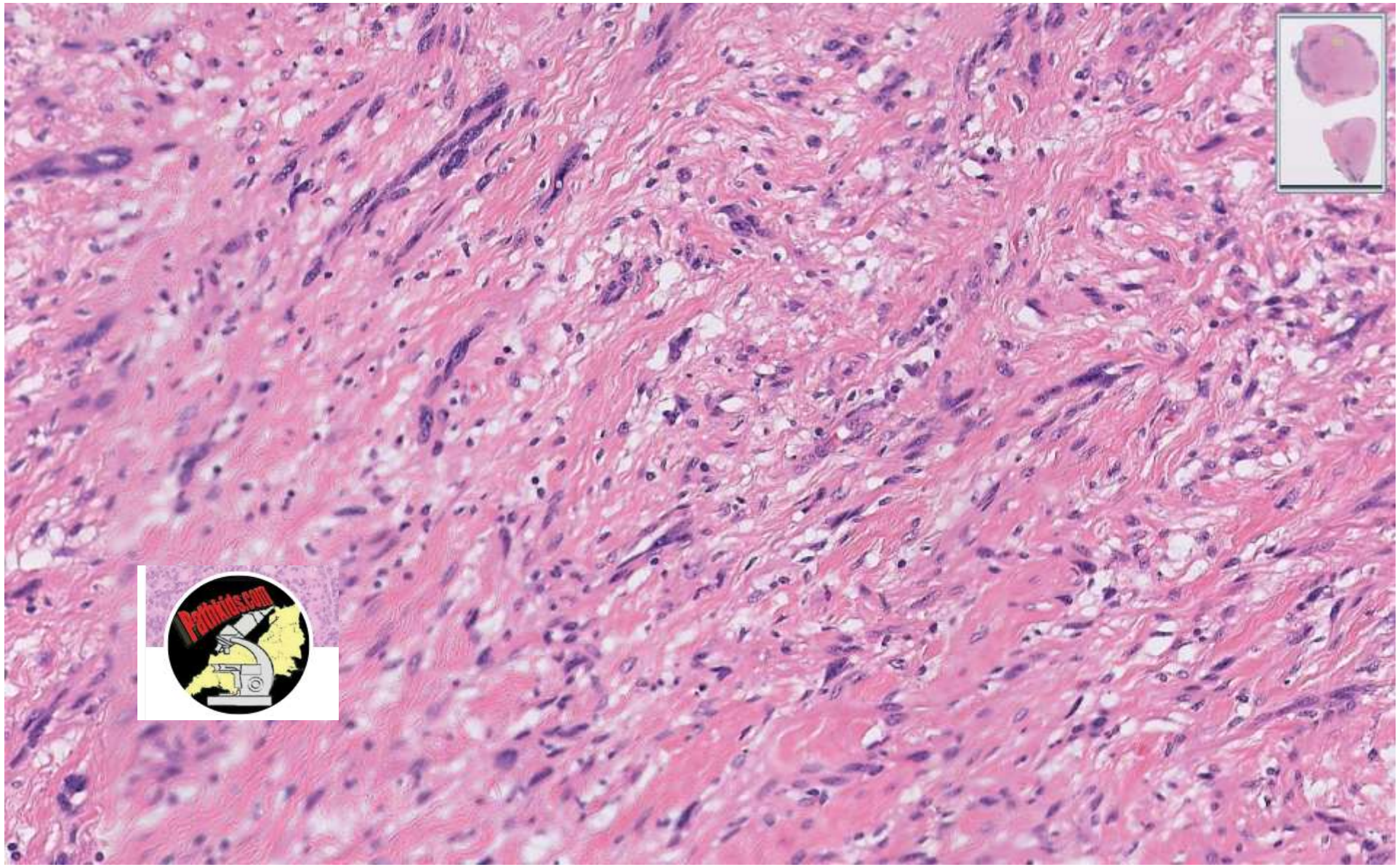
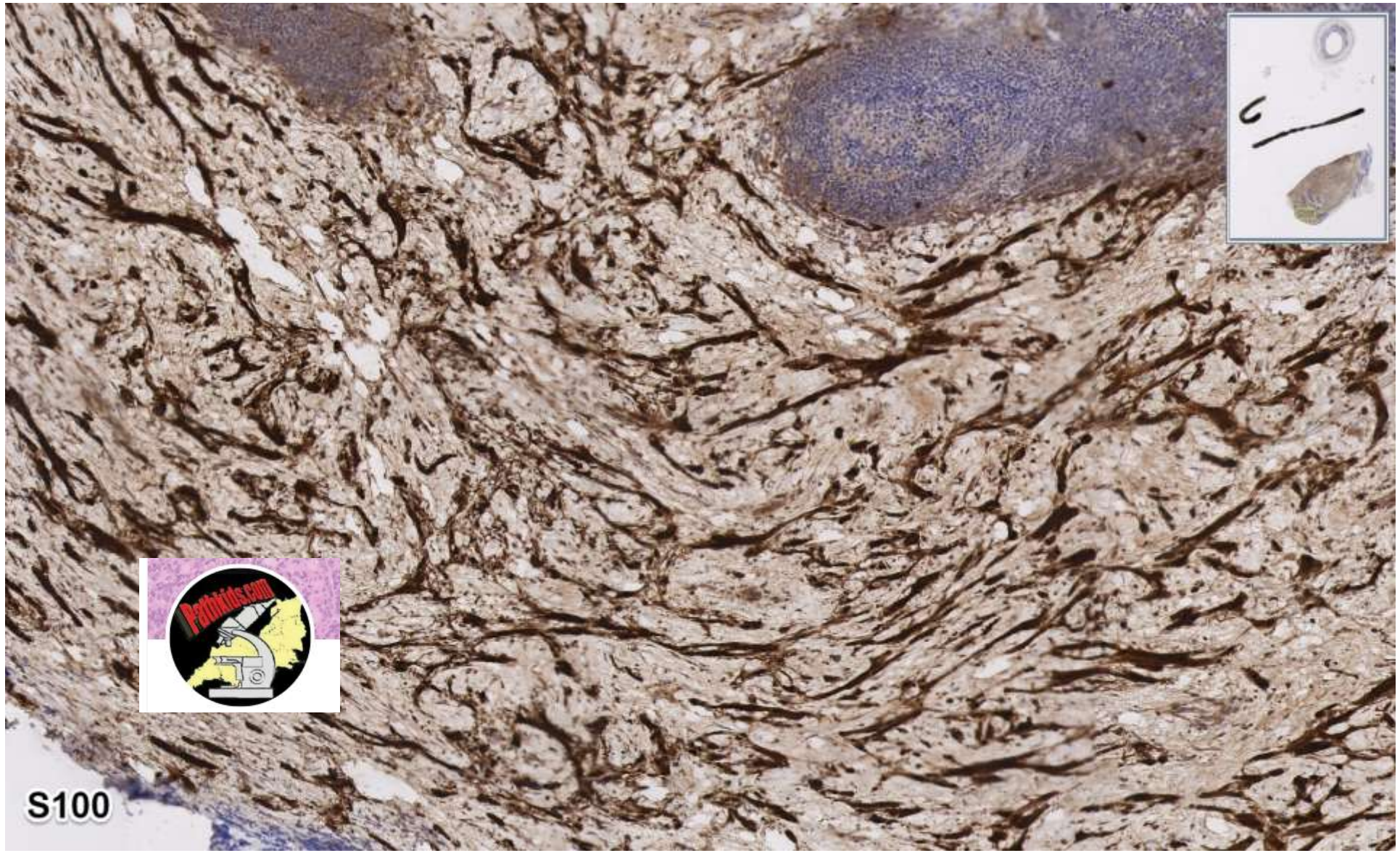

Pathkids.com


S100

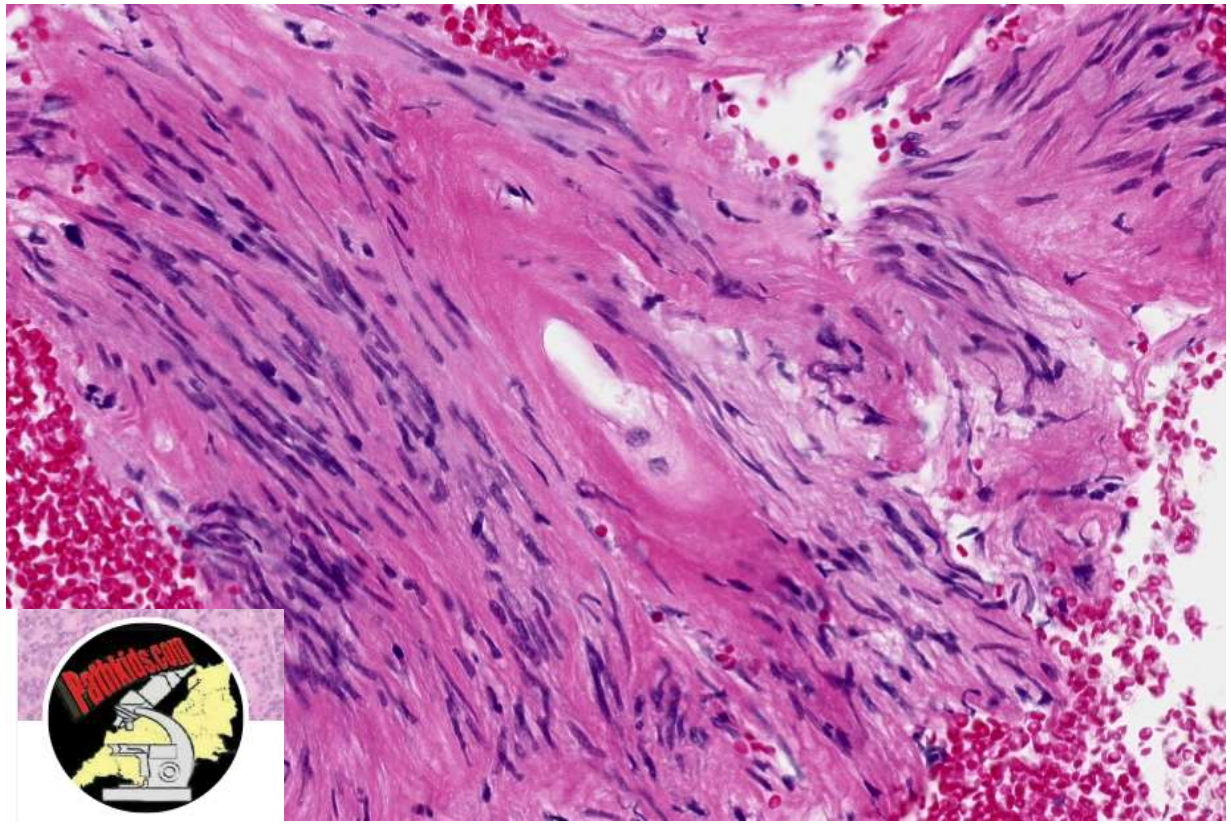
Case 3: Gastric Schwannoma

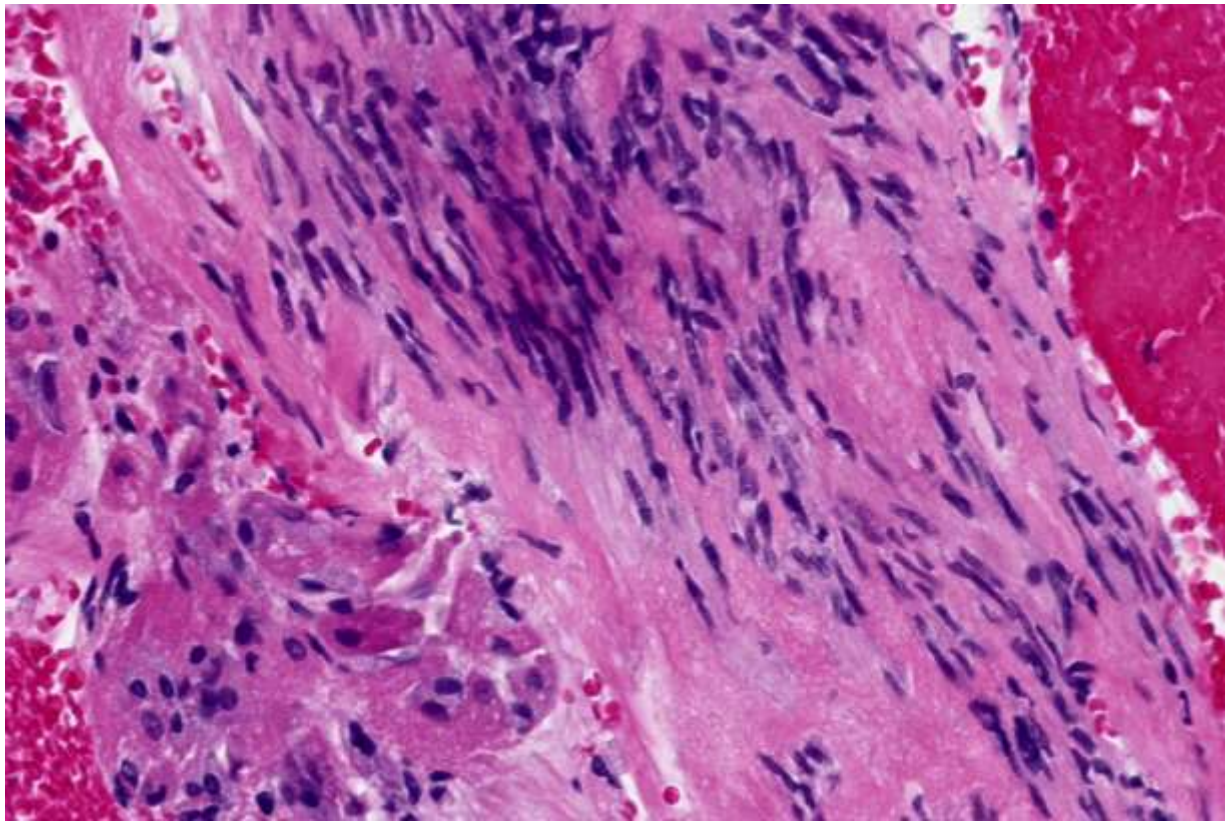
- Intramural stromal tumours resemble GIST clinically and histologically
- Well circumscribed but not encapsulated, with interlacing bundles of spindle cells and collagen
- Often nuclear pallisading, Verocay bodies, hyalinized vessels
- May have nuclear atypia, inflammatory cells, peripheral cuff of lymphoid aggregates
- No mitotic figures, no epithelioid features
- Lack NF2 mutations unlike extra-intestinal schwannomas

Case 4

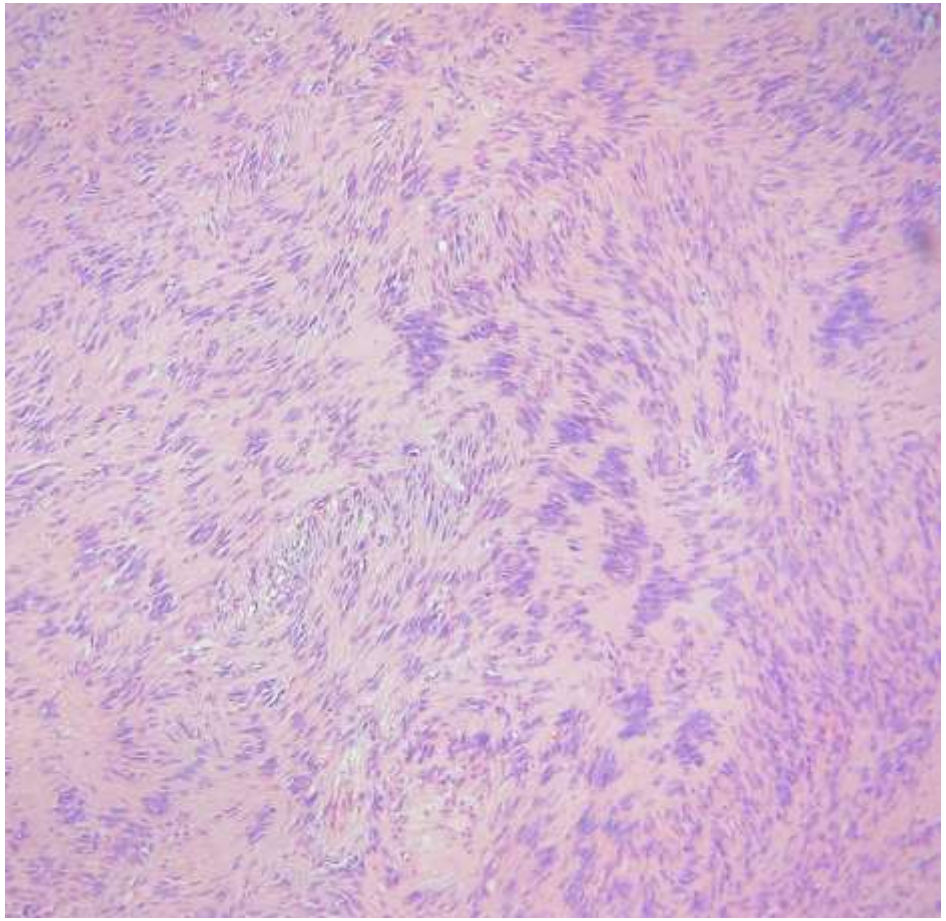
- 80F polypoid intraluminal mass EUS FNA
- . Click for WSI. CD117. DOG1.

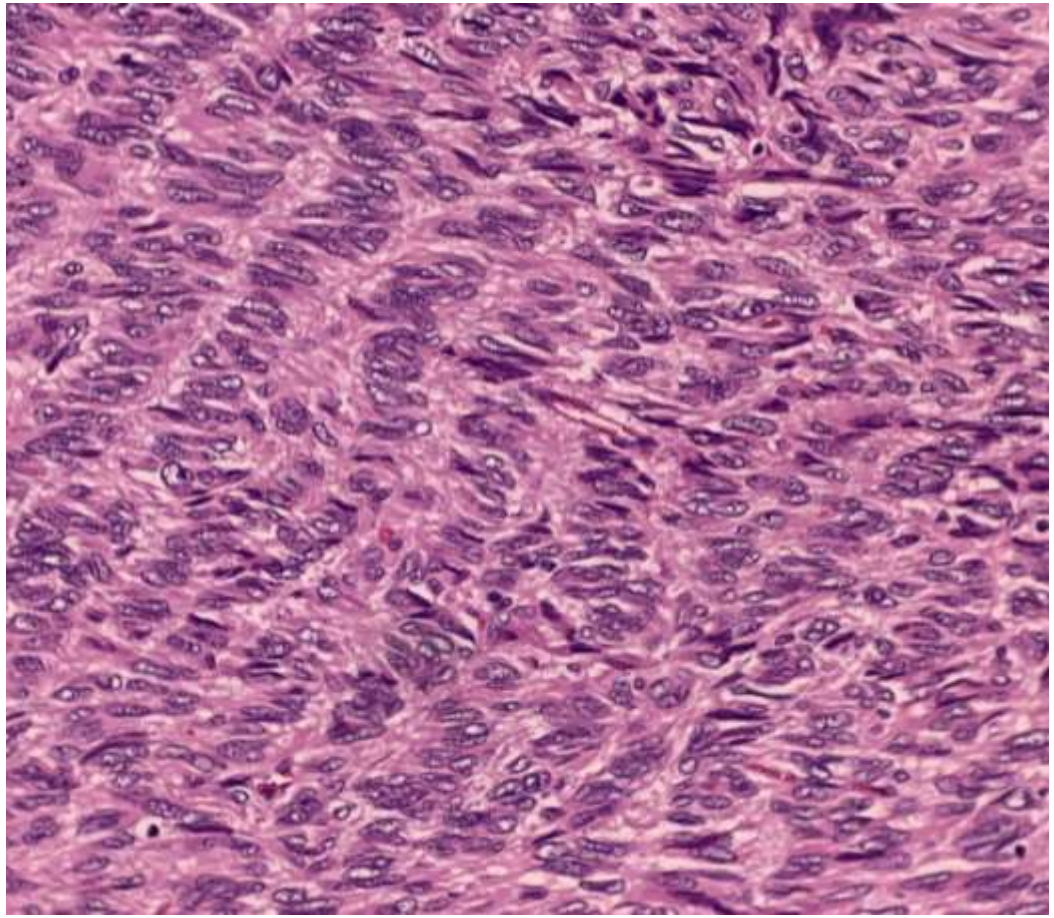
Case 4:

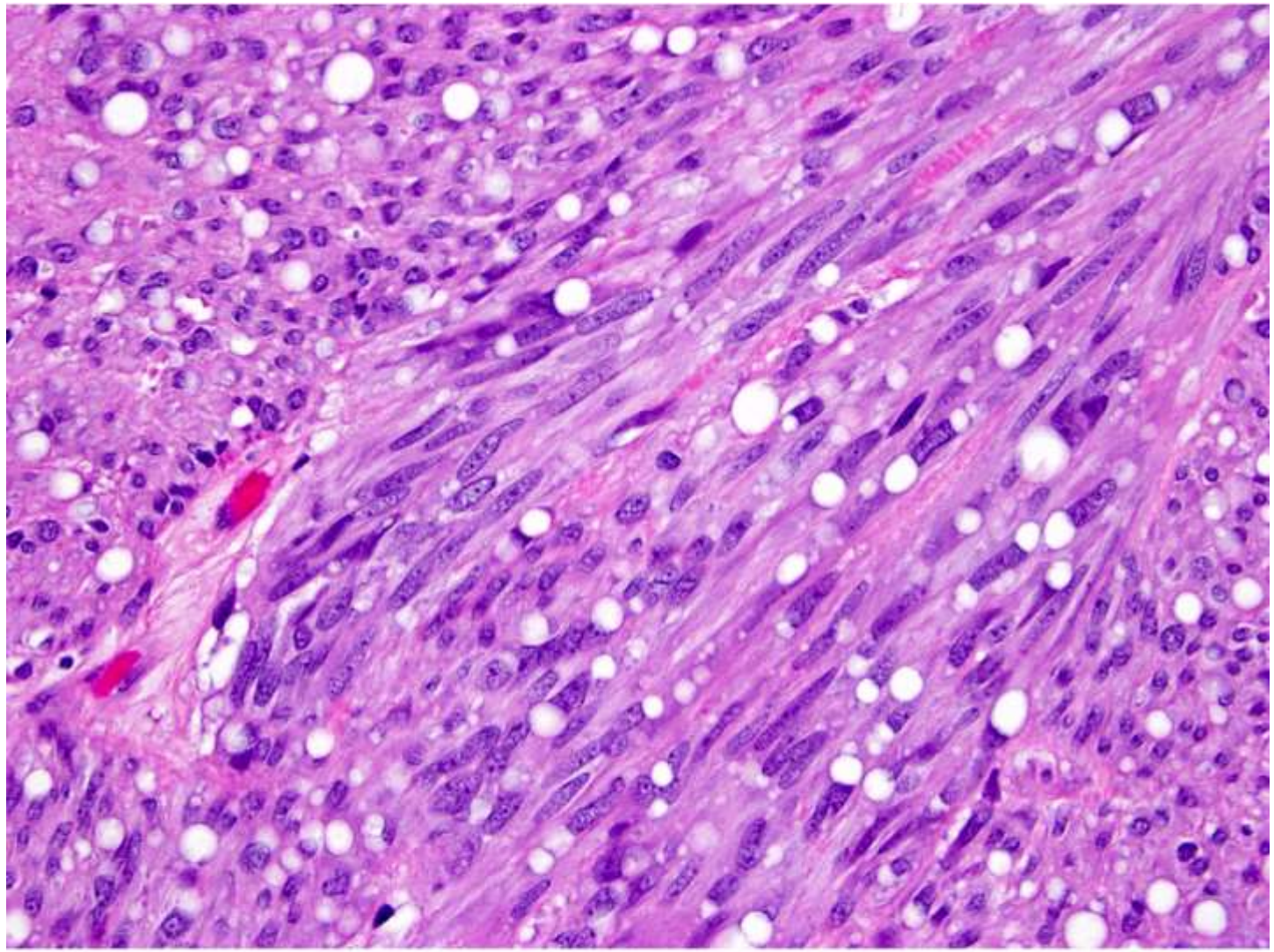




Palisading / Verocay bodies in GIST







Stomach GIST composed of spindle cells with densely eosinophilic cytoplasm and paranuclear vacuoles (high power).

Case 4. Spindle cell GIST

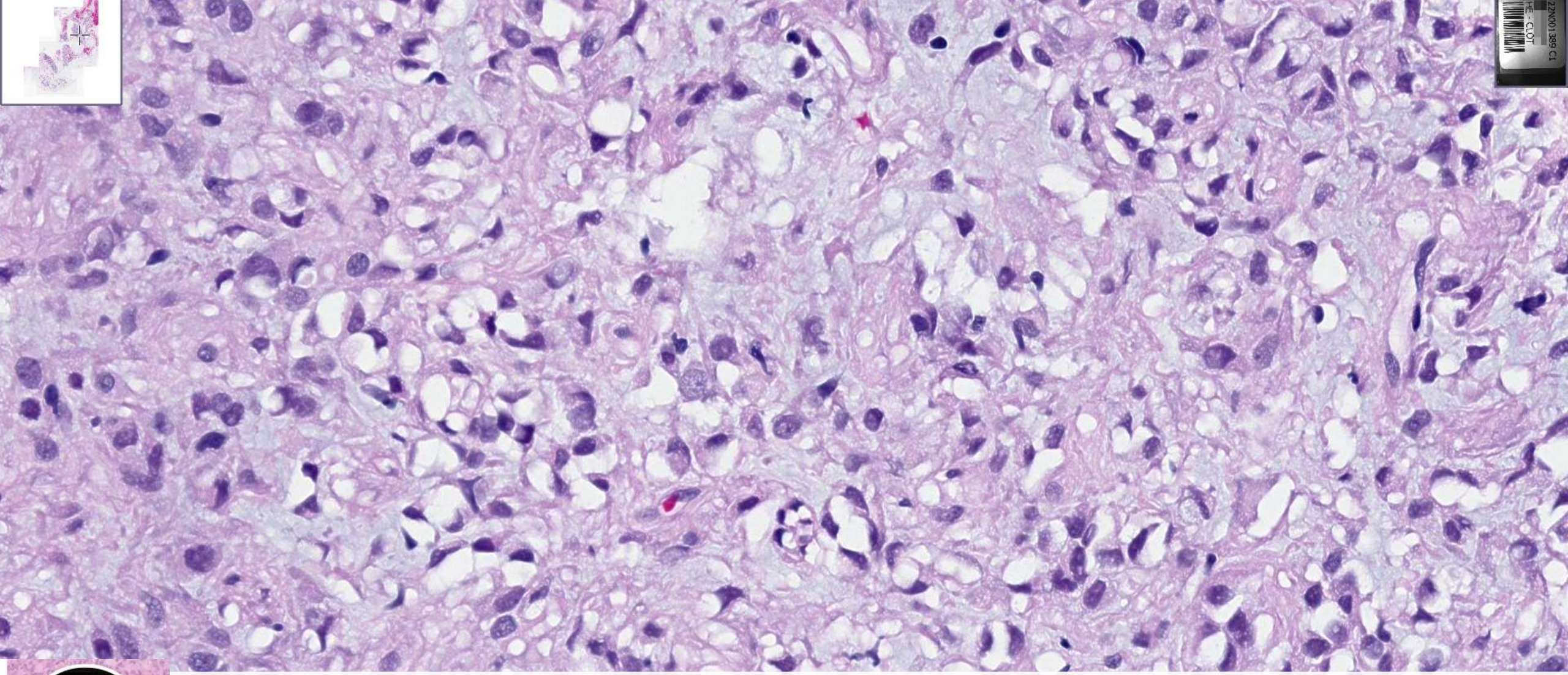
rcpath.org

Table 1: AFIP/Lasota-Miettinen classification.

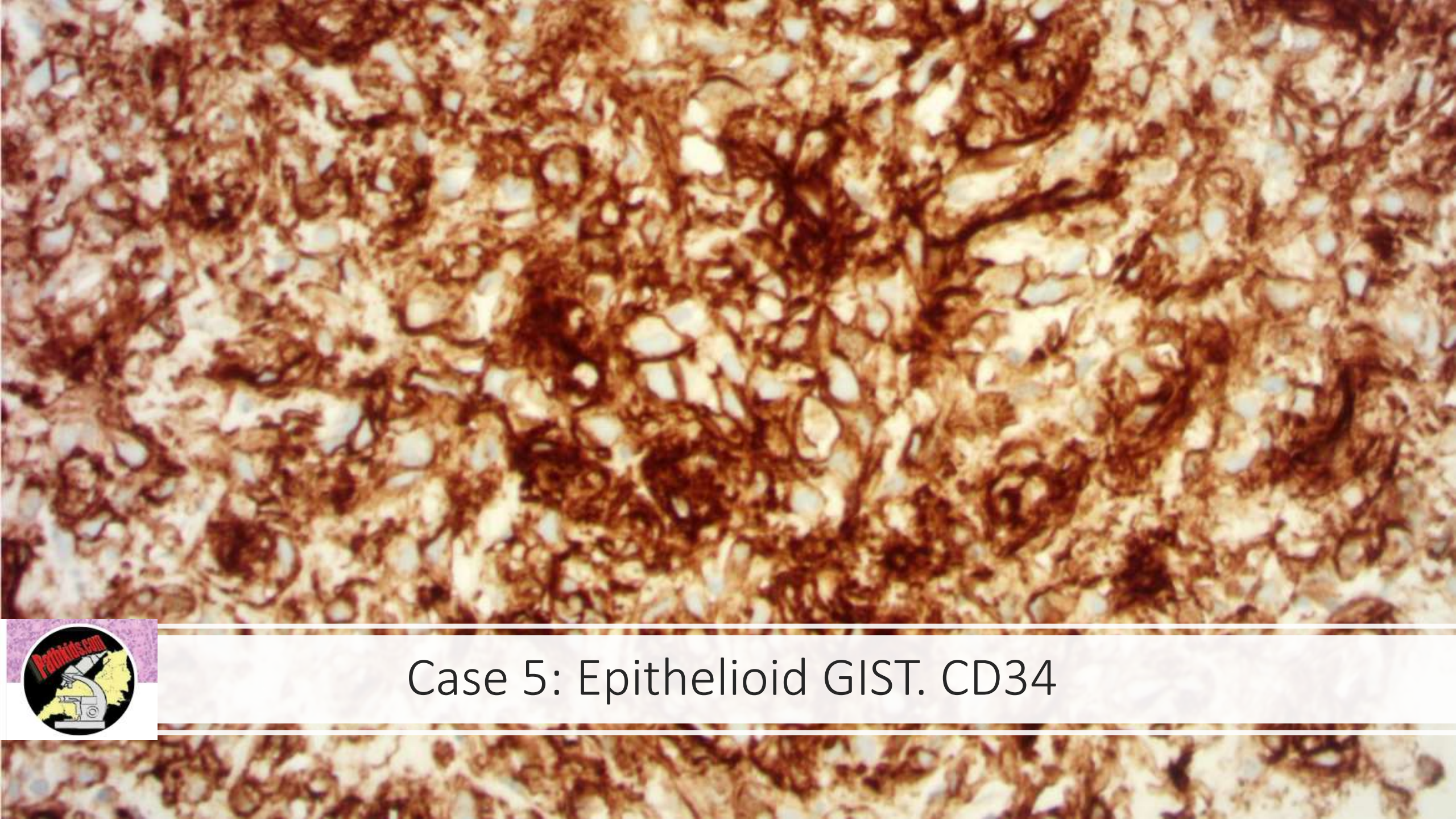
Tumour parameters		Tumour location and risk of progressive disease (metastasis or tumour-related death)			
Mitotic index	**Size**	**Gastric**	**Duodenum**	**Jejunum/ileum**	**Rectum**
≤5 (per 5 mm^2)*	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2–≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5–≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 (per 5 mm^2)*	≤2 cm	(Insufficient data)	(Insufficient data)	High (limited data)	High (54%)
	>2–≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5–≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

*With older microscopes, 50 HPF may be equivalent to 5 mm^2. However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for their microscope.

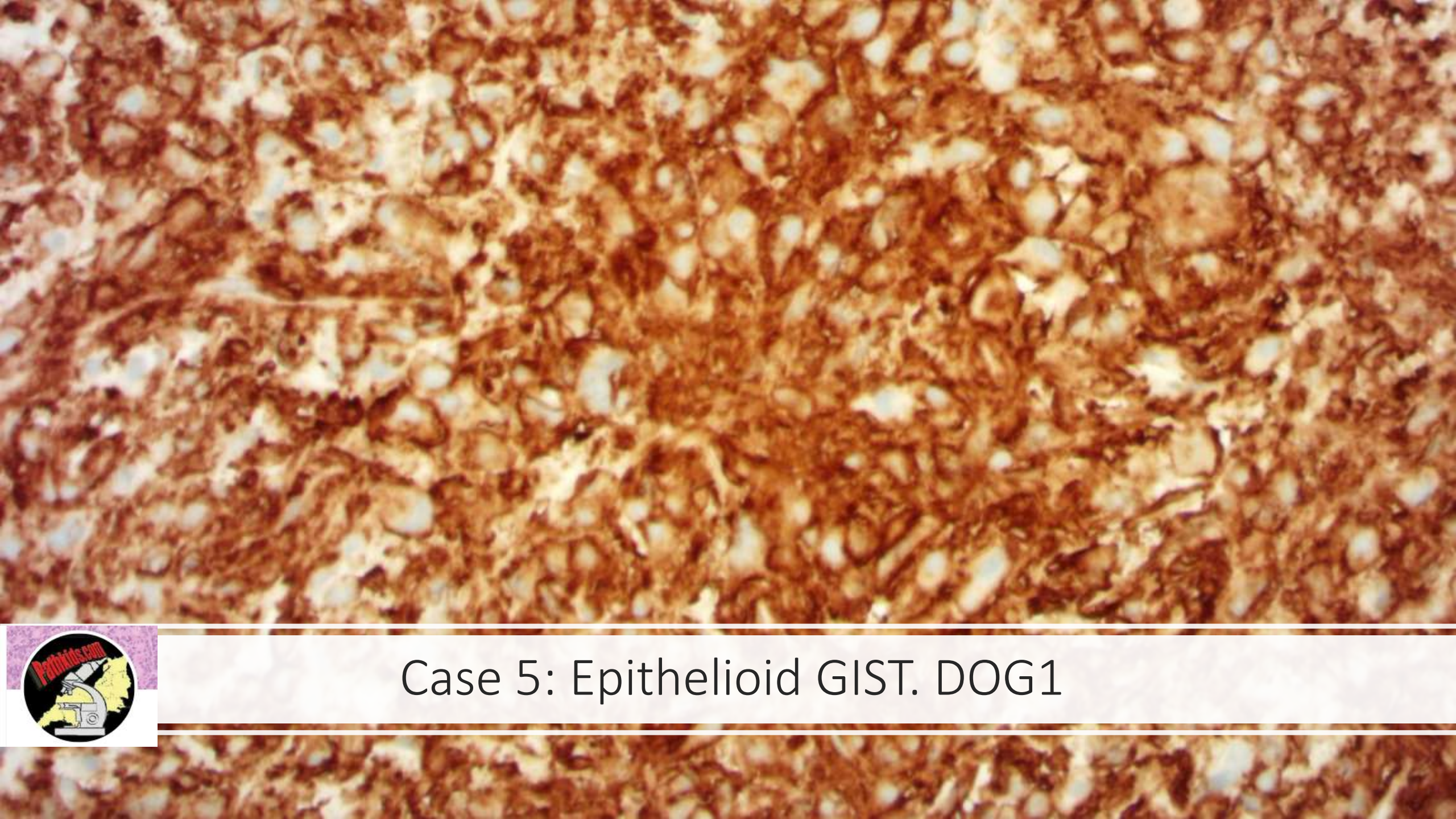
Case 5. 69F EUS FNA gastric submucosal mass. Click for WSI, CD117, DOG1.



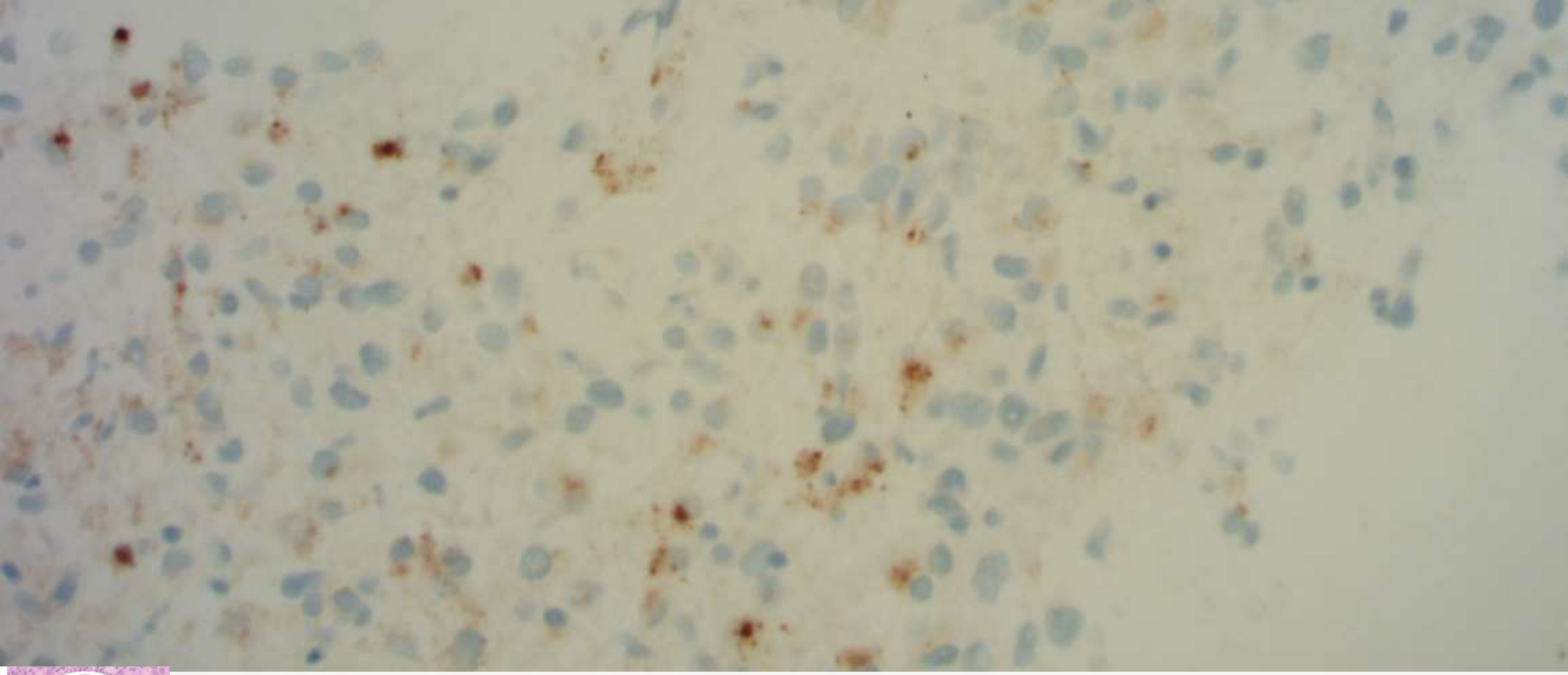
Case 5: Epithelioid GIST



Case 5: Epithelioid GIST. CD34



Case 5: Epithelioid GIST. DOG1



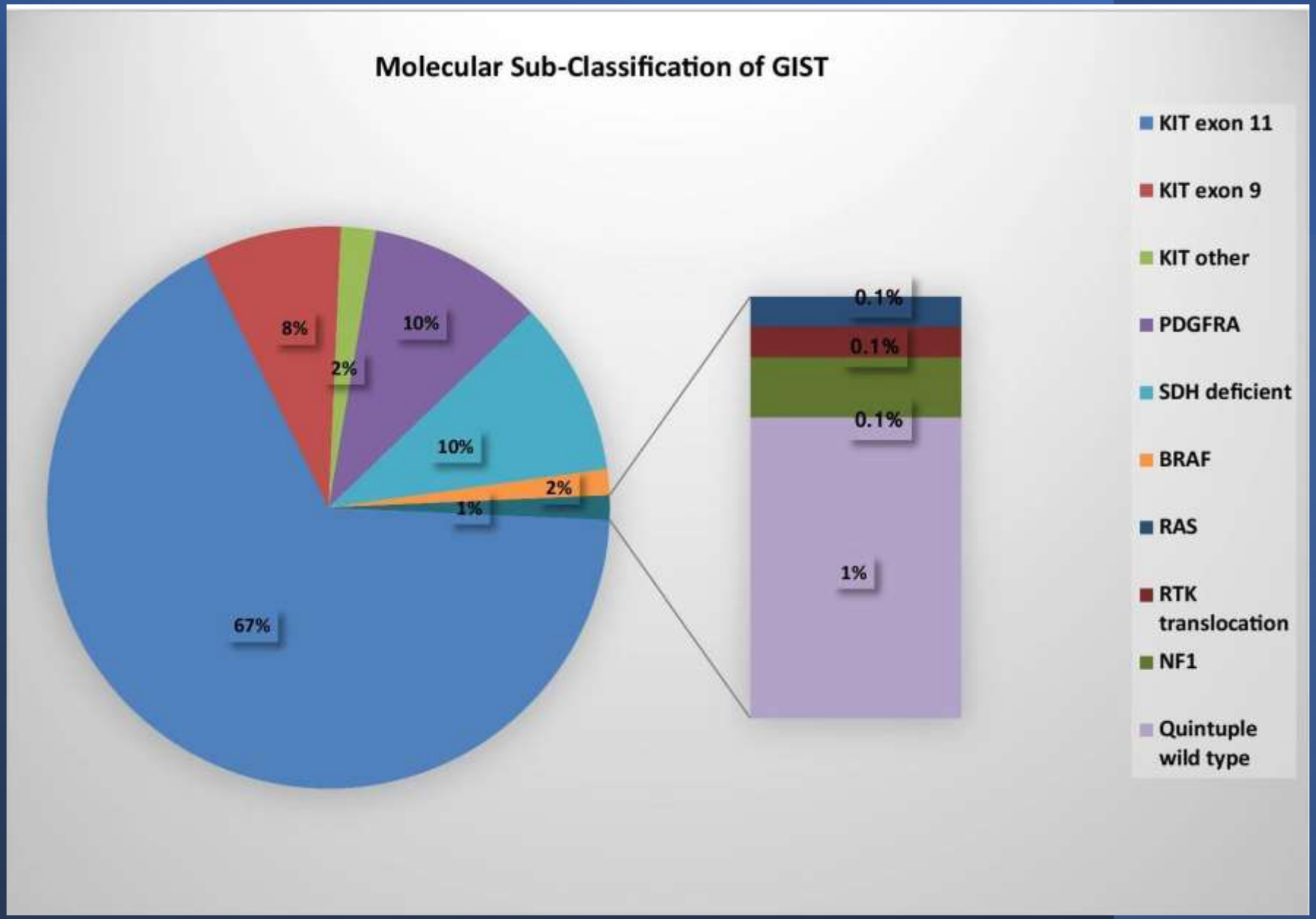
Case 5: Epithelioid GIST. CD117

Case 5: Epithelioid GIST. Molecular

- DNA extracted from the neoplastic tissue received shows a point mutation in **PDGFRA** exon 12: c. 1682>A p.(Val561Asp).

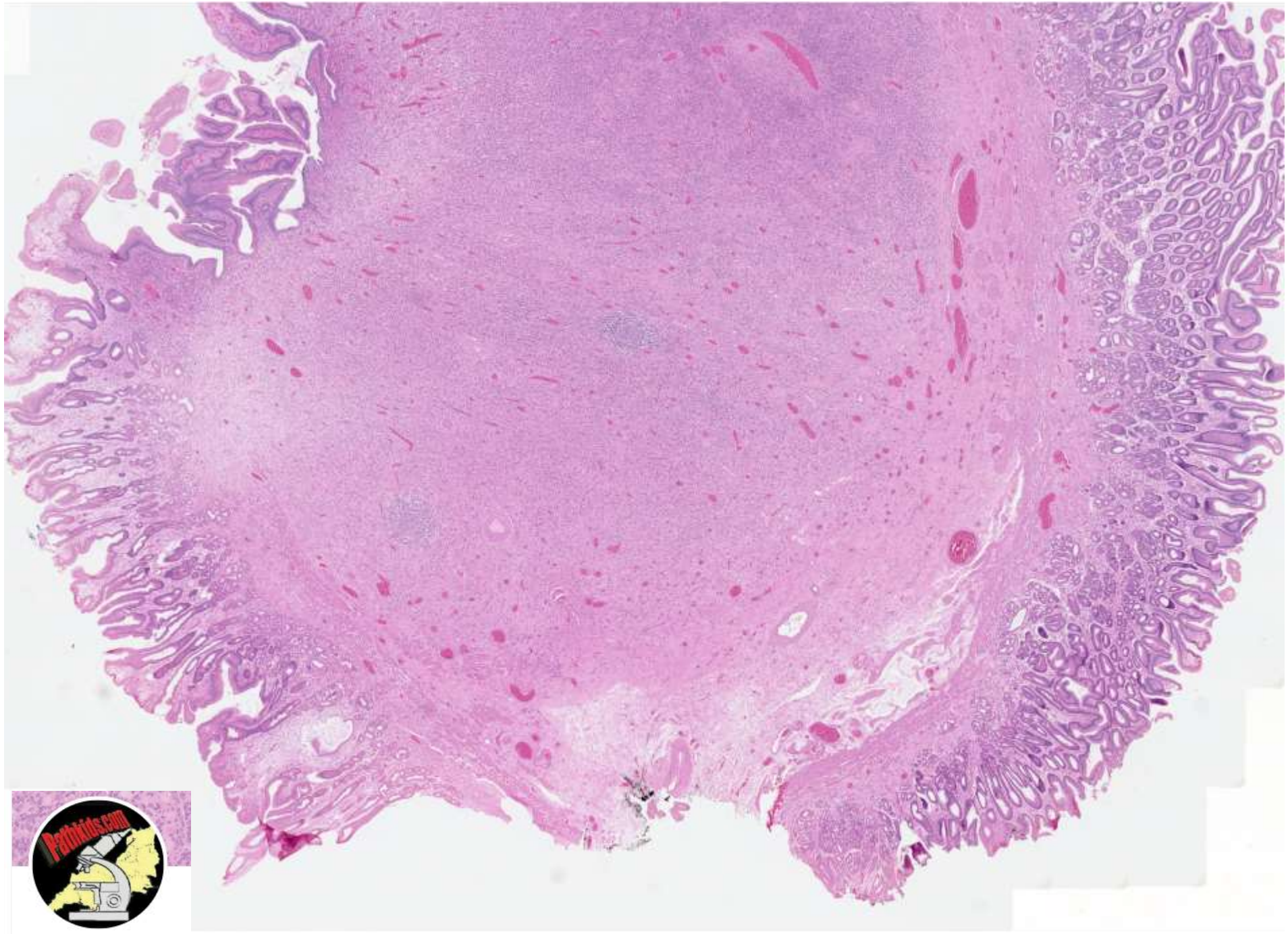
- the presence of a PDGFRA mutation would strongly support a diagnosis of GIST. PDGFRA mutated GISTs are typically epithelioid.

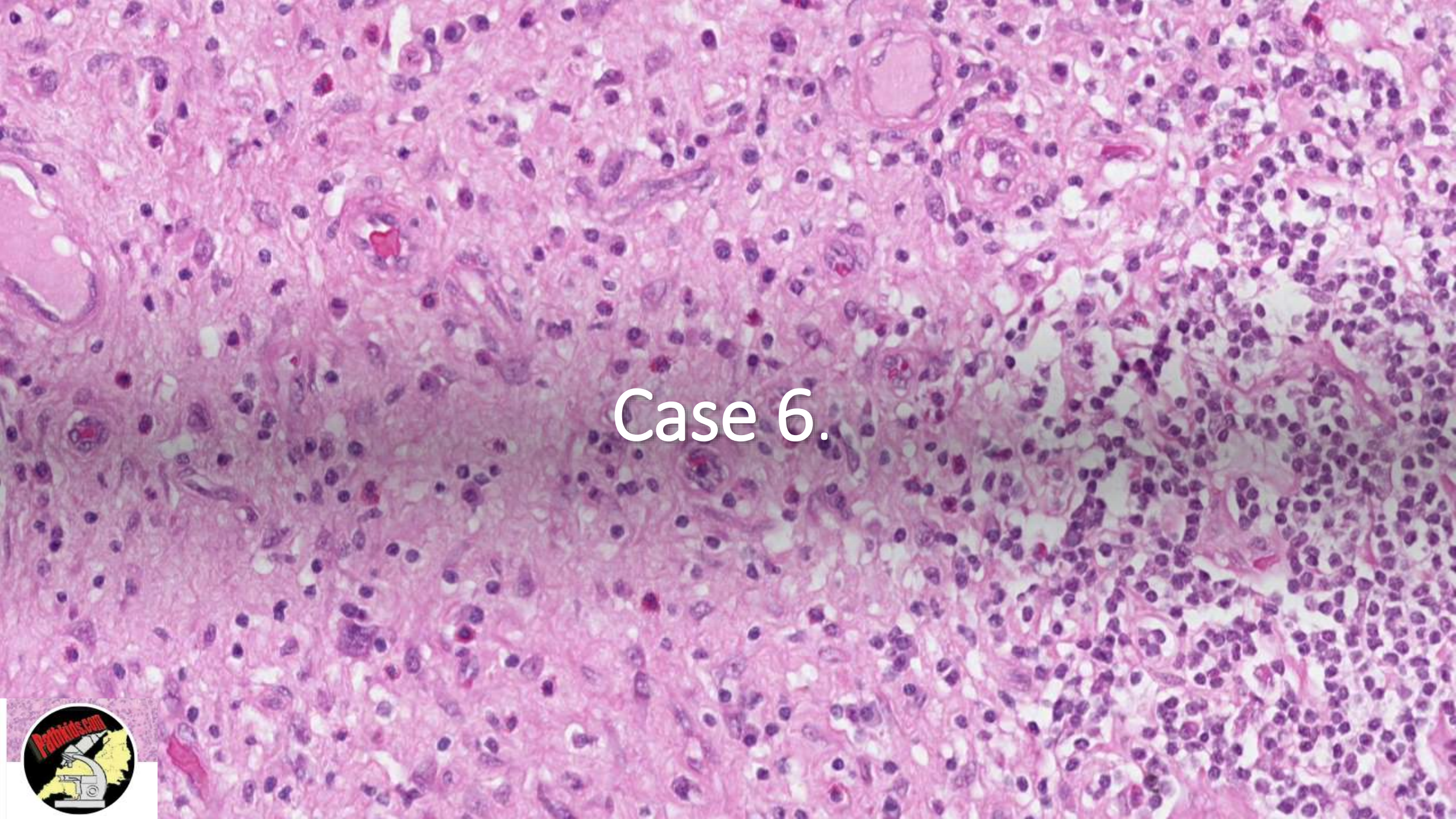
- The PDGFRA mutation would be consistent with the lack of CD117 expression and gastric location of this GIST. There are in-vitro data showing that this particular PDGFRA point mutation predicts for sensitivity to imatinib therapy.


Molecular Sub-Classification of GIST
67%
8%
2%
10%
10%
2%
1%
0.1%
0.1%
0.1%
1%
KIT exon 11
KIT exon 9
KIT other
PDGFRA
SDH deficient
BRAF
RAS
RTK translocation
NF1
Quintuple wild type

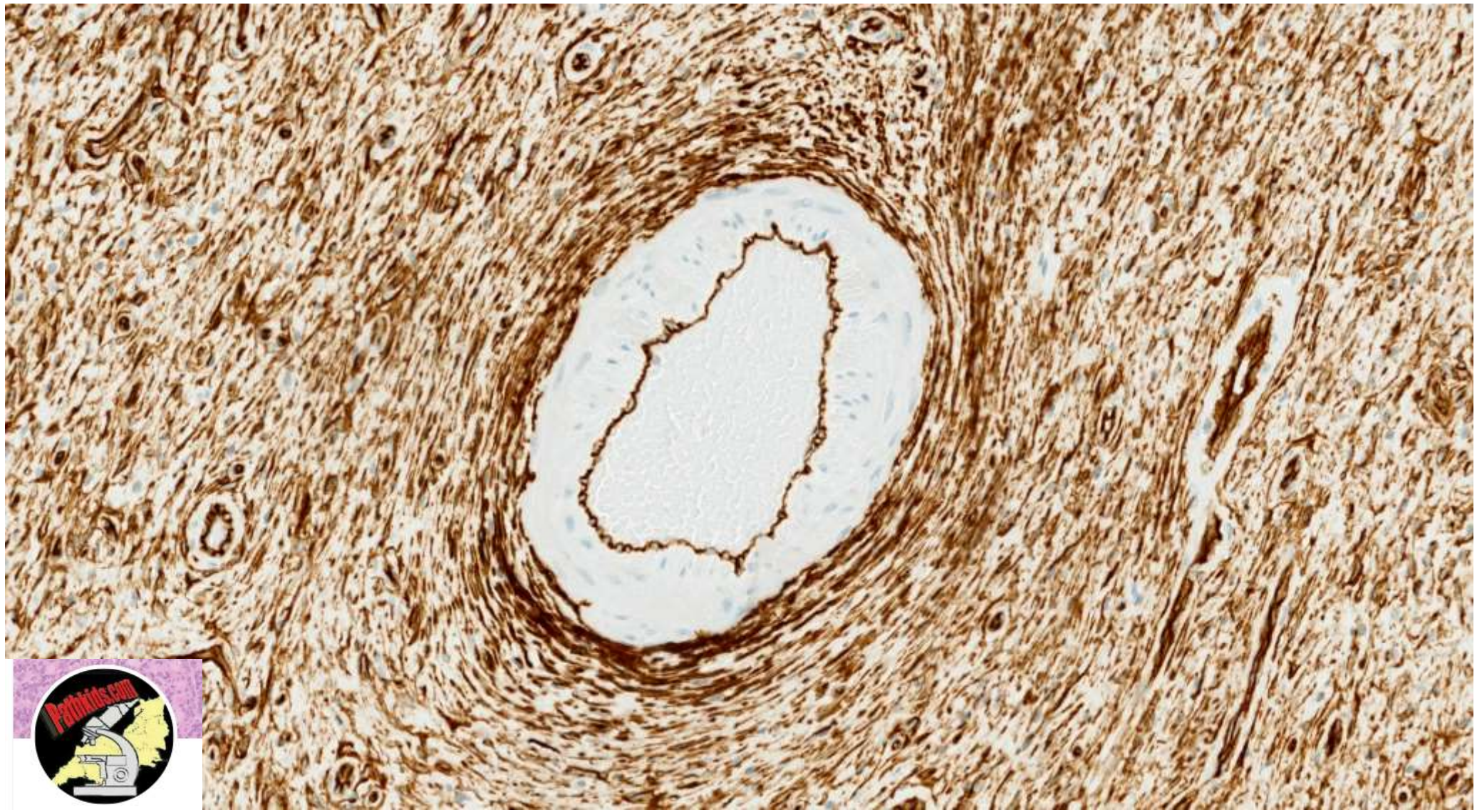
Case 6. 71F open removal of GIST from distal stomach. Click for H&E. IHC.

Case 6.




Case 6.

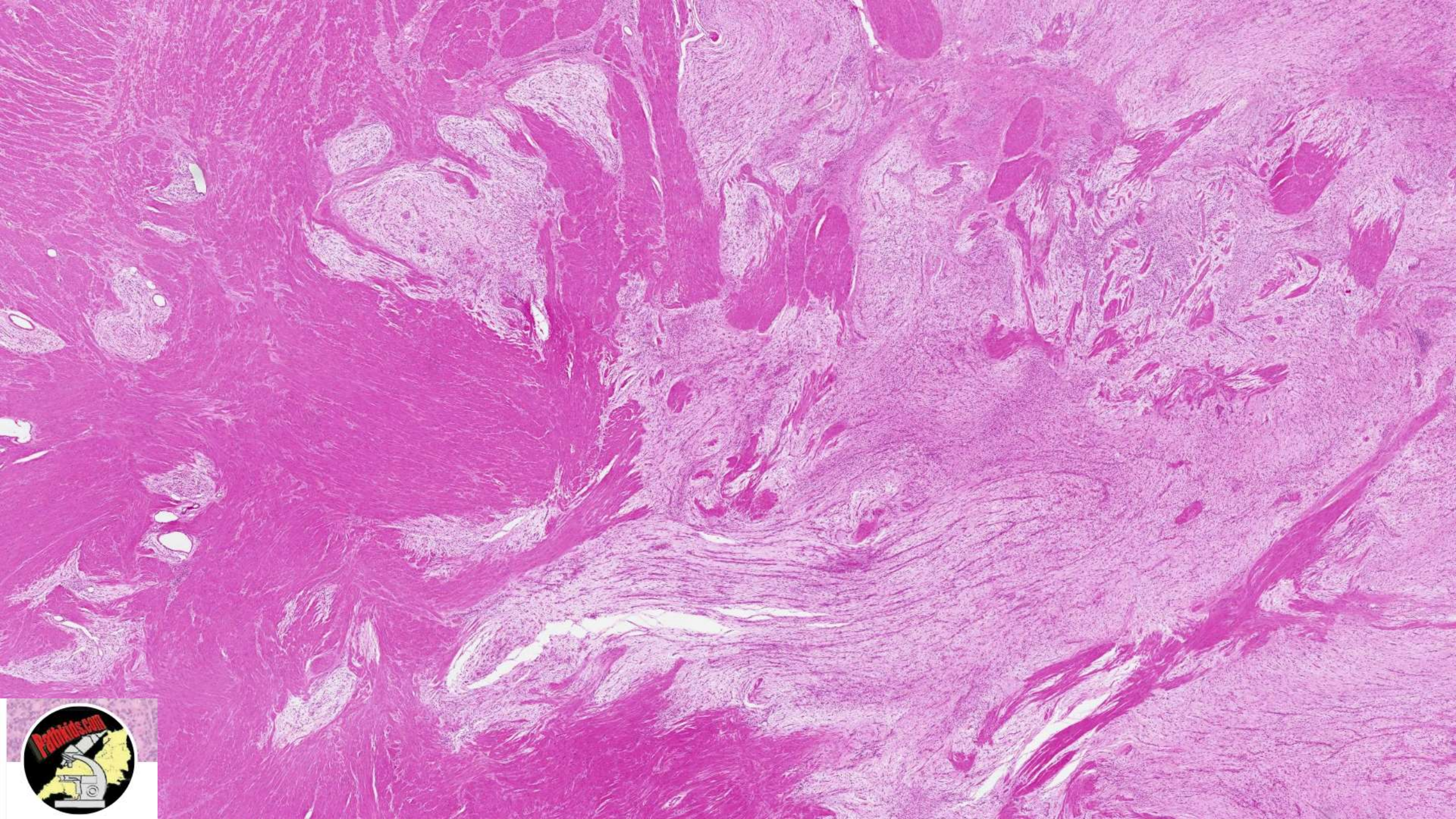
Case 6: CD34; onion skinning

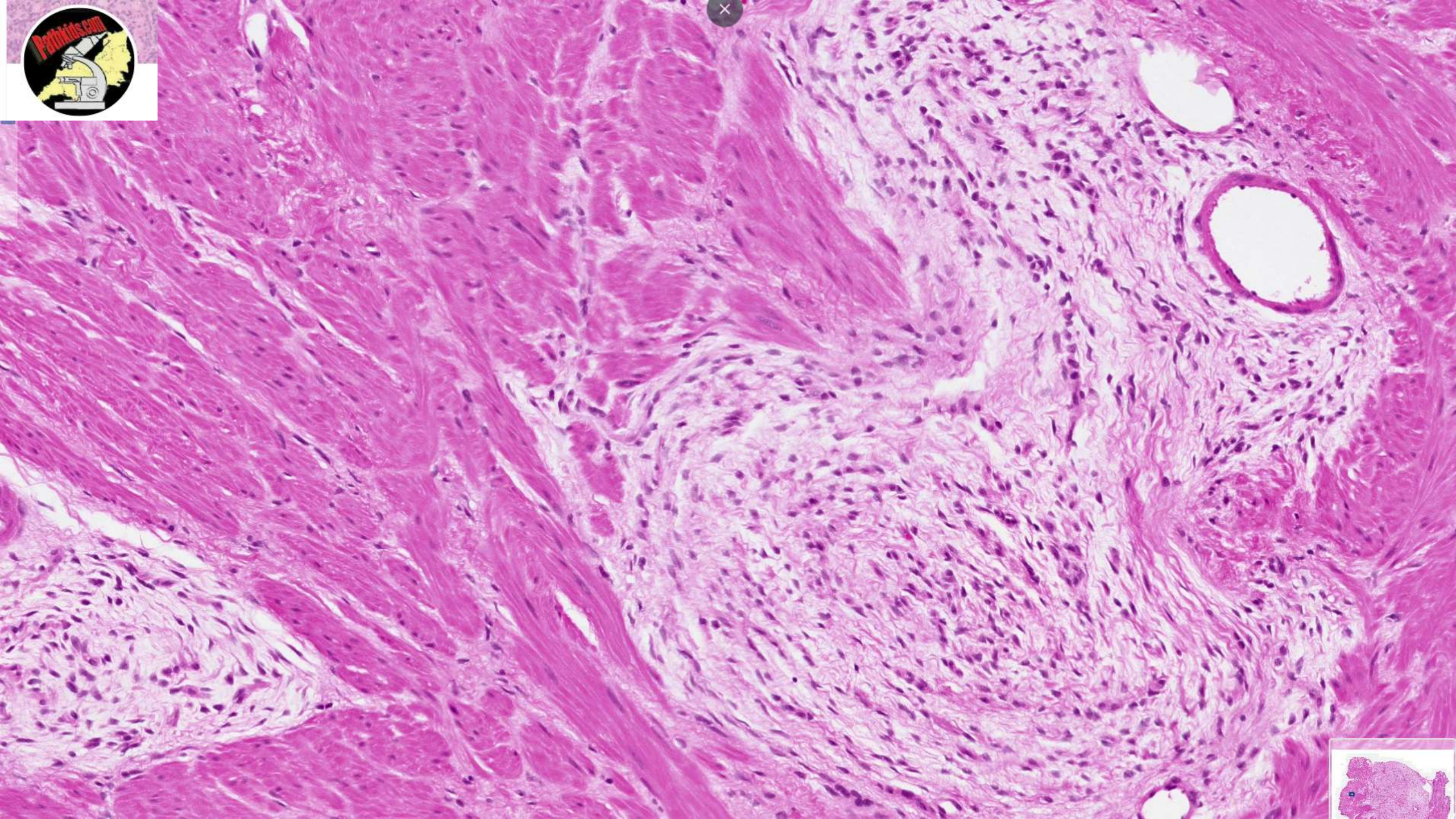


Case 6. Benign inflammatory fibroid polyp

- arises in the submucosa
- Previously called eosinophilic granuloma
- Often causes intersusseption in the small bowel
- Associated with activating mutation in the platelet derived growth factor receptor alpha (***PDGFRA***) gene, supporting a neoplastic origin
- Usually but not always CD34 positive
- Pitfall alert. GIST can also have PDGFRA mutations, particularly epithelioid and other unusual types.

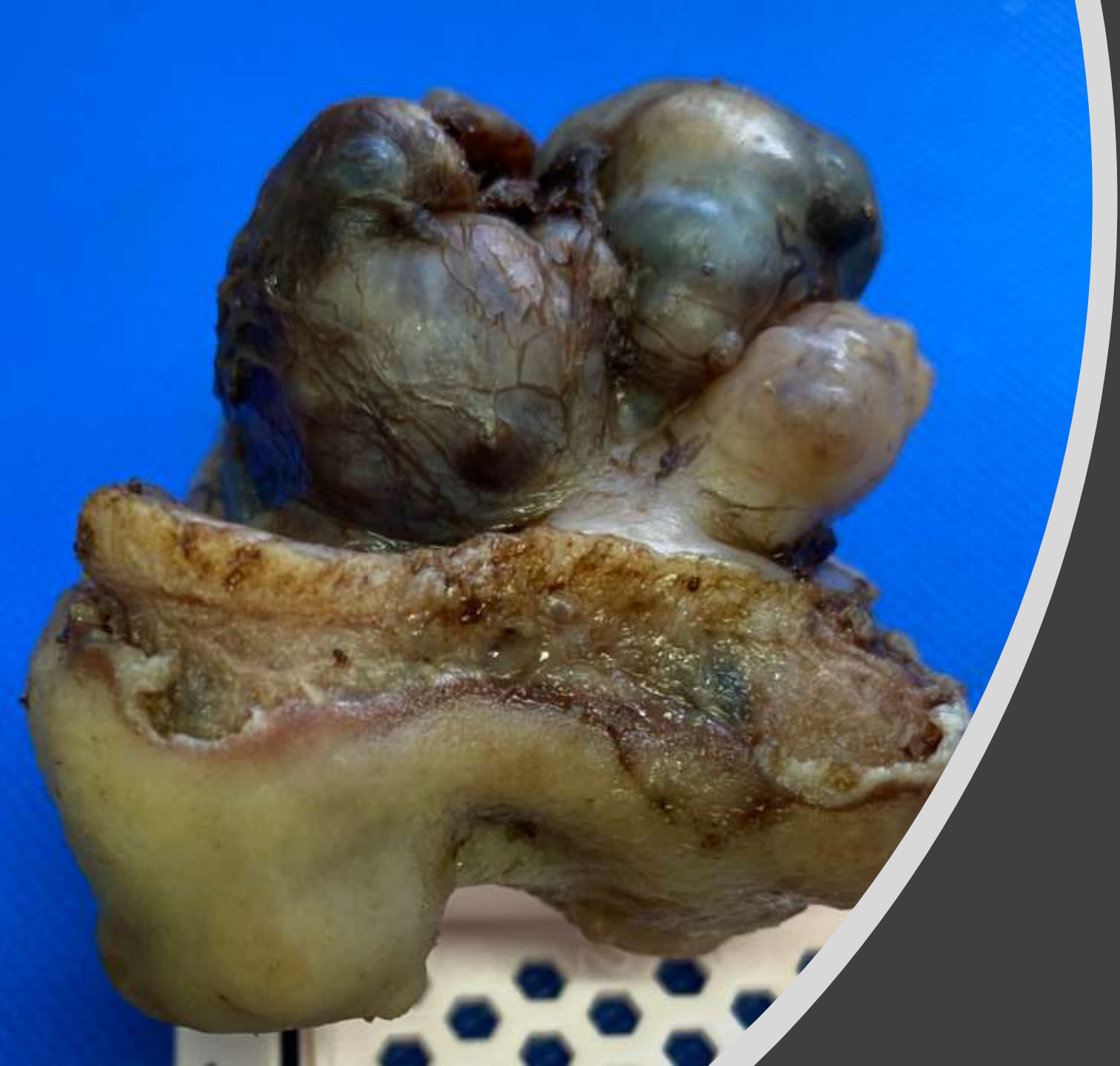
Case 7. Female early 40s. Intermittent gastric outlet obstruction. Antral polyp removed by gastrotomy. Whole slide image at this link. CD117, DOG1 and CD34 negative.





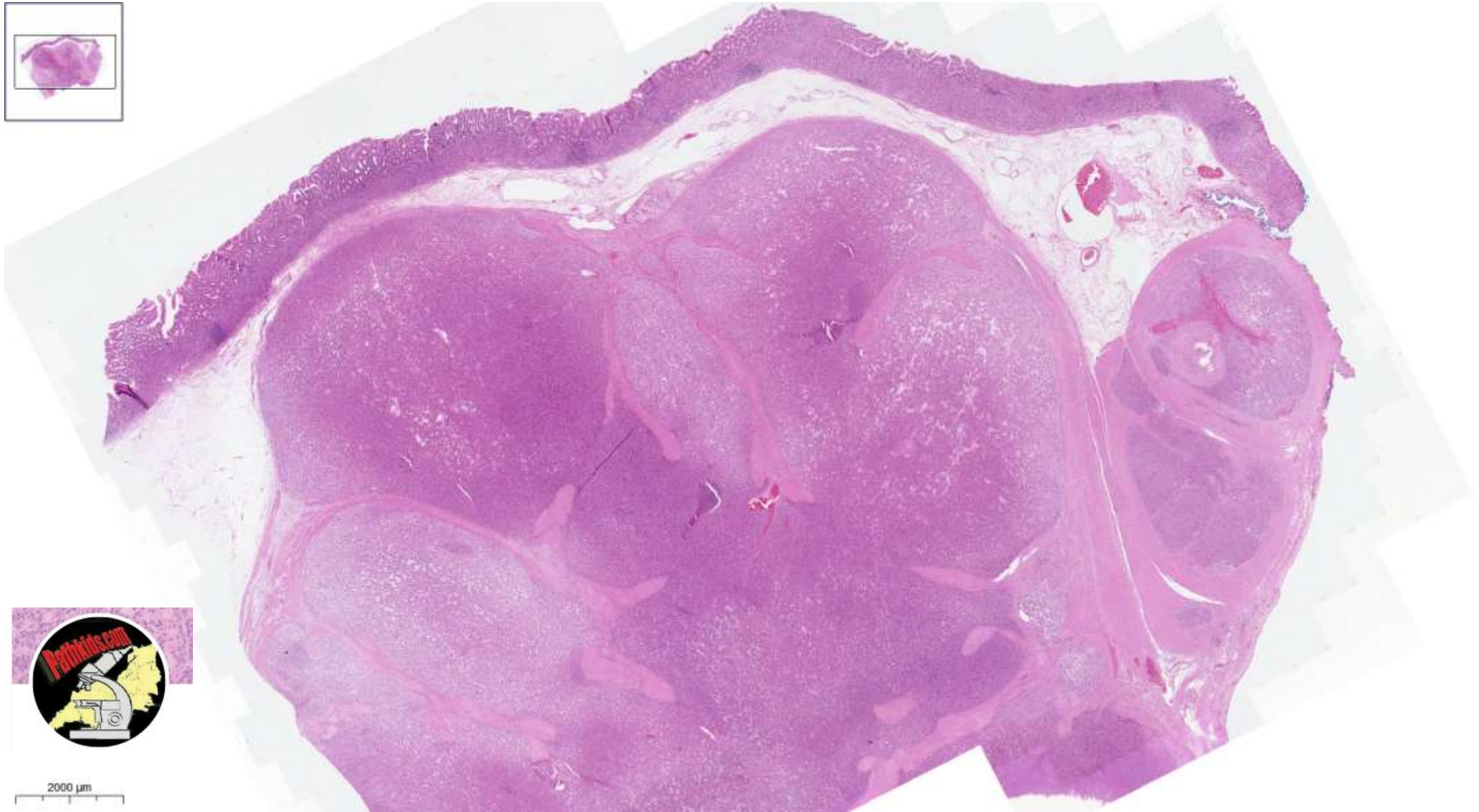
Case 7. Plexiform fibromyxoma

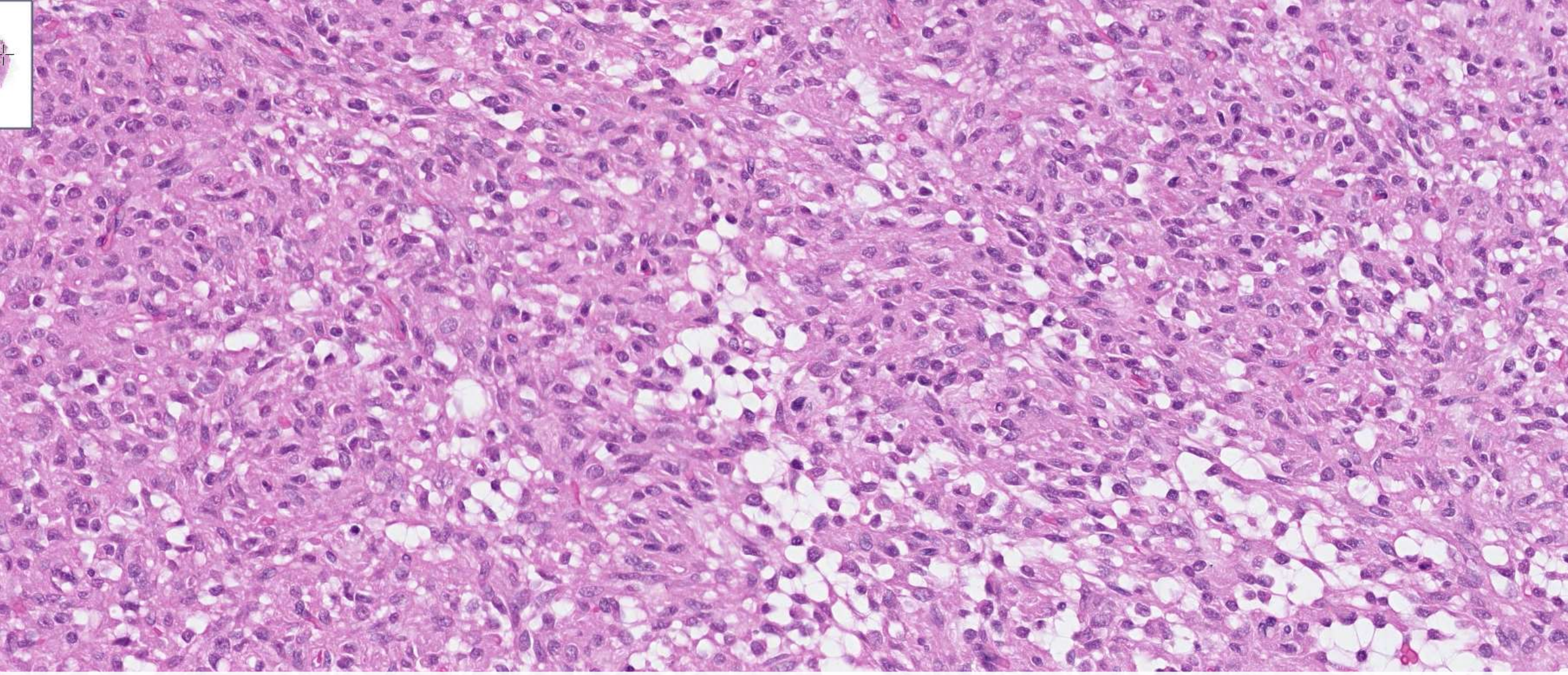
- A site specific gastric mesenchymal tumour WHO 2019
- Antral / Pyloric location and mimic of GIST
- Infiltrative (plexiform) and micronodular
- Stains for smooth muscle but not GIST markers or MUC4
- No reports of metastasis or recurrence so far!



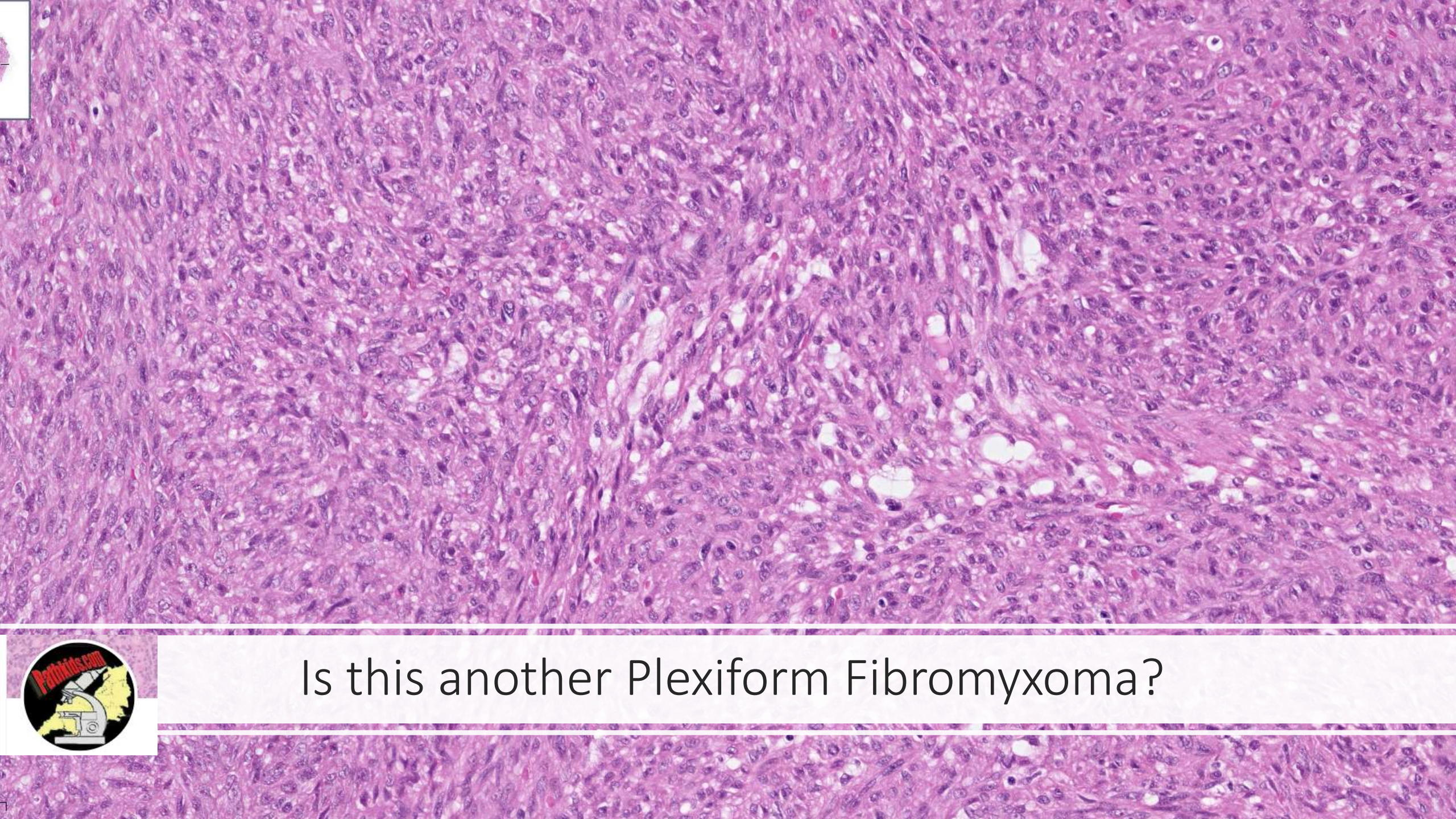
11 year old girl gastric wedge

Is this another Plexiform Fibromyxoma?





Is this another Plexiform Fibromyxoma?



Is this another Plexiform Fibromyxoma?

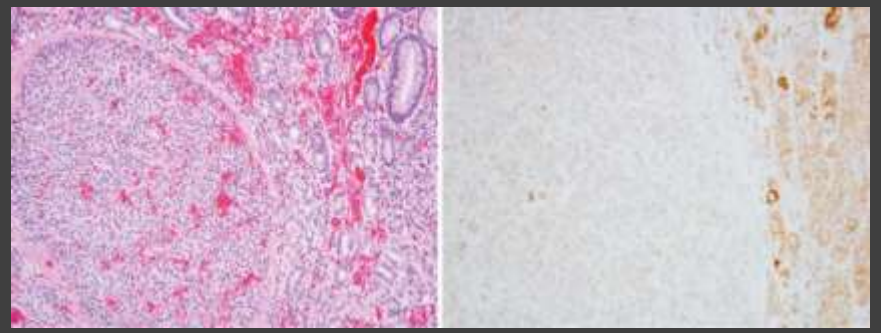
But its CD117 and DOG1+

11 year old girl gastric “paediatric-type / wild-type” GIST

mitotic count = 3/5mm2 (therefore very low risk but…)

Molecular analysis did not detect a KIT, PDGFRA, KRAS, NRAS, or BRAF mutation.

SDHB deficiency on IHC predicts mutation



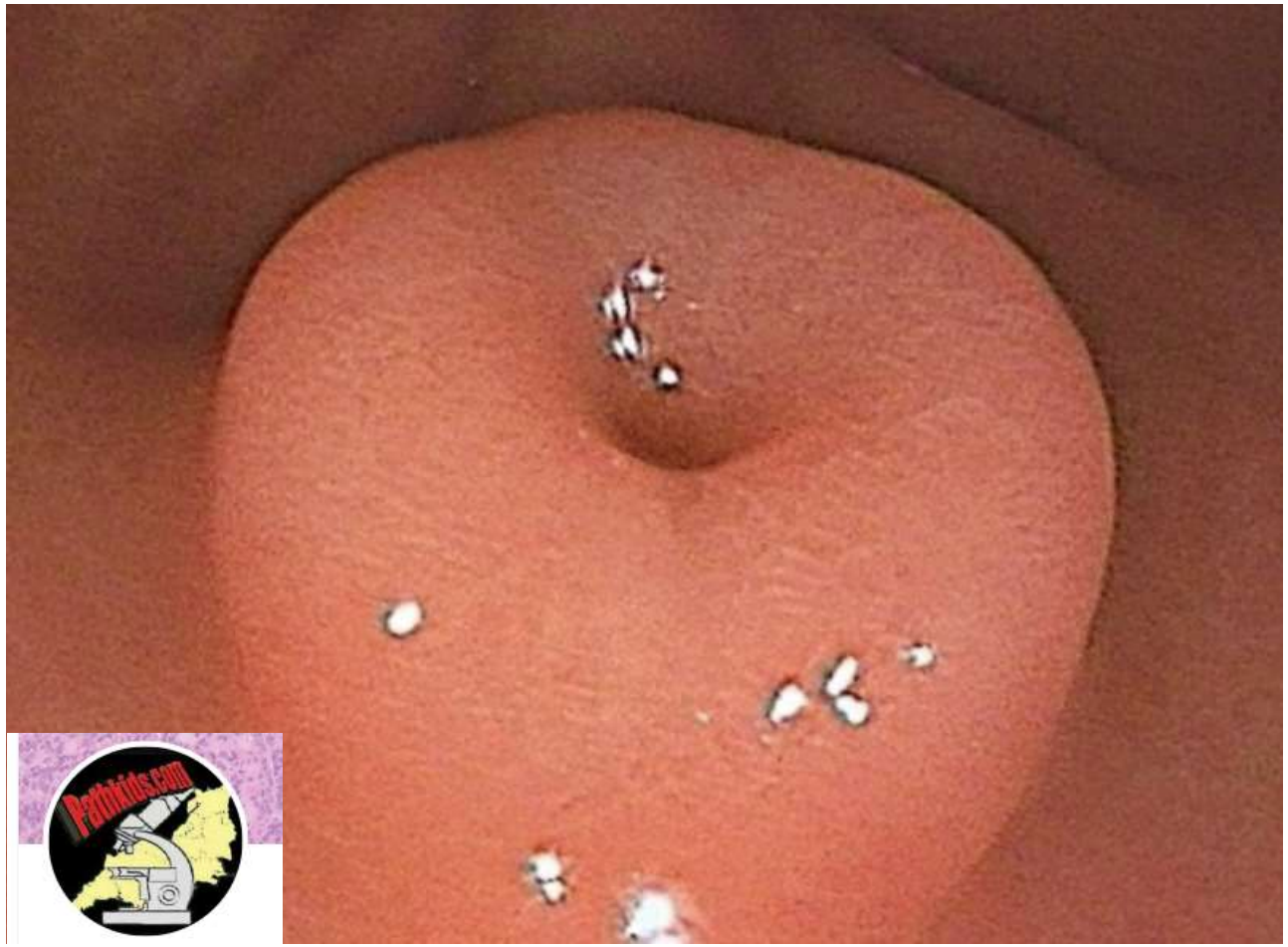
Loss of expression of SDHA predicts SDHA mutations in gastrointestinal stromal tumors September 2012. Modern Pathology 26(2). Andrew J Wagner, …Jason L Hornick
DOI: 10.1038/modpathol.2012.153

Case 8. Female 40s. Gastric outlet obstruction for “GIST”.
H&E slide from Leeds.

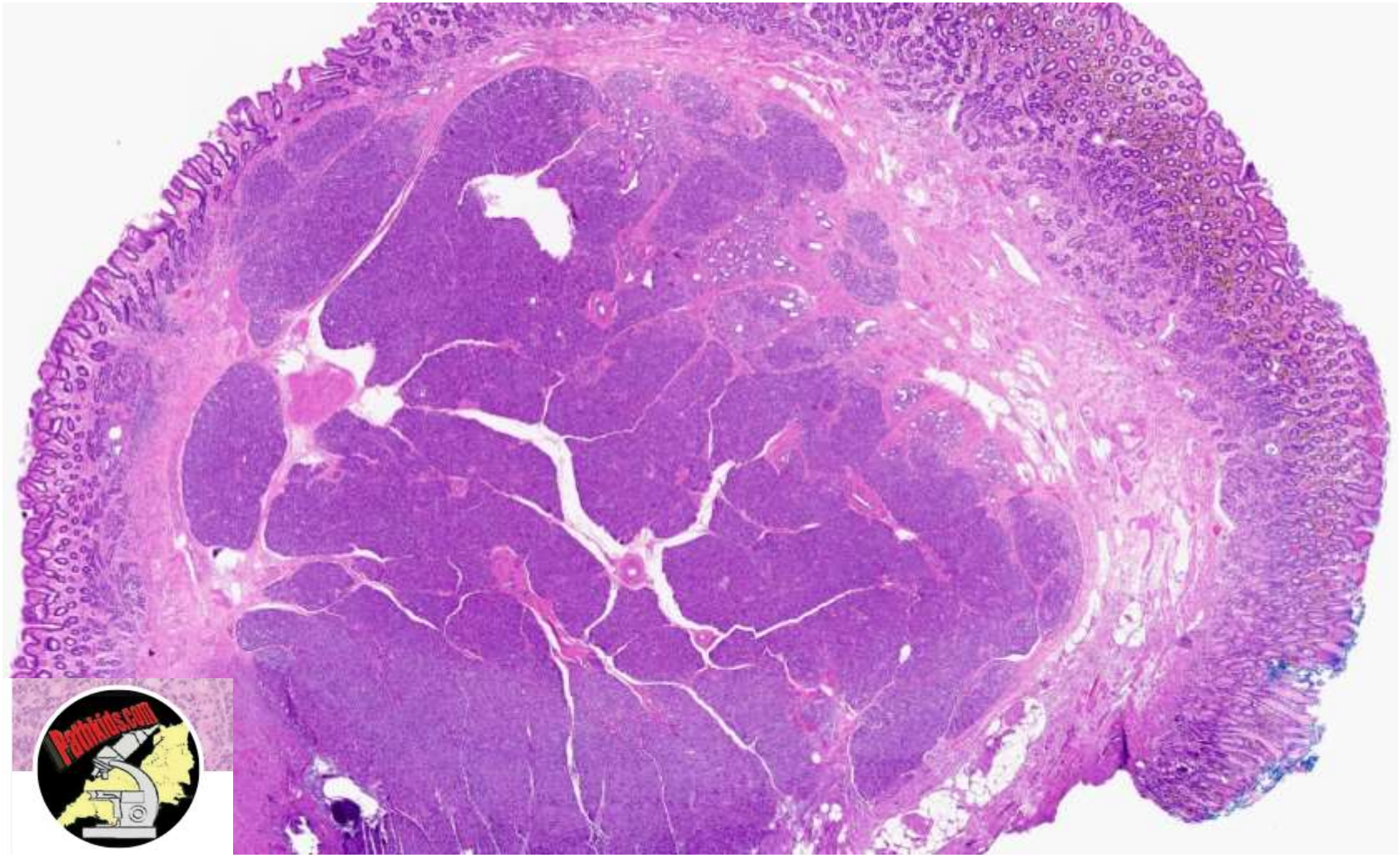
Case 8. Pancreatic heterotopia

- Most commonly seen as a small pancreatic “rest” in distal stomach
- "Umbilicated" endoscopy appearance
- Can be pure exocrine exocrine or contain islets
- Can be several cms in diameter
- Can mimic cancer on frozen section
- Tumours / pancreatitis can develop in it and cause obstruction

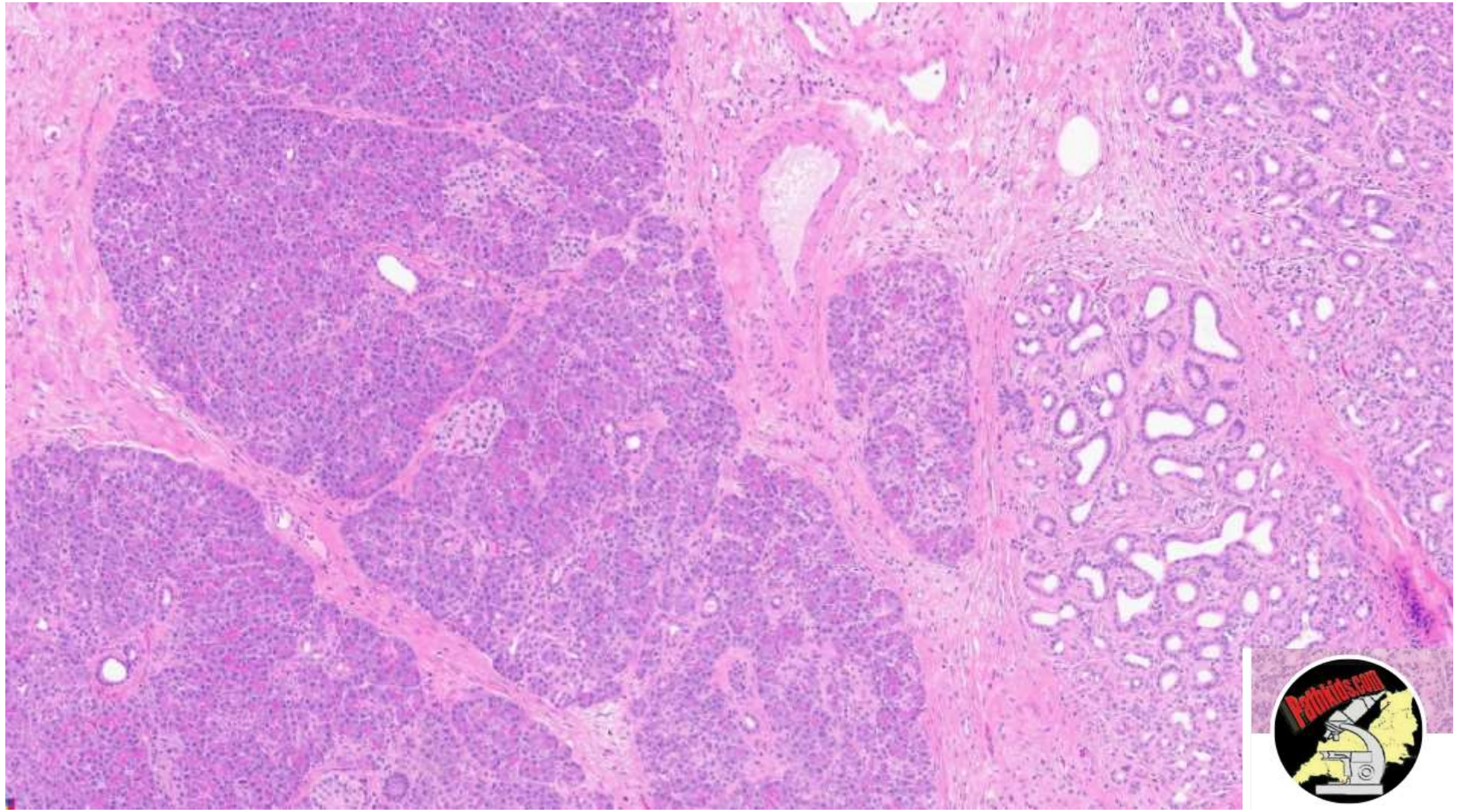
"Umbilicated" endoscopic appearance of heterotopic pancreas



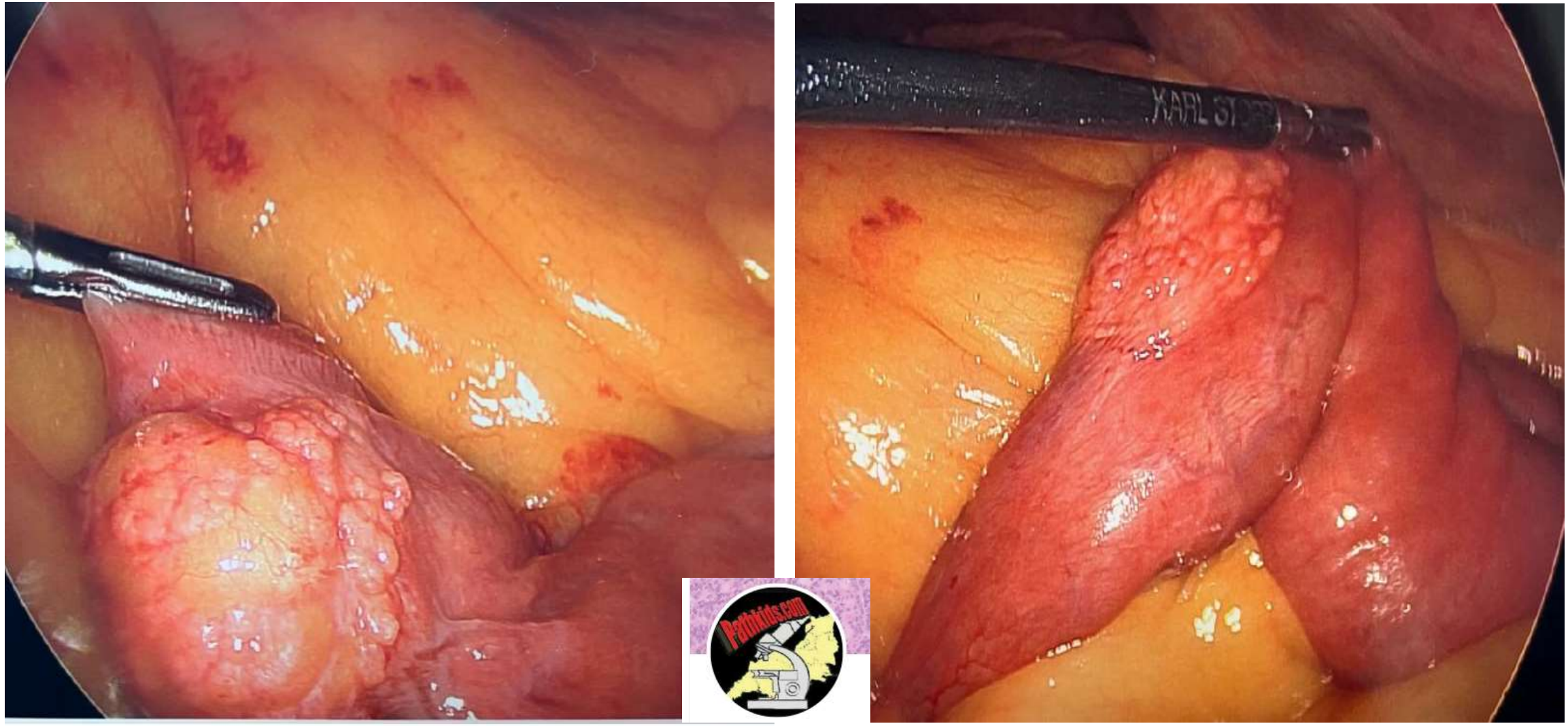
Low power H&E histology of heterotopic pancreas



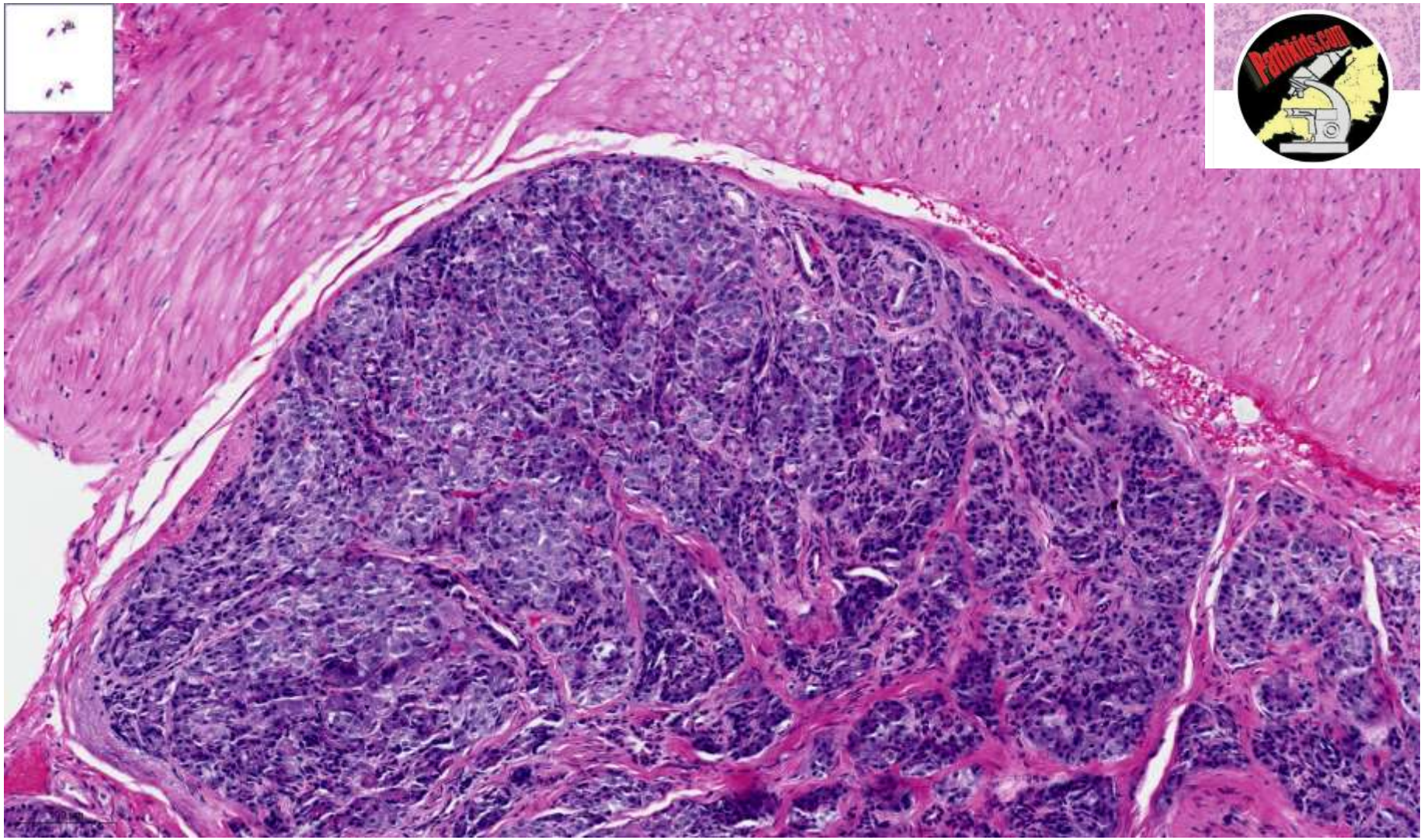
Medium power histology of "type 1" heterotopic pancreas



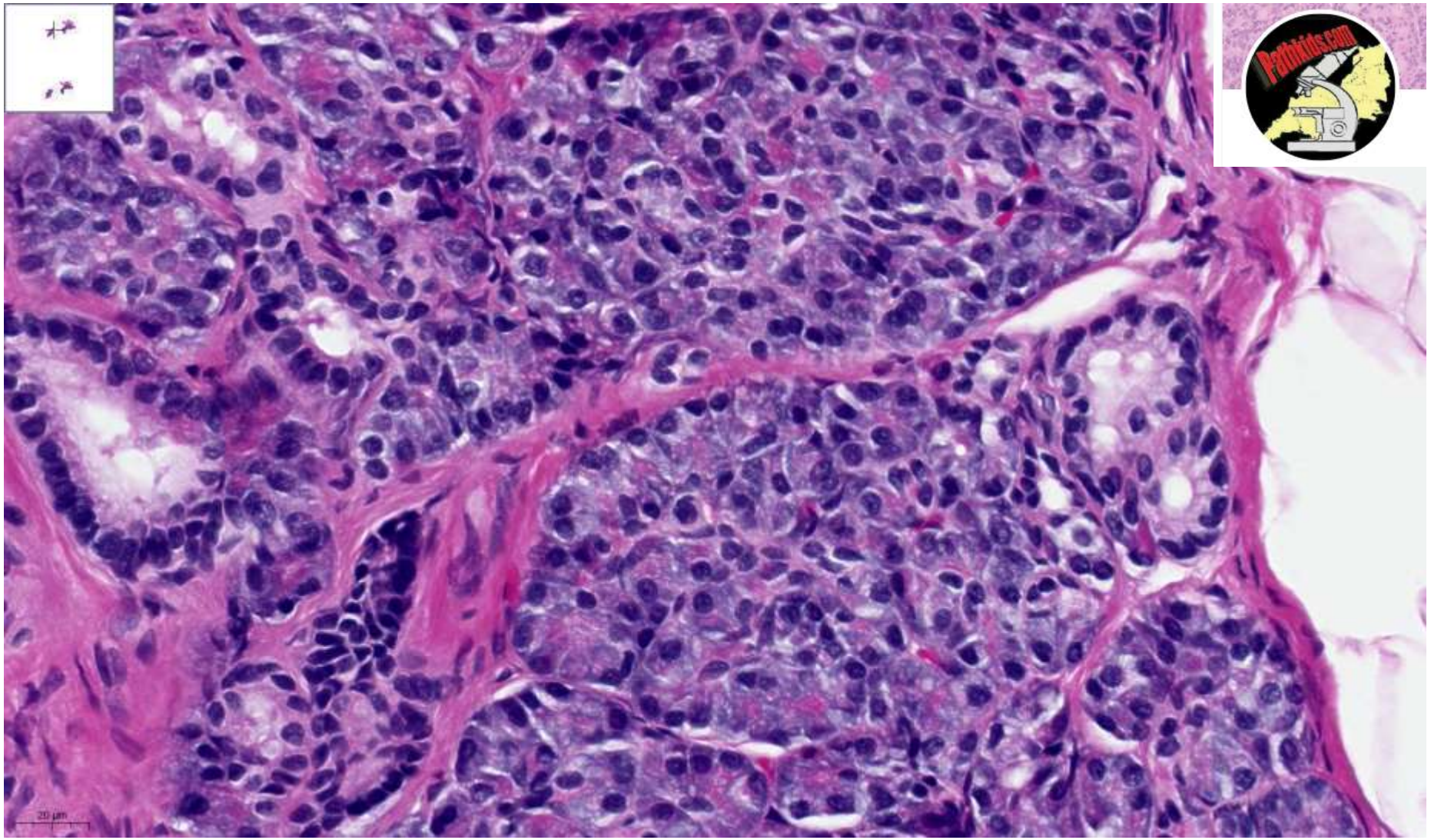
"type 2" heterotopic pancreas mimicking small bowel malignancy



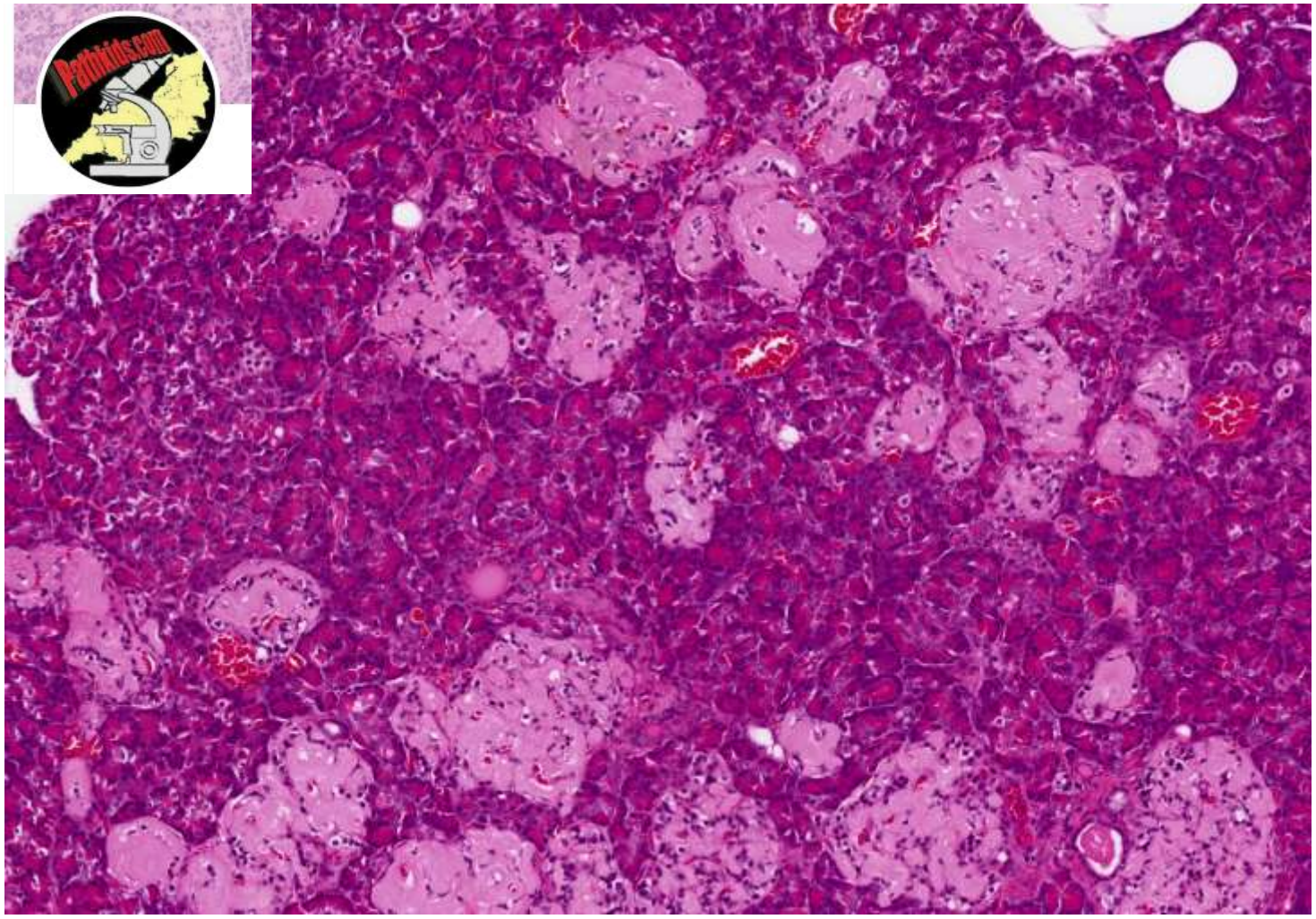
"type 2" heterotopic pancreas mimicking small bowel malignancy



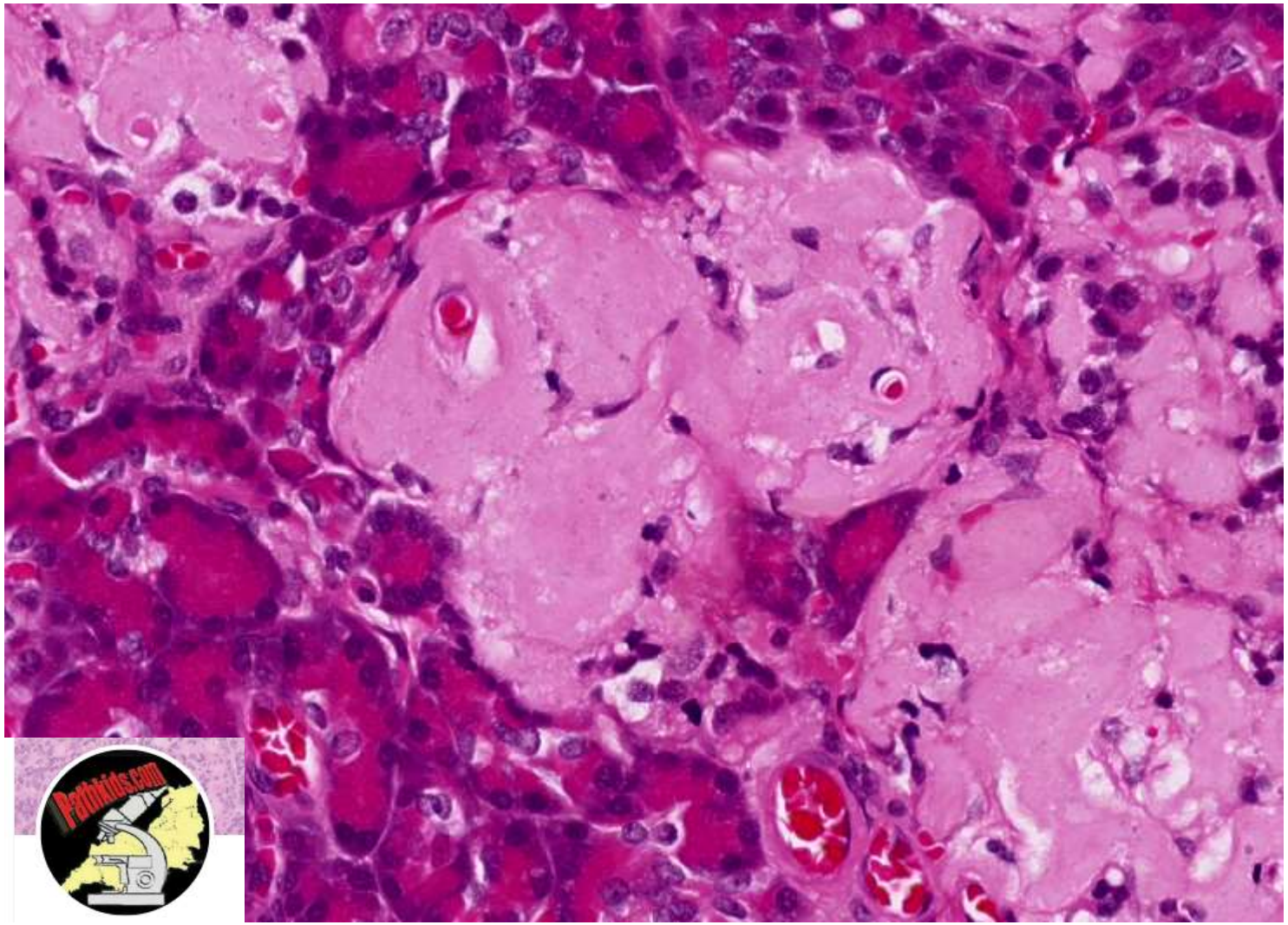
"type 2" heterotopic pancreas mimicking small bowel malignancy



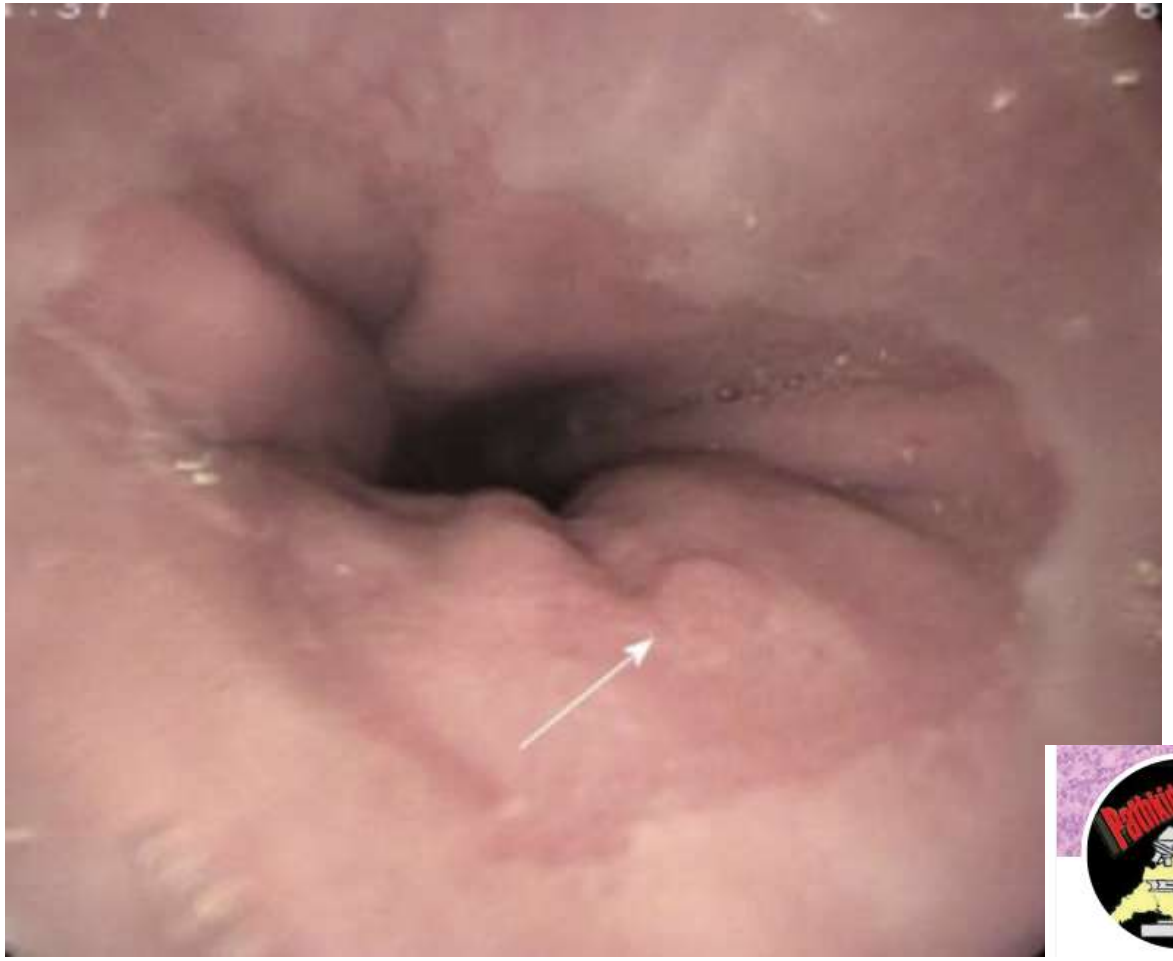
When one unusual finding isn't enough!

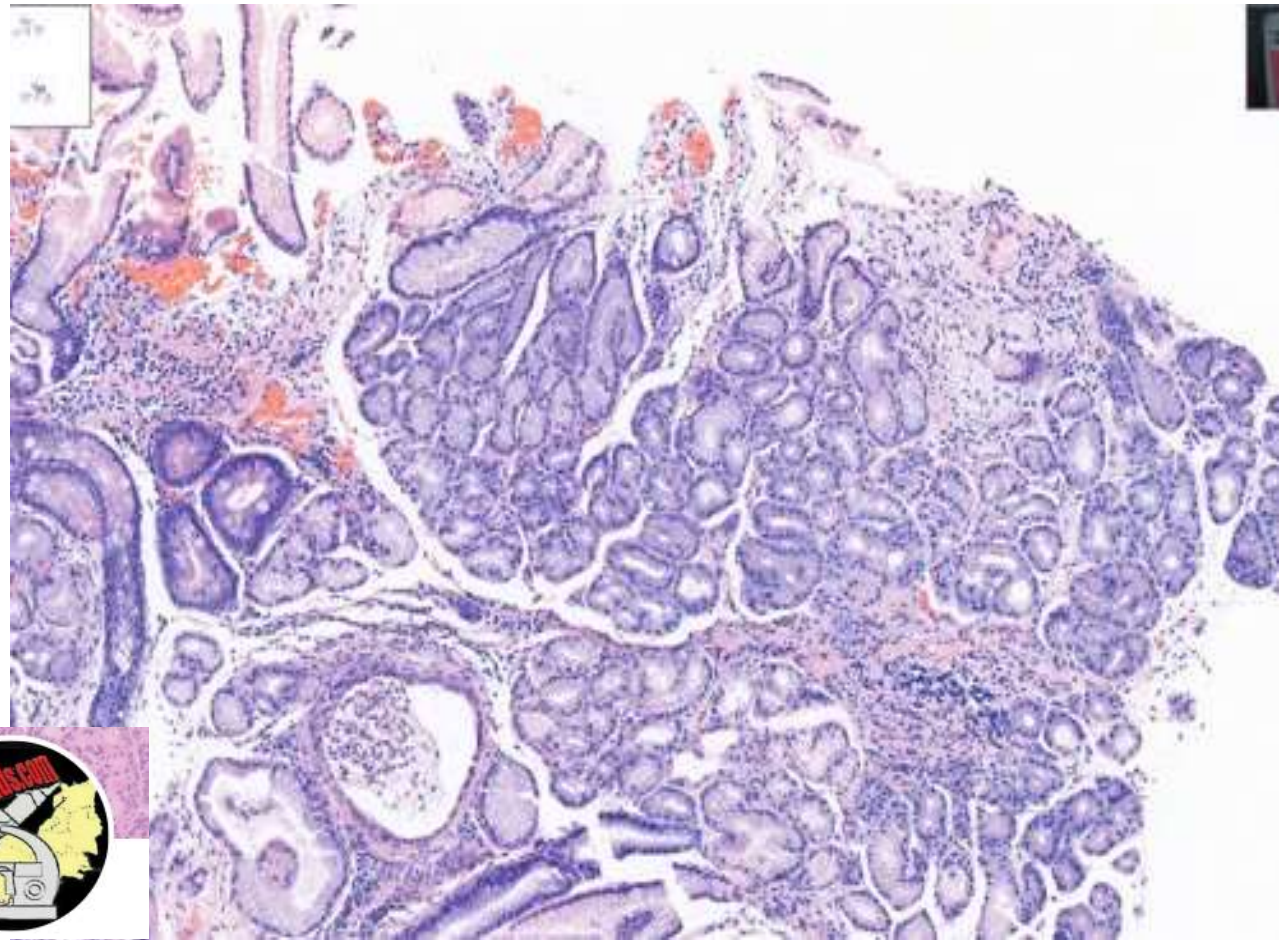


AA-Amyloid in heterotopic pancreatic islets!

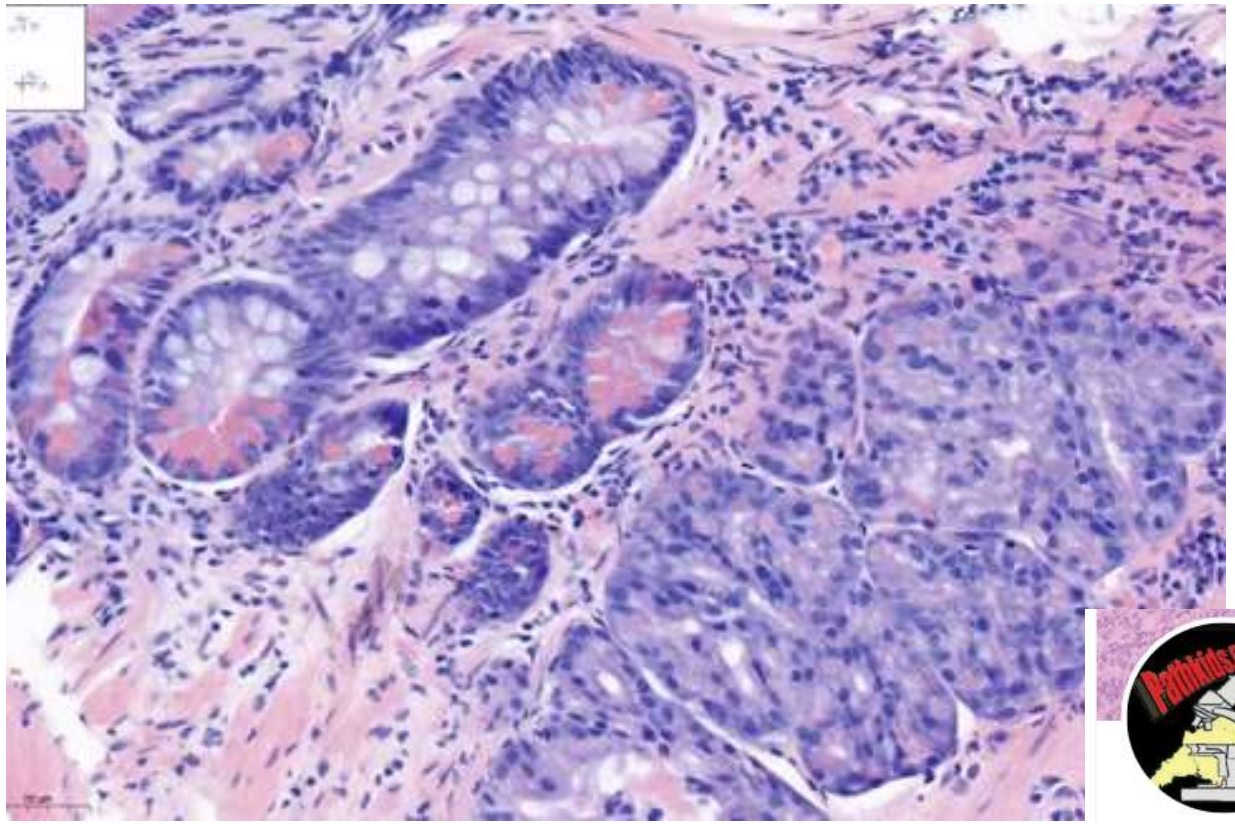


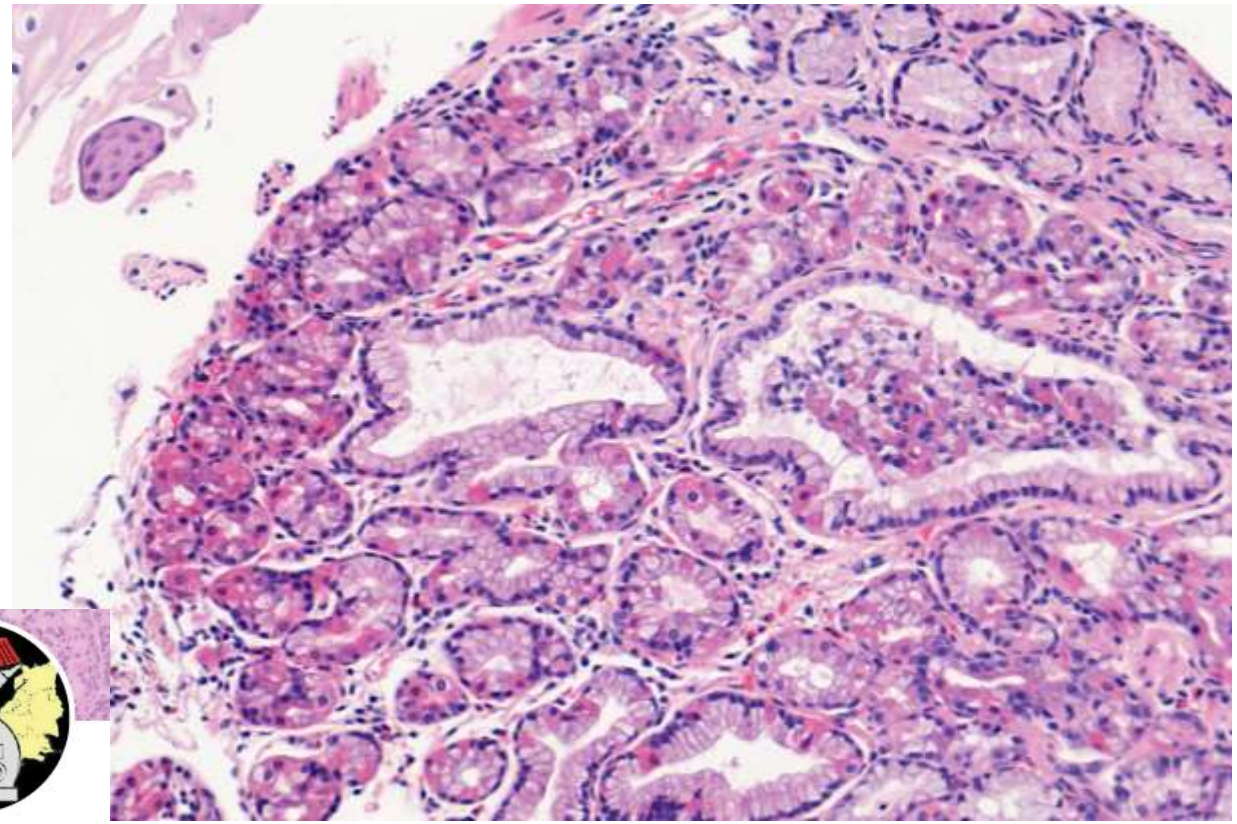
Pancreatic *metaplasia* at the OGJ





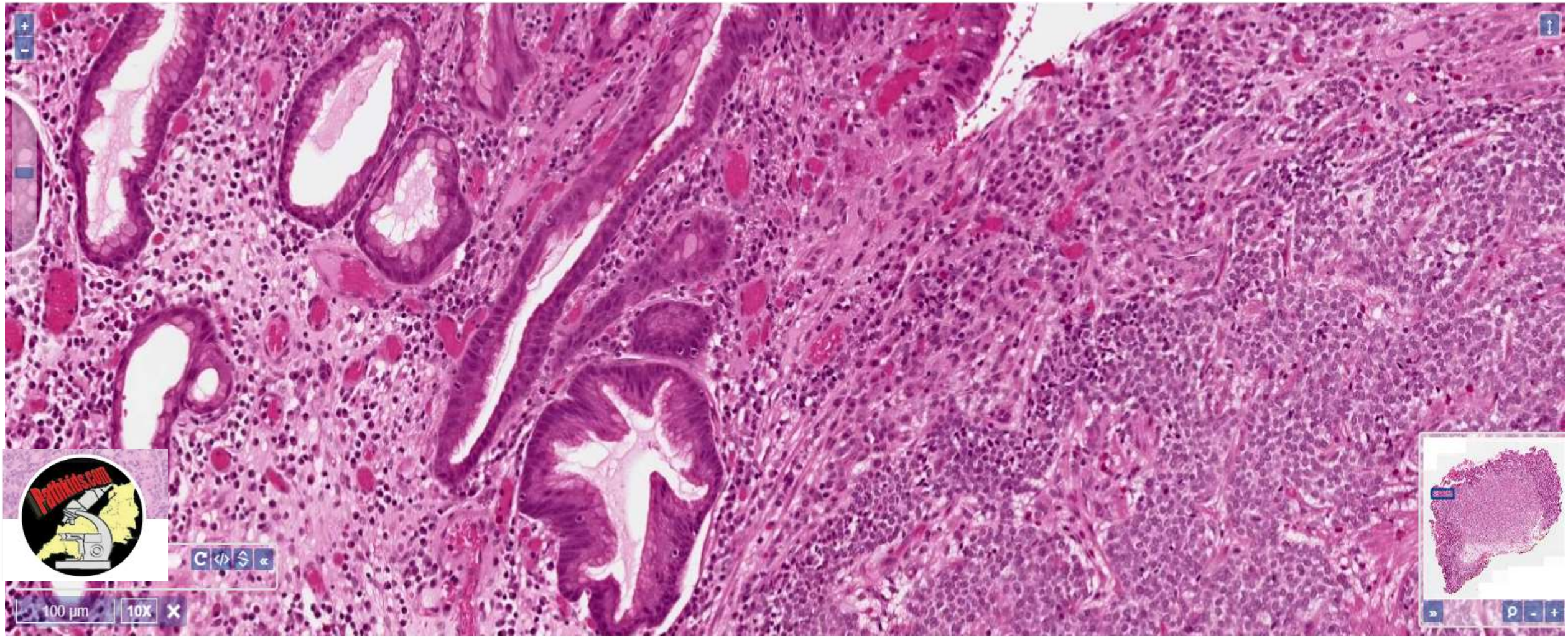
Pancreatic *metaplasia* at the OGJ





Case 9. 62F gastric body submucosal polyp in gastric body mucosa. WSI of H&E. Chromogranin.

Case 9. Type 1 G1 well diff neuroendocrine tumour



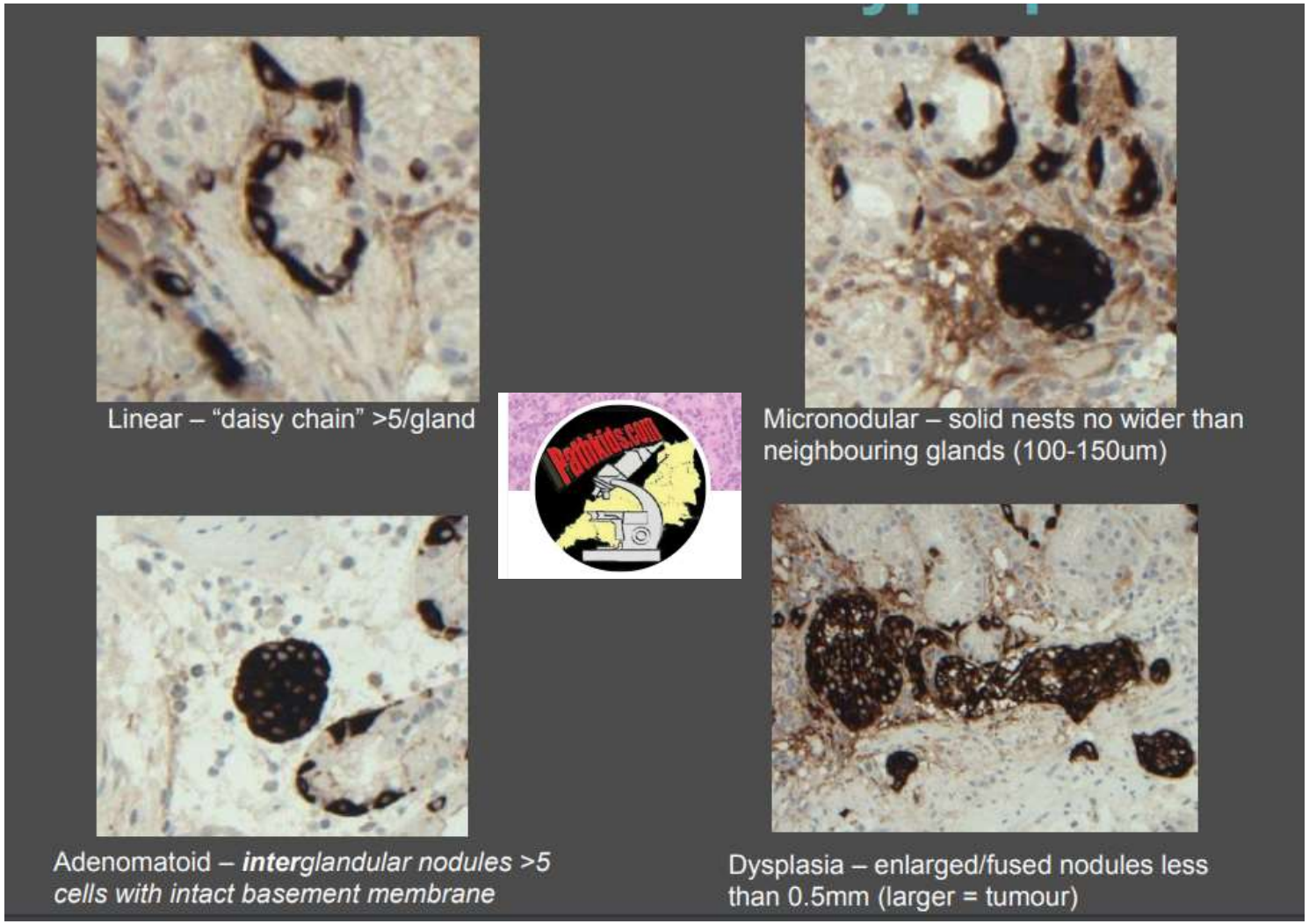
Case 9. Type 1 G1 well diff neuroendocrine tumour

Table 2: Pathological/clinical features of gastric NENs.[4,29]

Features	Type		
	I	II	III
Histology	ECL-cell WD-NET	ECL-cell WD-NET	ECL-cell WD-NET
Grading	G1 G2 (rare) G3 (exceptional)	G1 G2 (rare)	G1 (rare) G2 G3 (rare)
Background mucosa	CAG + ECL-cell hyperplasia[26] +/− antral G-cell hyperplasia	Hyperplasia of parietal cells + ECL-cell hyperplasia[26]	Normal
Location	Fundus/corpus	Fundus/corpus	Anywhere
Number of tumours	Multifocal	Multifocal	Solitary
Serum gastrin level	Secondary hypergastrinaemia (resulting from achlorhydria)	Primary hypergastrinaemia (resulting from gastrin-secreting tumours)	No hypergastrinaemia
Pathogenetic mechanism	Autoimmune gastritis	ZES, MEN I	Undetermined
Clinical course	Indolent, regress spontaneously, endoscopic removal often adequate	Somatostatin analogues effective	Aggressive behaviour

CAG: Chronic atrophic gastritis; ECL: Enterochromaffin-like; MEN I: Multiple endocrine neoplasia syndrome, type I; WD-NET: Well-differentiated neuroendocrine tumour; ZES: Zollinger–Ellison syndrome.

Neuroendocrine hyperplasia in atrophic body



Don't overcall prominent antral G cells as neuroendocrine hyperplasia

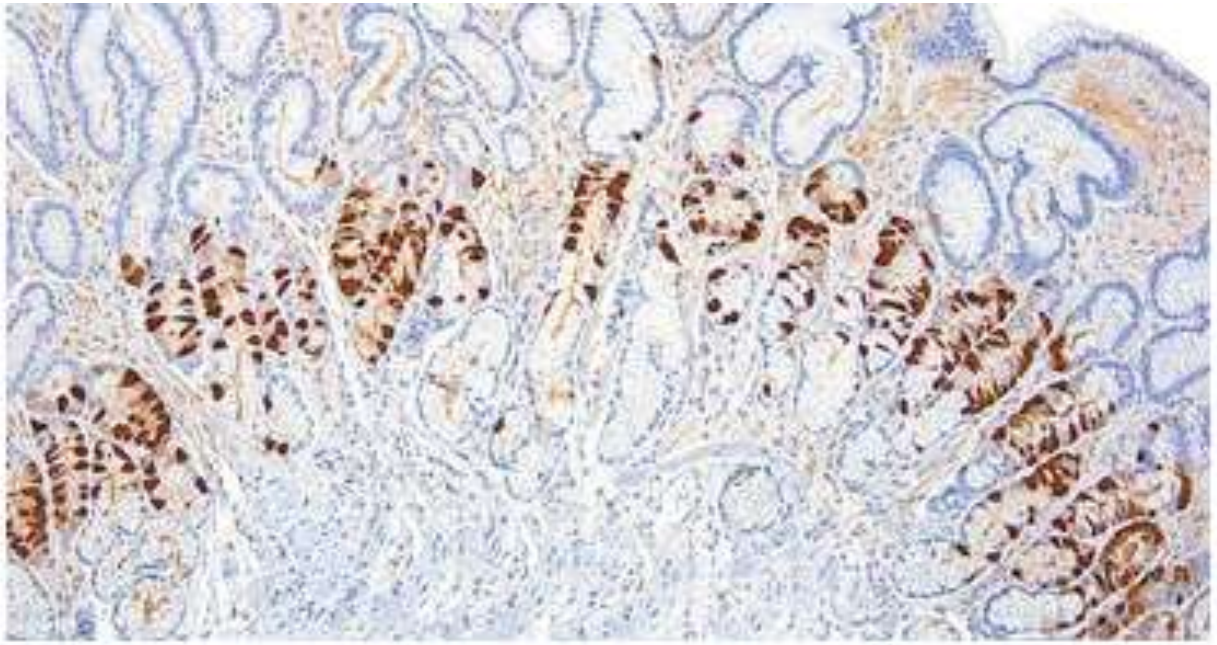
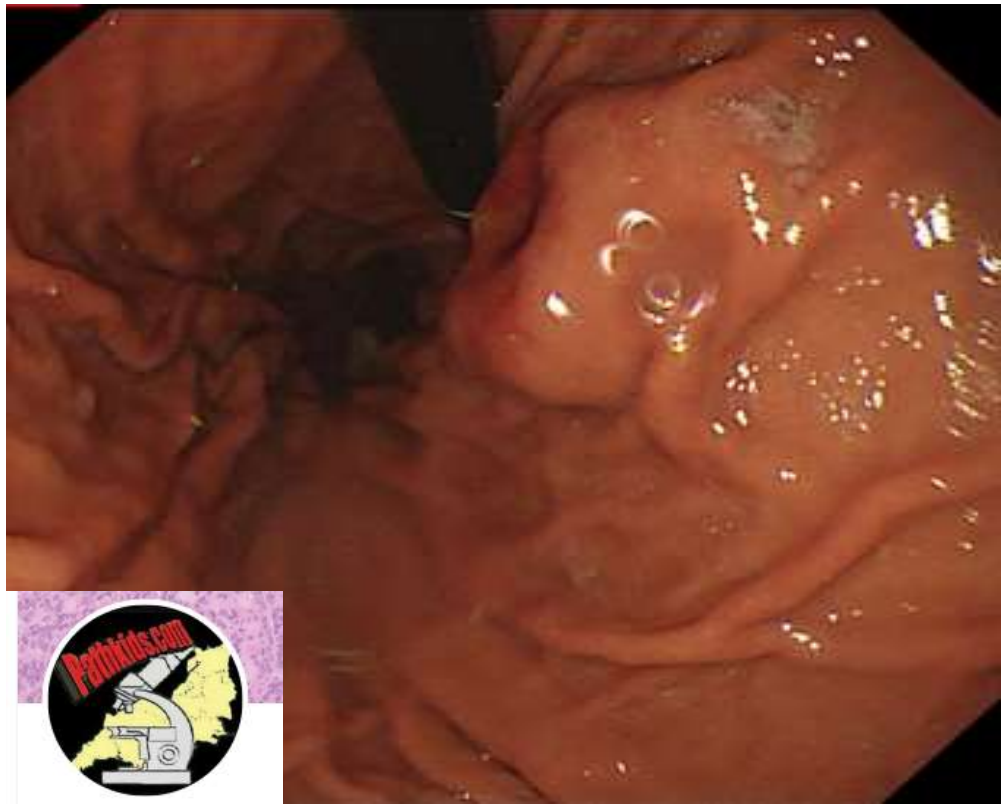
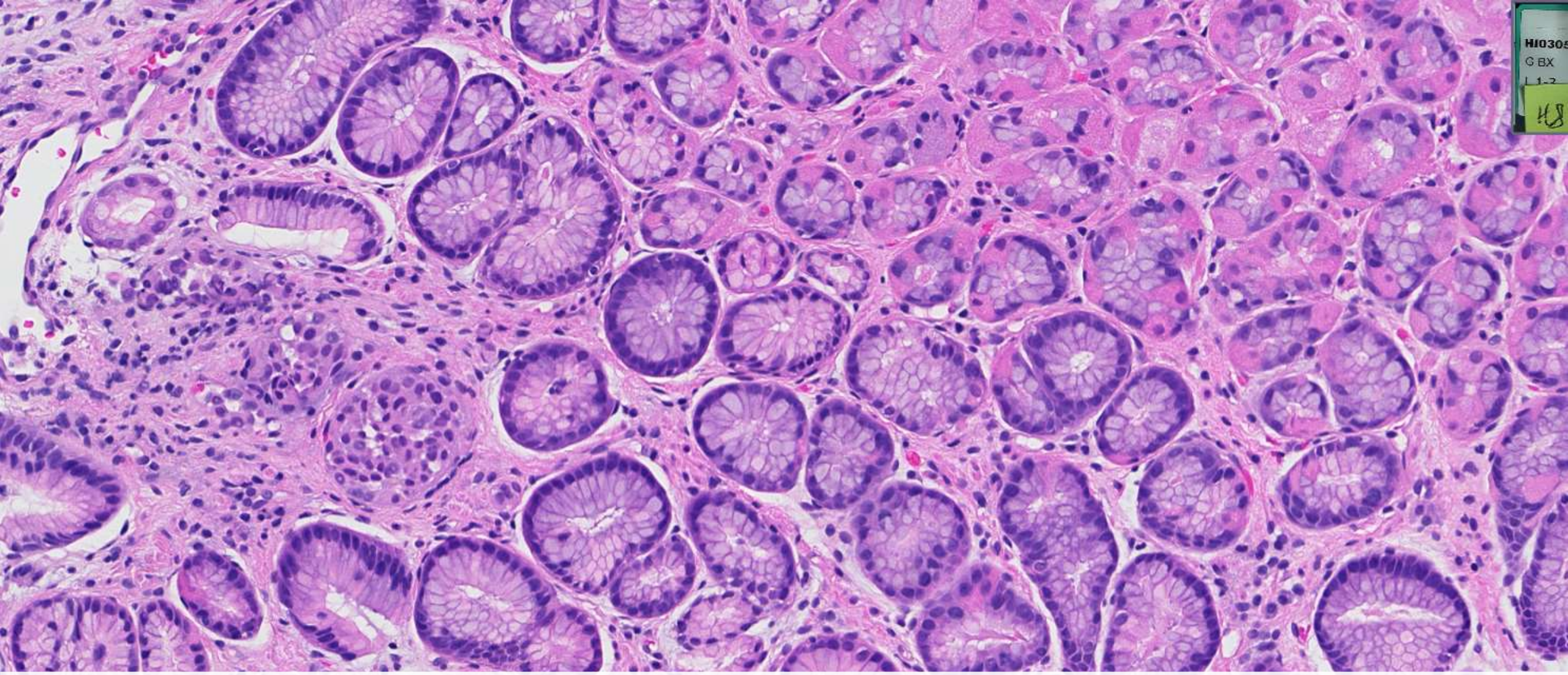


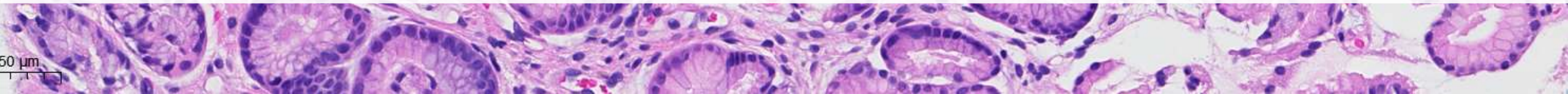
FIGURE 15.19 In normal antral mucosa, a band of G cells is highlighted by immunohistochemical staining.

Case 10. 46M with a 3.5cm lesser curve gastric tumour TXN1 on CT. H&E slide. Synaptophysin.

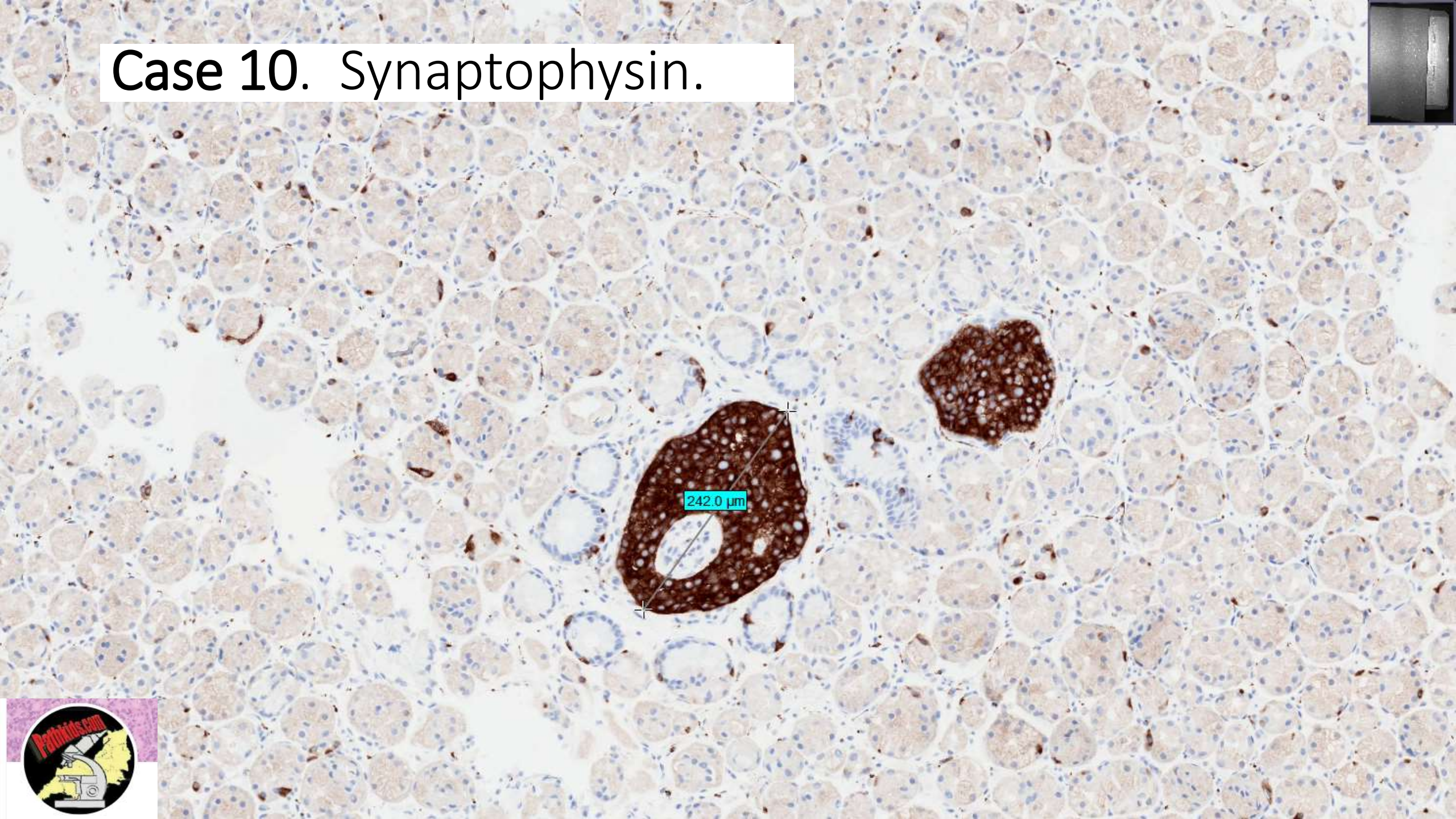




Case 10. H&E.



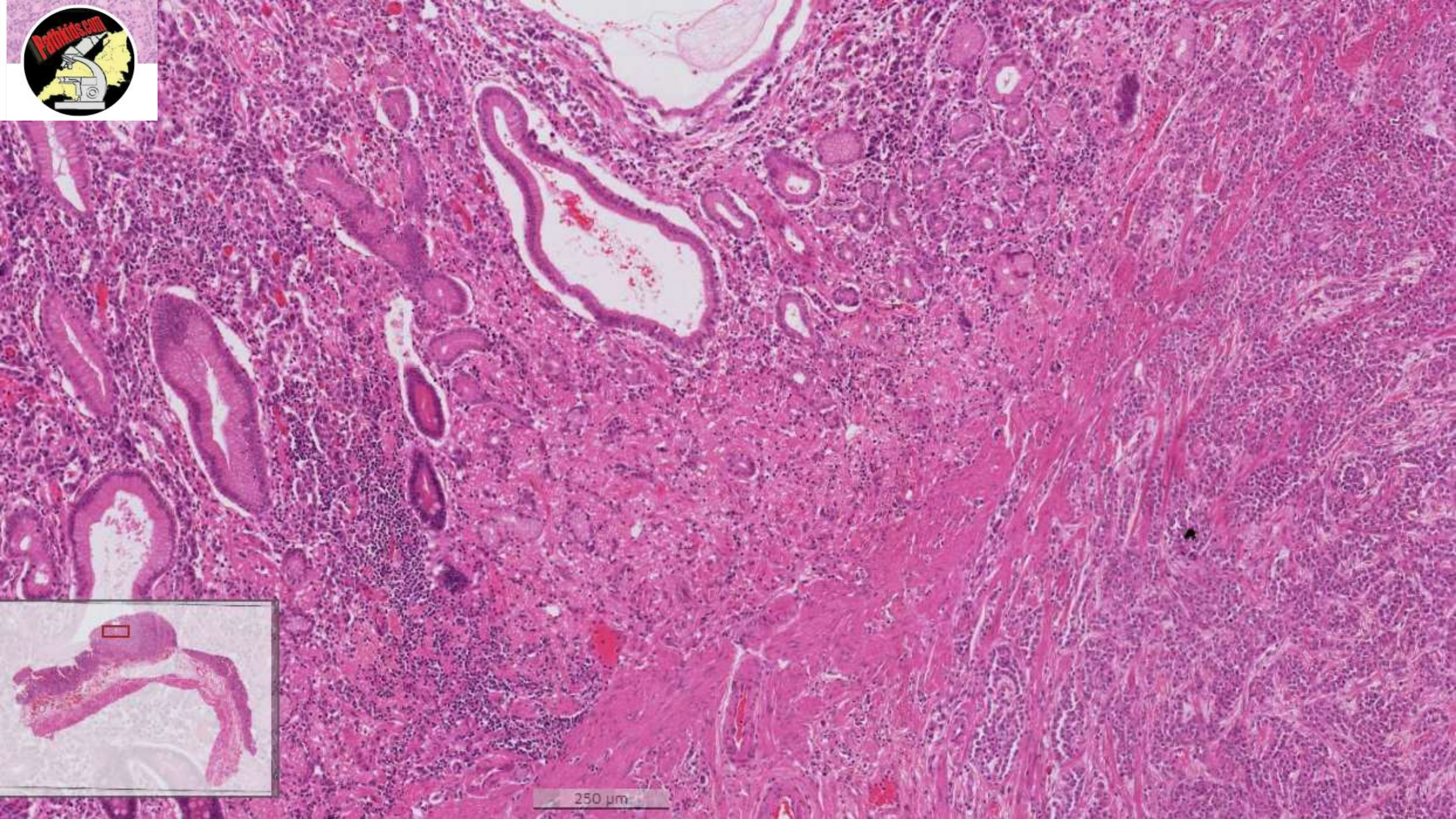
Case 10. Synaptophysin.



Case 10. Type III well diff gastric NET.

- Sporadic and potentially aggressive in contrast to indolent type 1 NET
- Occurrence in otherwise normal mucosa suggests not type 1 or 2
- Grading not possibly on a small incisional biopsy (most end up G2)
- Most present at a larger size and have already disseminated
  - Octreotide scans are used in contrast to FDG PET for staging

Case 11 59F Gastrectomy for gastric tumours. History of pituitary, pancreatic and parathyroid tumours. H&E slide from body of stomach.

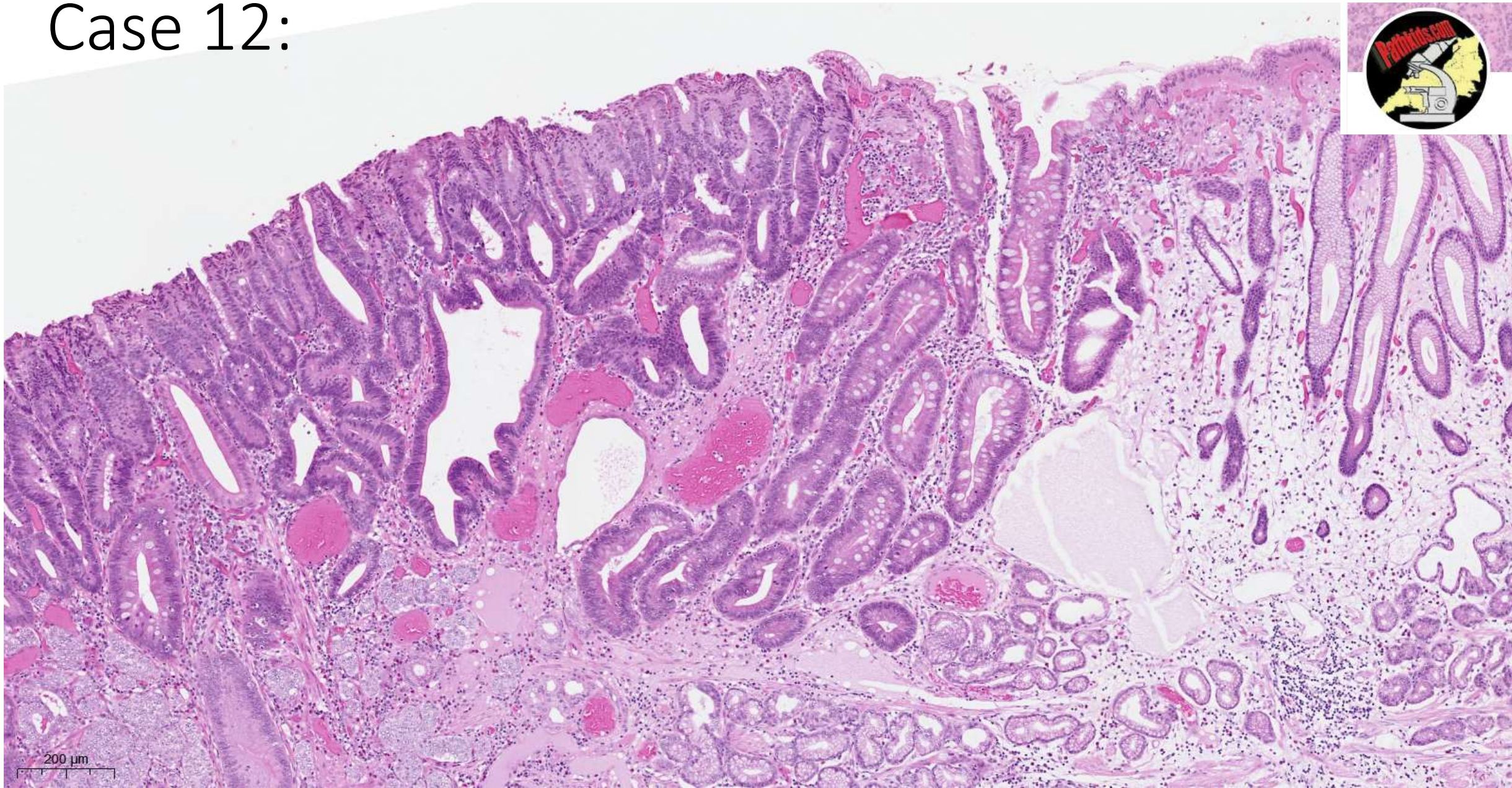

250 µm

Case 11: Type II gastric NET (Zollinger-Ellison syndrome)

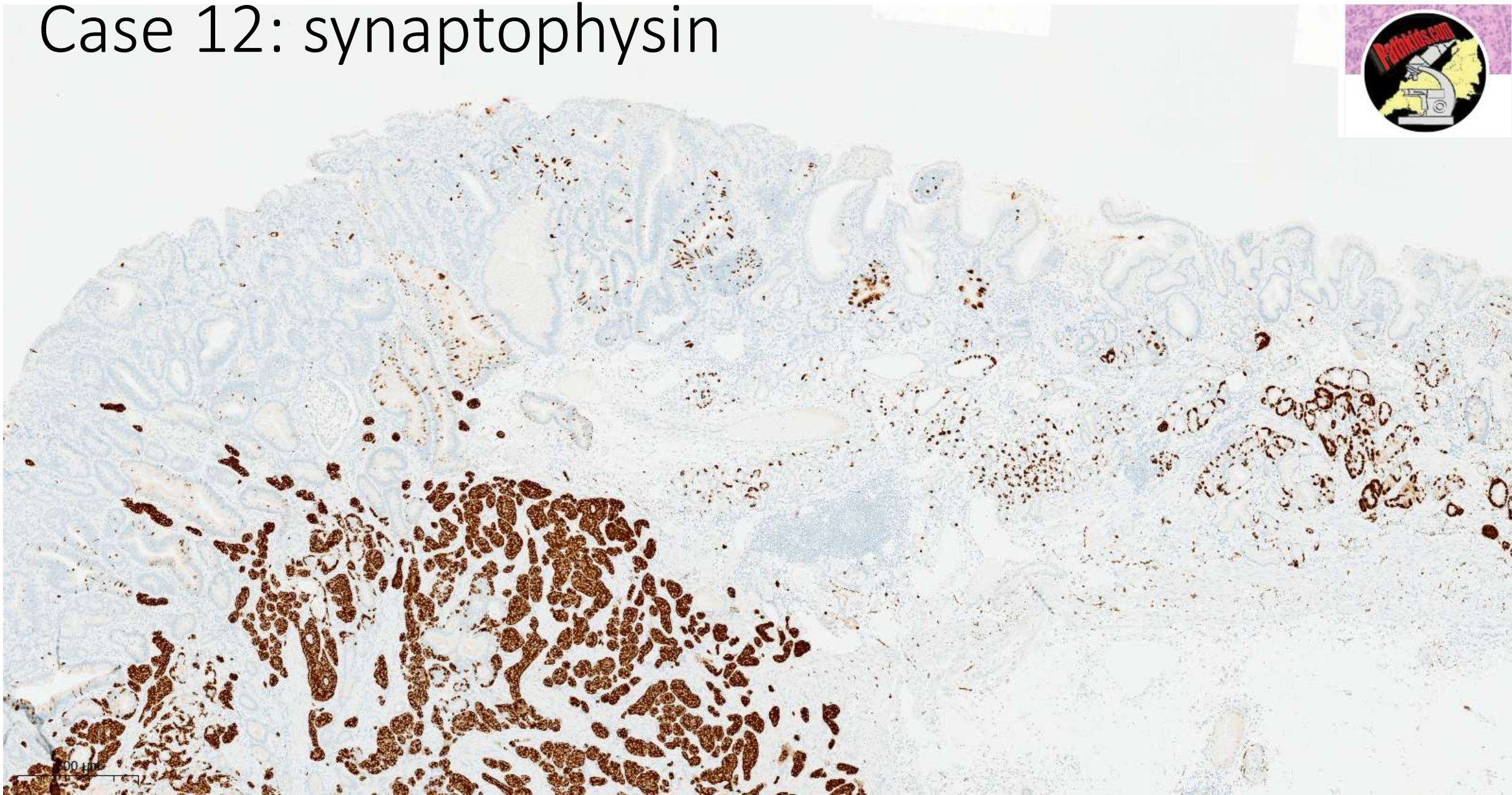
- Well differentiated neuroendocrine tumour multifocal + NE hyperplasia
- Note mucosa is *abnormal* but not atrophic in contrast to type 1
- Did you spot the additional diagnosis at the edge of the slide?

Case 12 . 58F large gastric polyp EMR, previous gastric adenoma. WSI of H&E. WSI of Synaptophysin stain

Case 12:



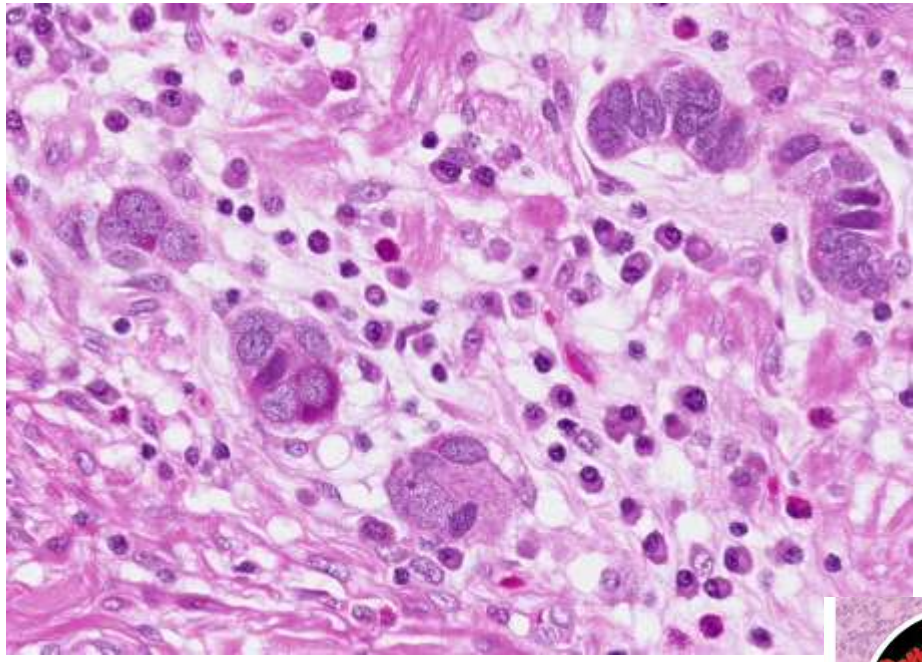
Case 12: synaptophysin

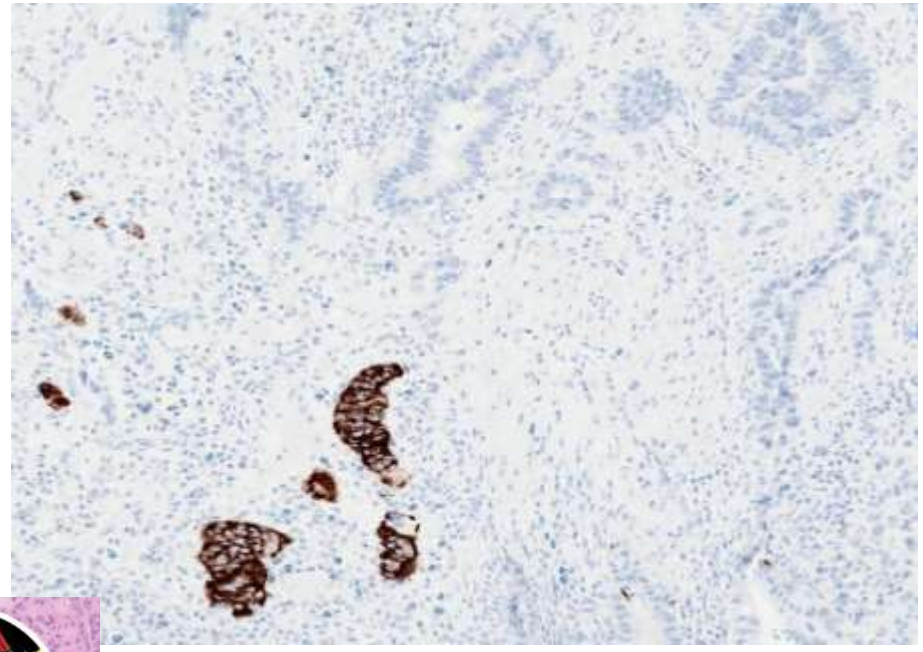


Case 12 . MANET (combined tubular adenoma and G1 type 1 NET)

Case 13. Man in 70s. Post chemo oesophagectomy. Whole slide image at this link. Chromogranin.

Case 13. Adenocarcinoma or MINEN?

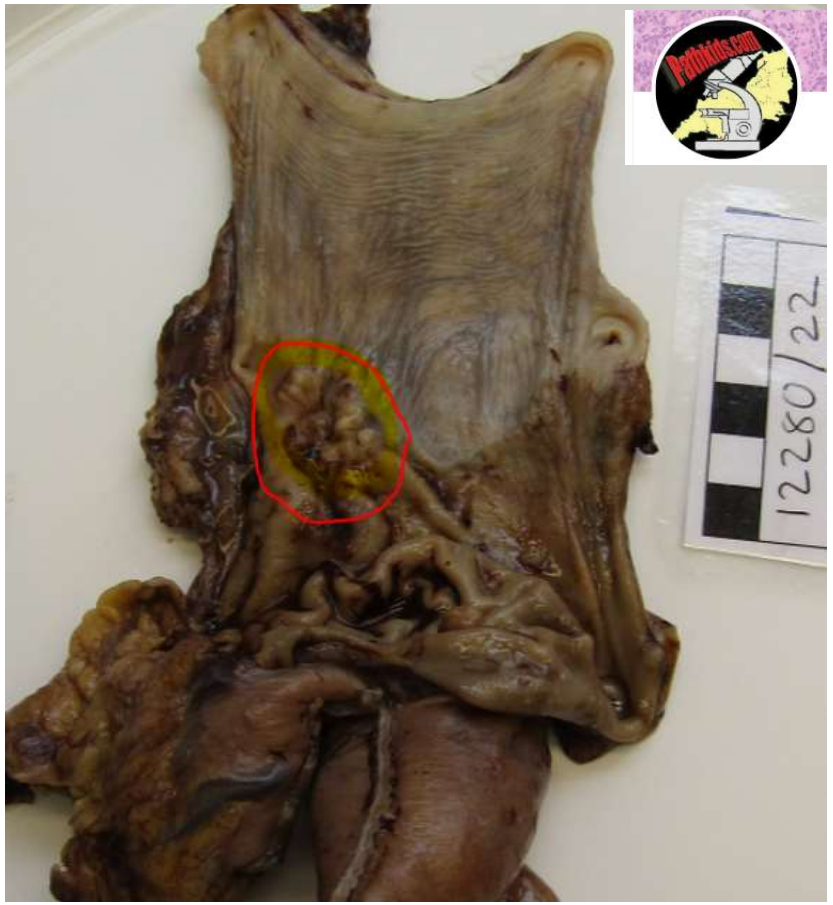




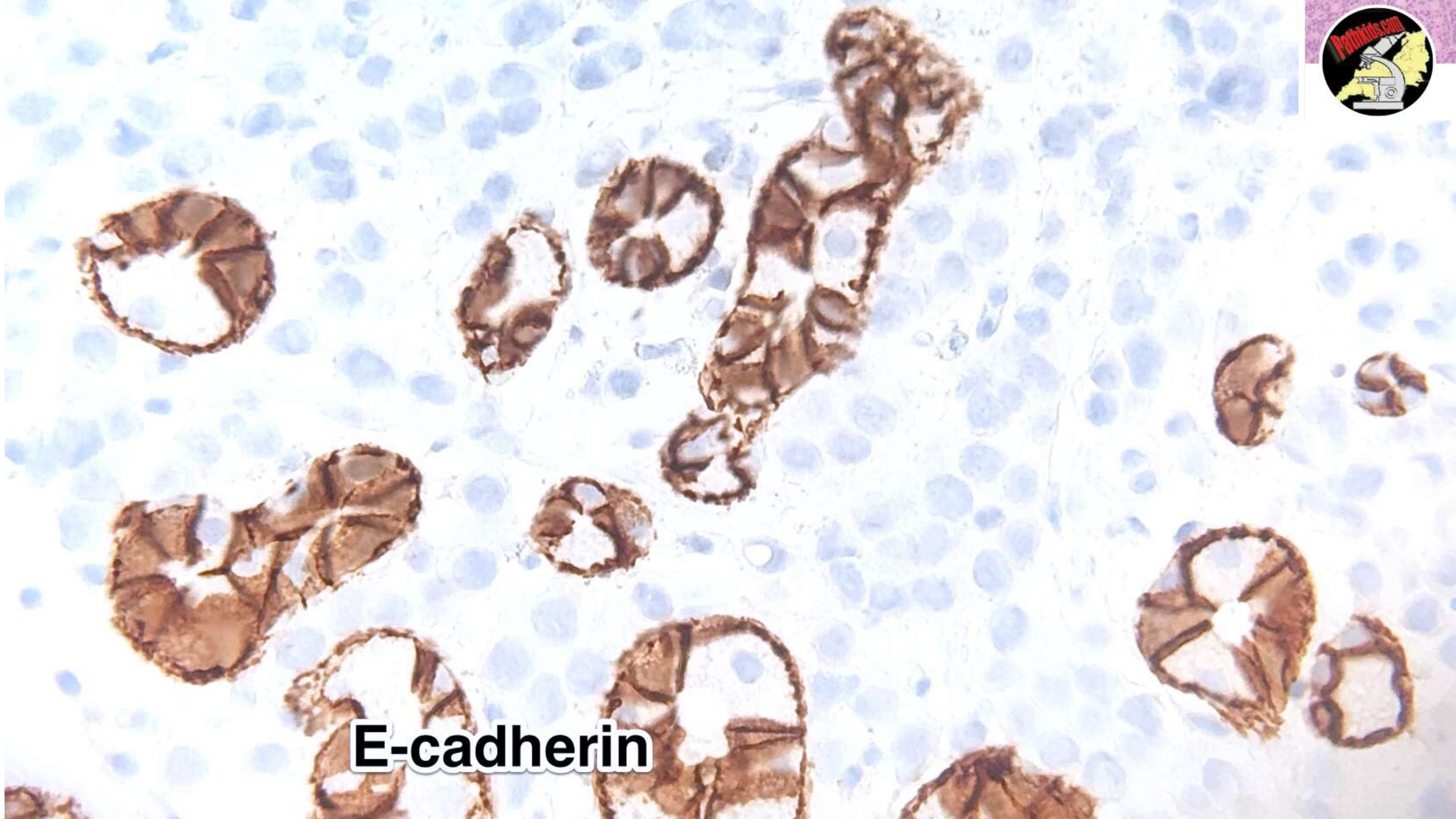
MiNEN

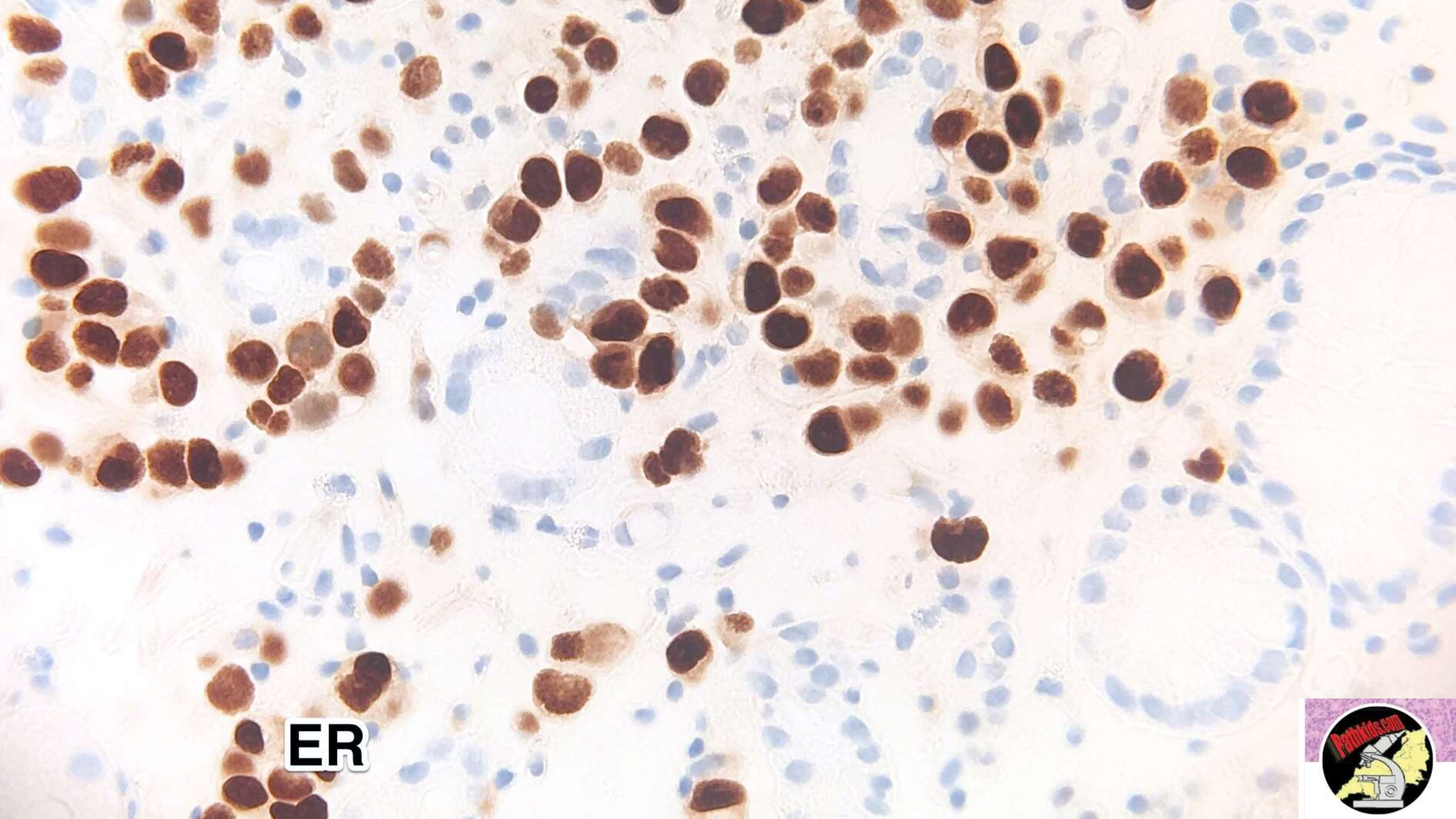
- Previously MANEC
- Very rare when carefully diagnosed. On biopsy cannot be sure whether at least 30% of each component and postop can be effect of chemotherapy
- Small cell carcinoma component not uncommon in oesophagus
- Do not diagnose neuroendocrine carcinoma on IHC alone
- Can be mixed or amphicrine (c/w goblet cell adenocarcinoma)
- This case was considered to be adenocarcinoma with NE diff related to the chemotherapy

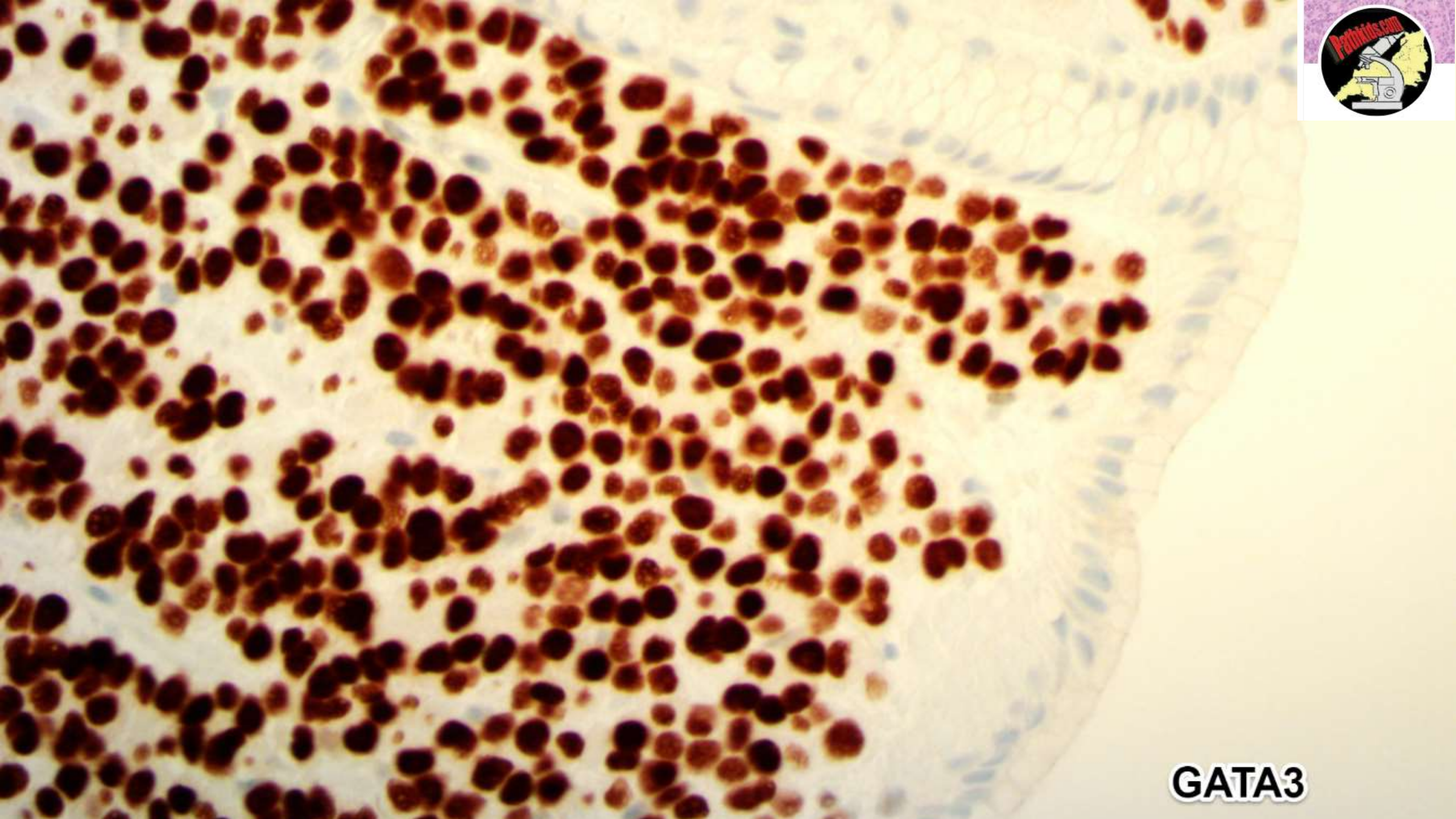
Case 14. Female in 70s. Oesophagectomy no preop treatment. WSI at this link. Chromogranin 1. CDX2.



Case 15. Woman in 60s, suspected linitis on CT but mucosal surface looks normal. H&E slide here. Look at slide labels for IHC. IHC1. IHC2. IHC3.

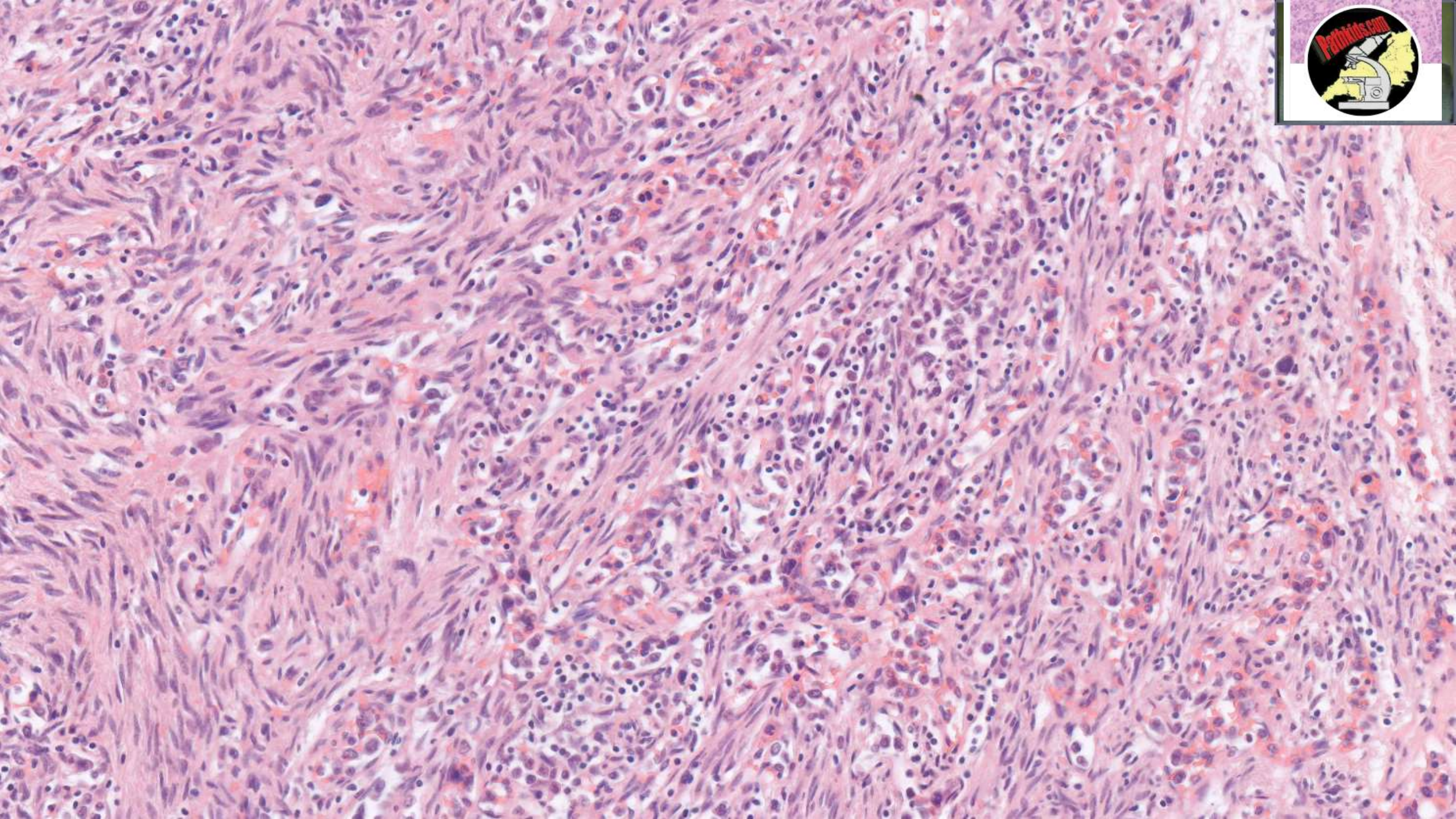

E-cadherin

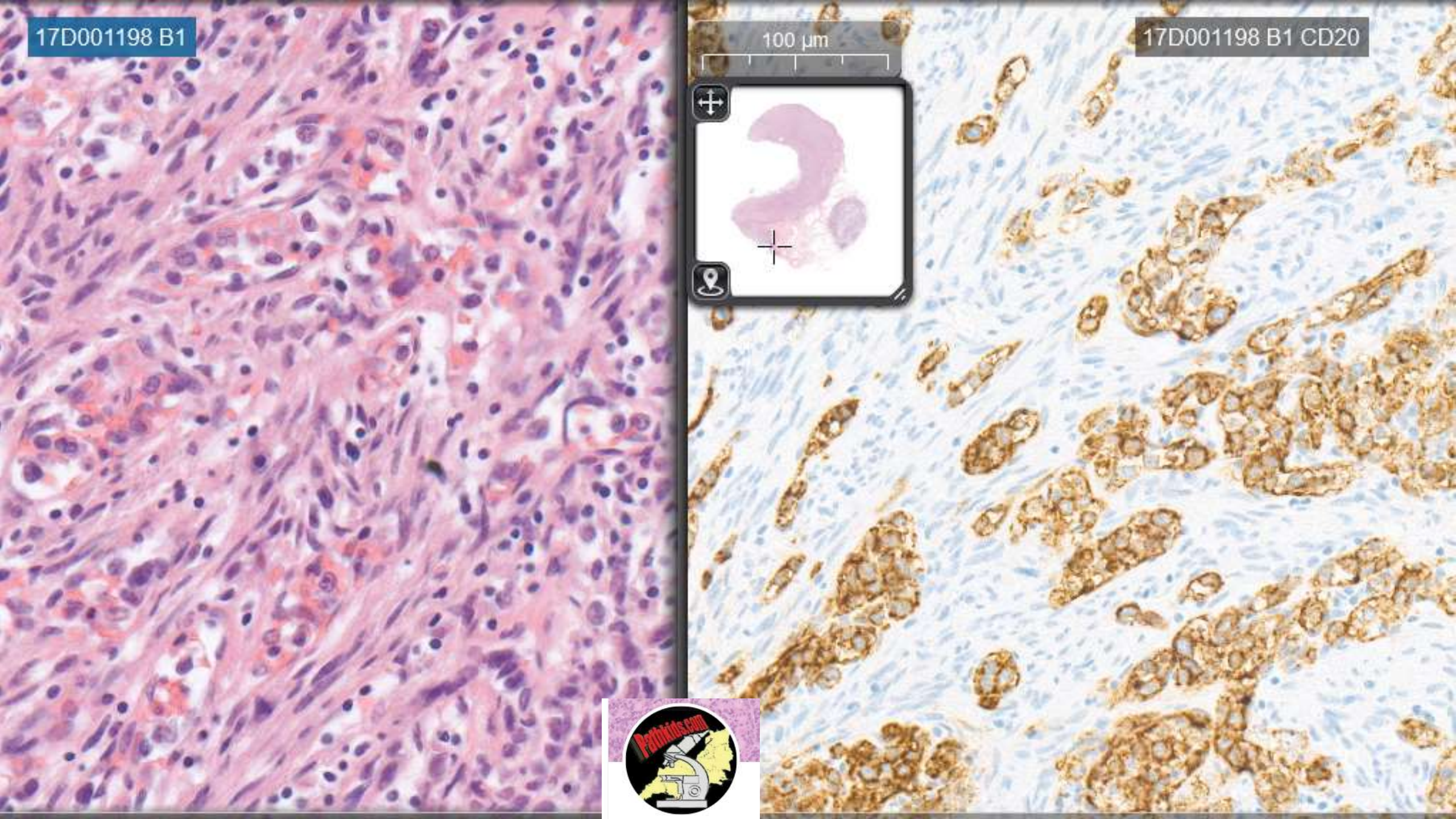

ER

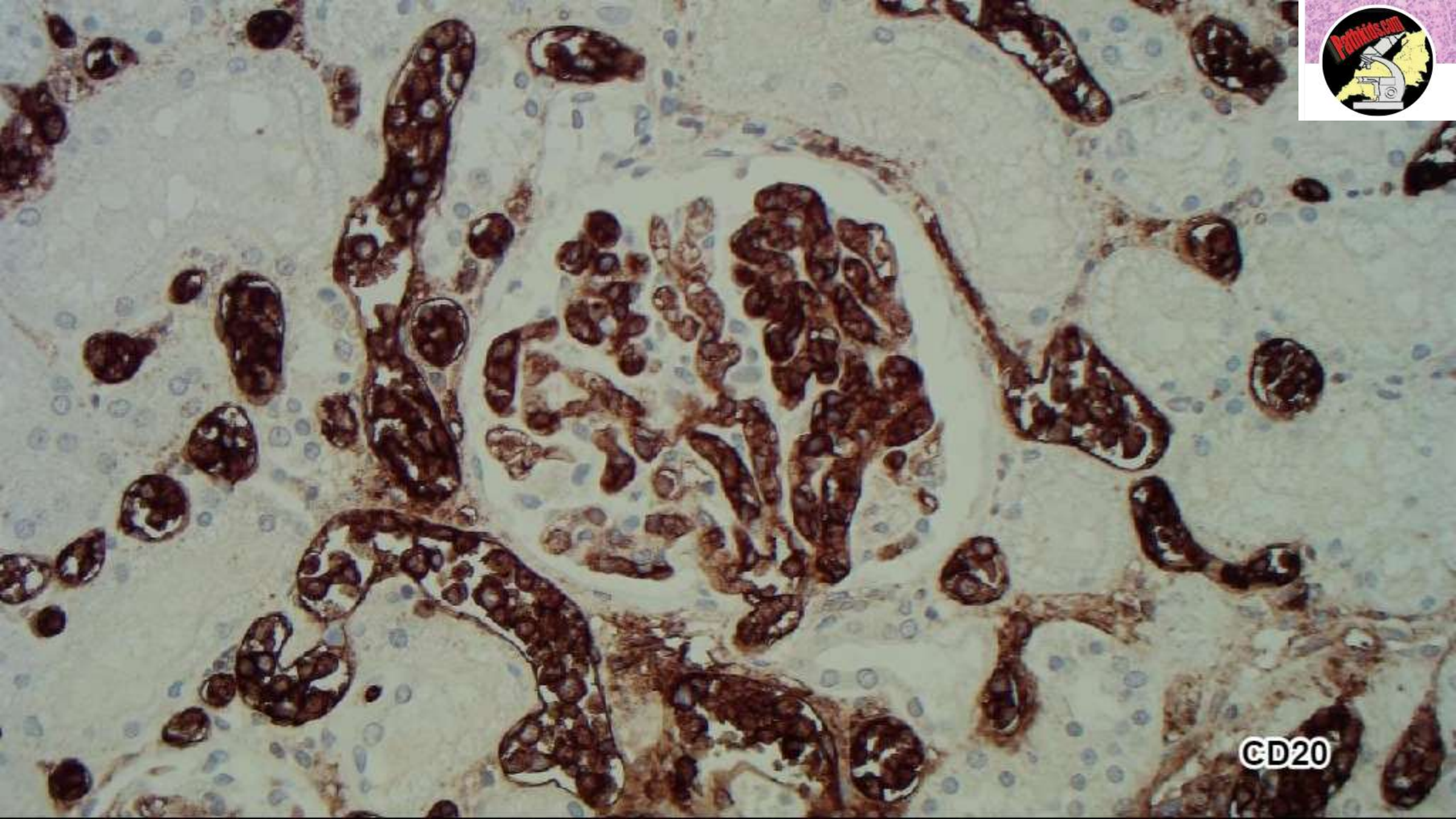

GATA3

Case 15. Metastatic lobular breast carcinoma

Case 16. Pyrexia of unknown origin. Obstructing small bowel GIST at postmortem.




17D001198 B1
100 µm
17D001198 B1 CD20
PathKids.com


CD20

Case 16. Instravascular Large B cell lymphoma

- characterised by lymphoma cells, predominantly within lumina of blood vessels, especially capillaries, with the exclusion of larger arteries and veins
- Few to no circulating lymphoma cells in peripheral blood
- Malignant angioendotheliomatosis, angioendotheliomatosis proliferans syndrome, intravascular lymphomatosis, angioendothelilotropic lymphoma (all obsolete)
- Clinical presentation ("classic / western" form) ranges from a few mild symptoms (fever of unknown origin, pain, organ specific local symptoms) to severe symptoms (B symptoms and signs of multiorgan failure) (**Cancer Sci 2021;112:3953**). Usually postmortem diagnosis.