Three commonly missed pancreatic pathologies that are NOT simple neuroendocrine tumours

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Glucagon Cell Adenomatosis

Mahvash syndrome

Glucagon cell hyperplasia and neoplasia

Pancreatic alpha cell hyperplasia

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Pancreatic alpha cell hyperplasia

"New syndrome" – recognised as a distinct entity under the WHO 2017 classification

Glucagon cell adenomatosis

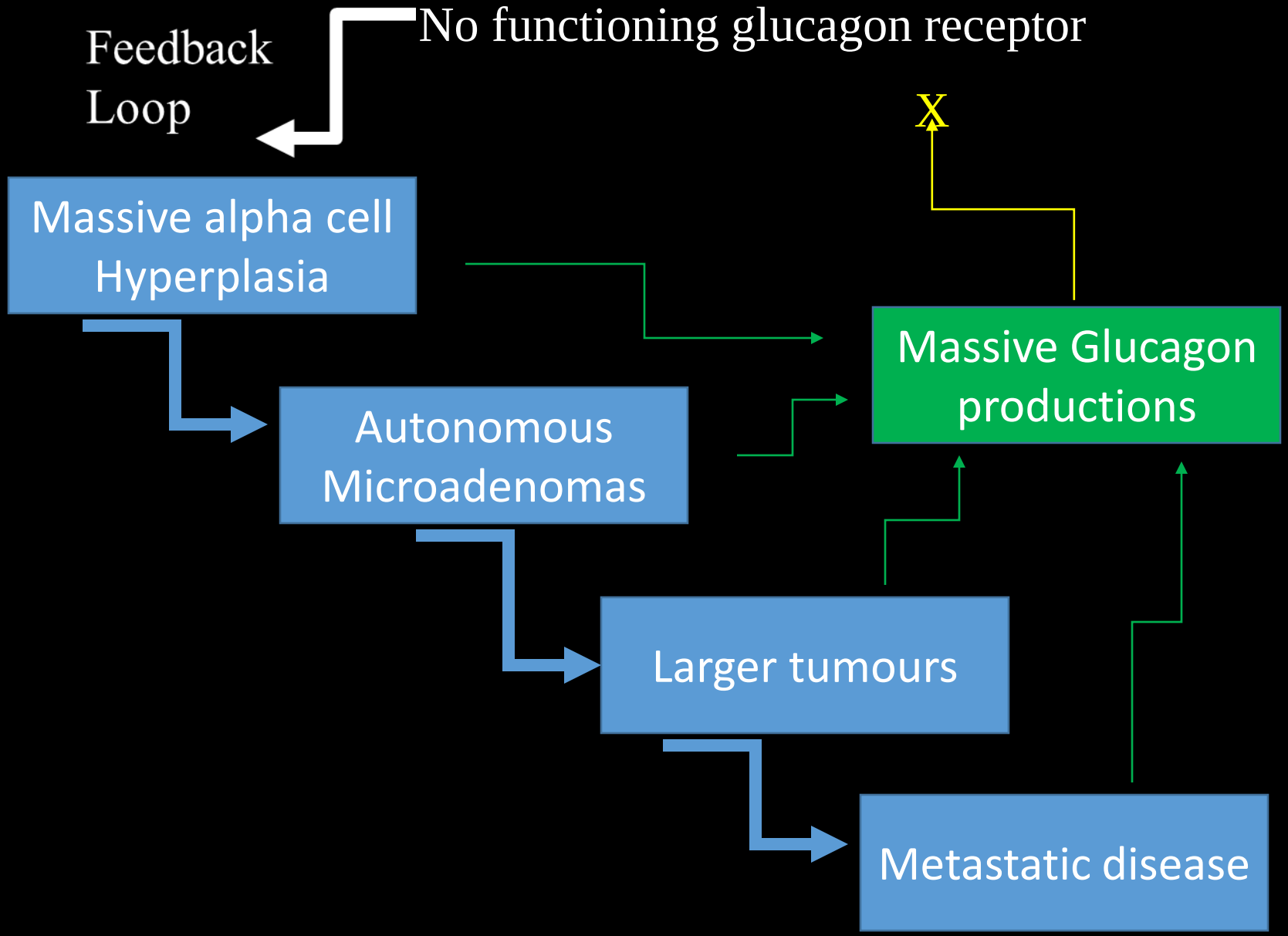
Primary pathology is germline autosomal recessive inactivation of GCGR (glucagon receptor gene)

As GCGR is dysfunctional – massive elevation of serum glucagon levels.

But no clinical syndrome due to hyperglucagonemia – paradoxically may suffer hypoglycemia

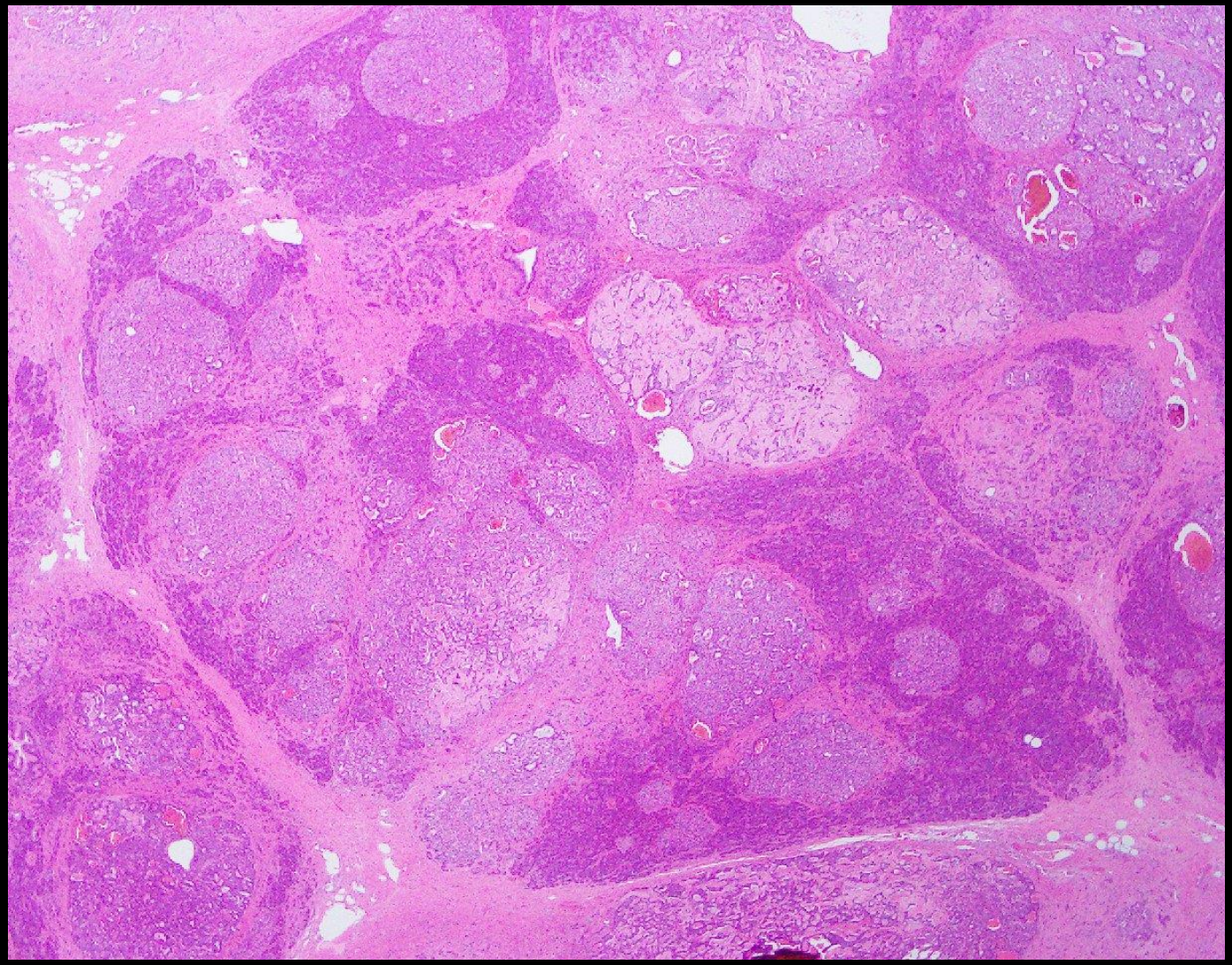
Glucagon cell adenomatosis

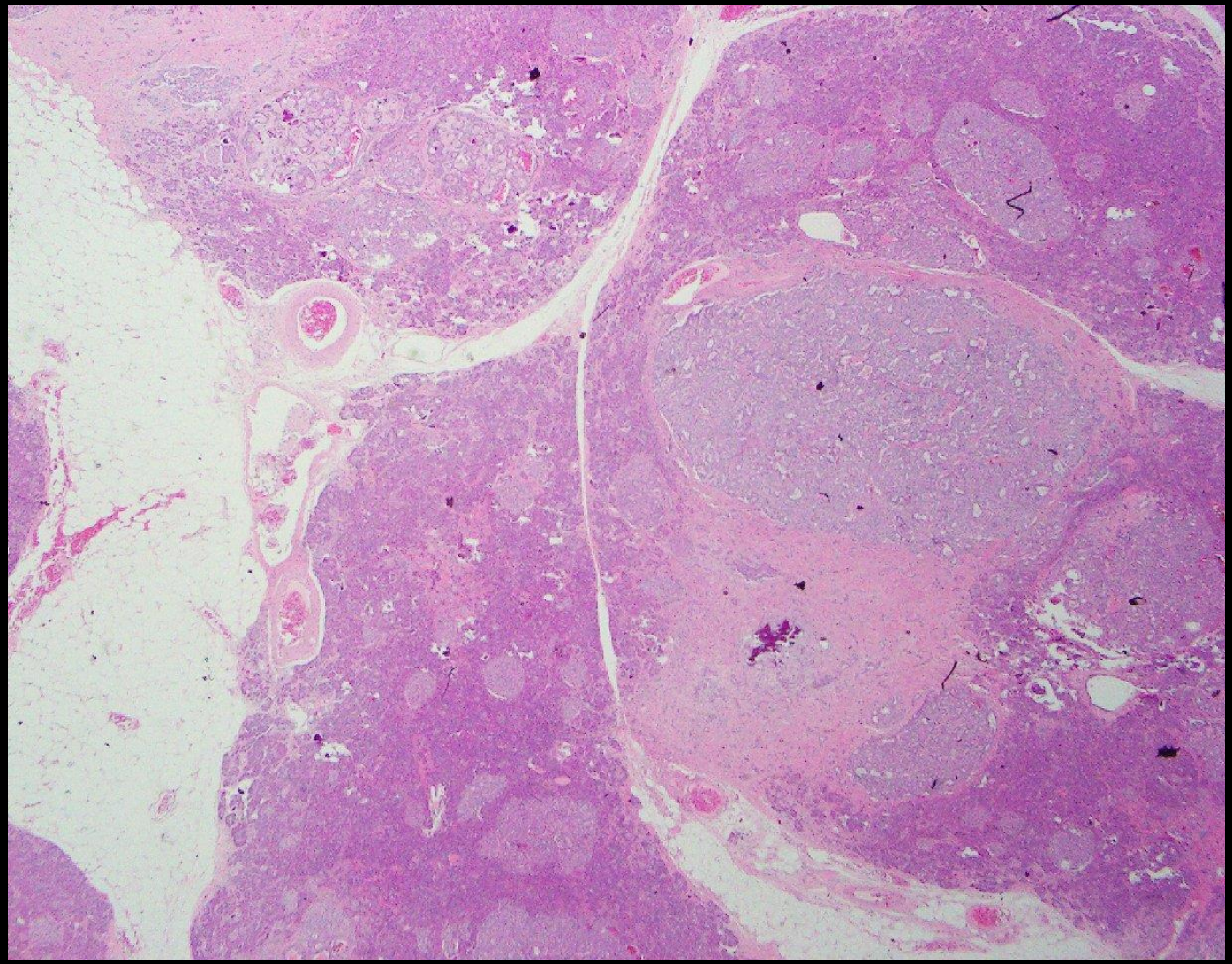
- Absence of GCGR causes a feedback loop which drives massive glucagon cell hyperplasia -> Neoplasia
- Symptoms due to multiple pancreatic tumours, direct effect of glucagon (calcificatoin),

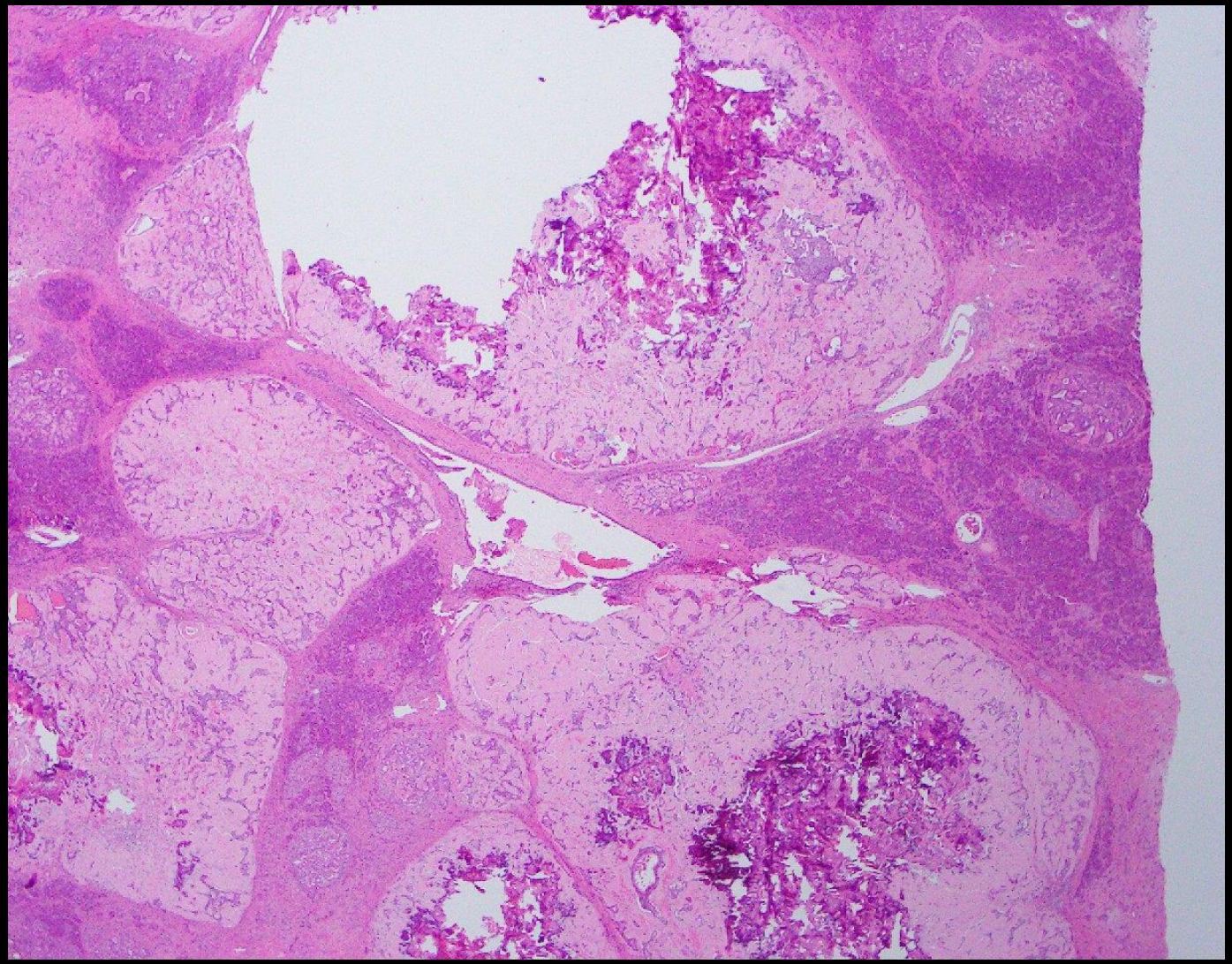

Feedback Loop
No functioning glucagon receptor
X
Massive alpha cell Hyperplasia
Massive Glucagon productions
Autonomous Microadenomas
Larger tumours
Metastatic disease

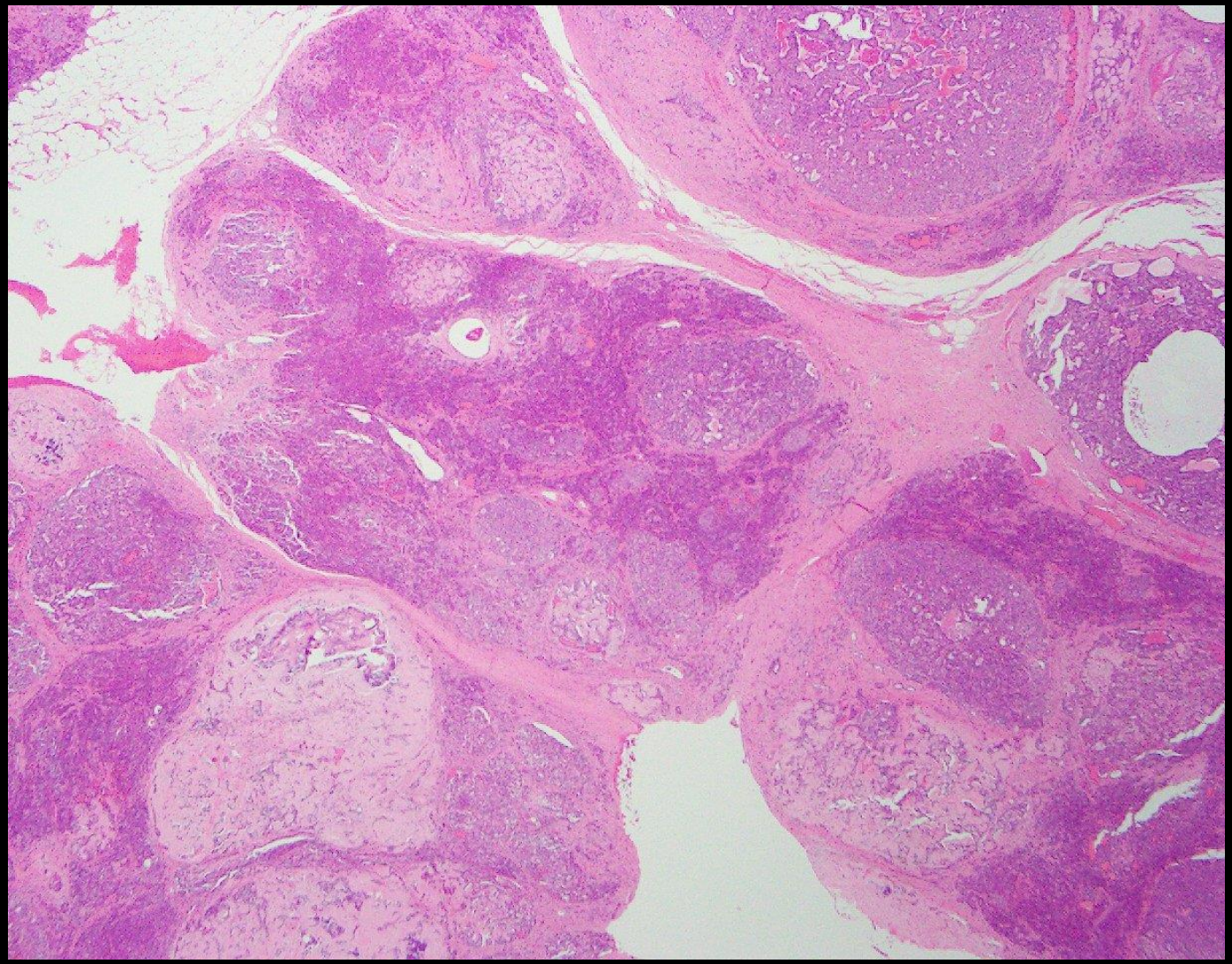

0 1 2 3 4 5
Centimeters

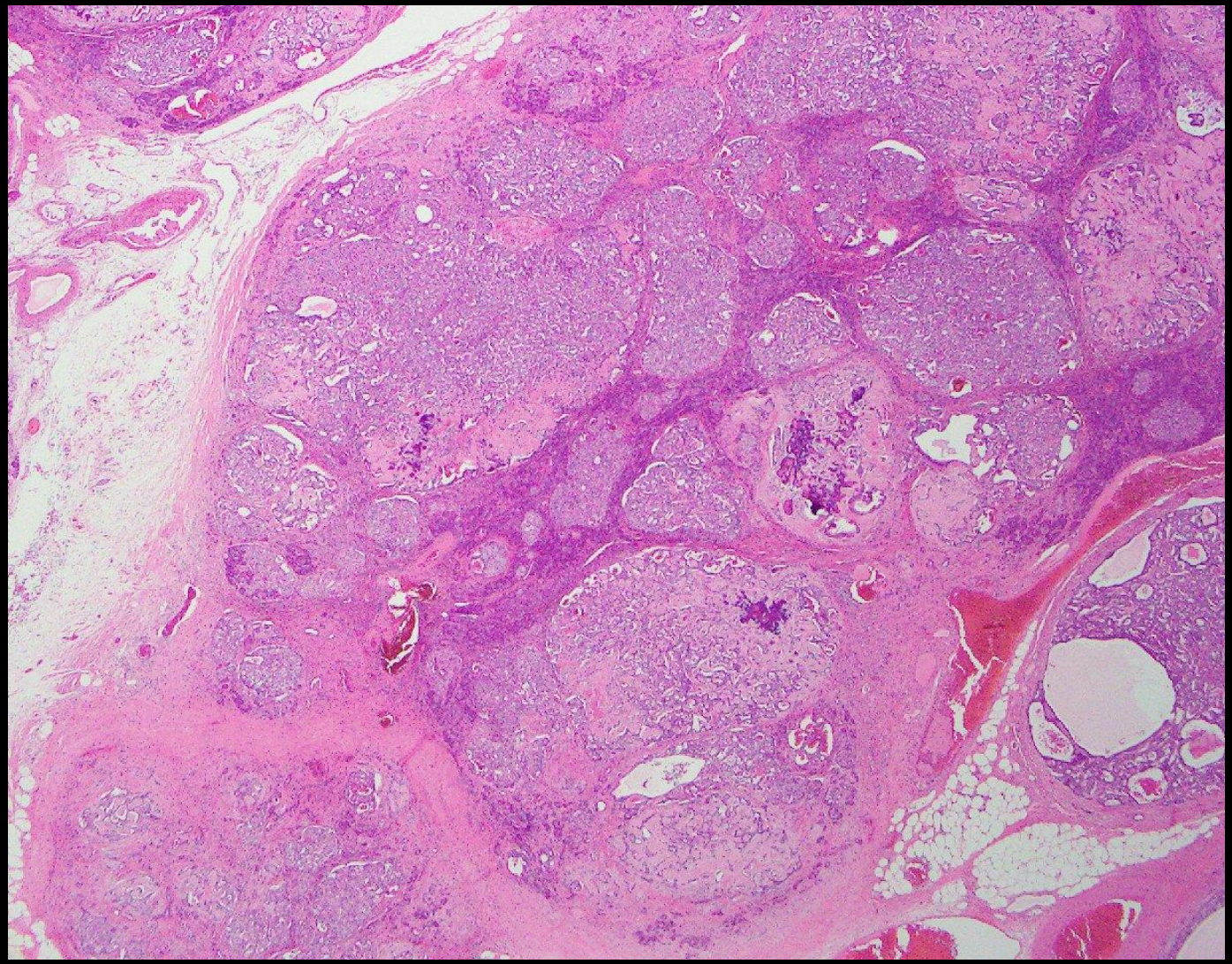

0 1 2 3 4 5
Centimeters

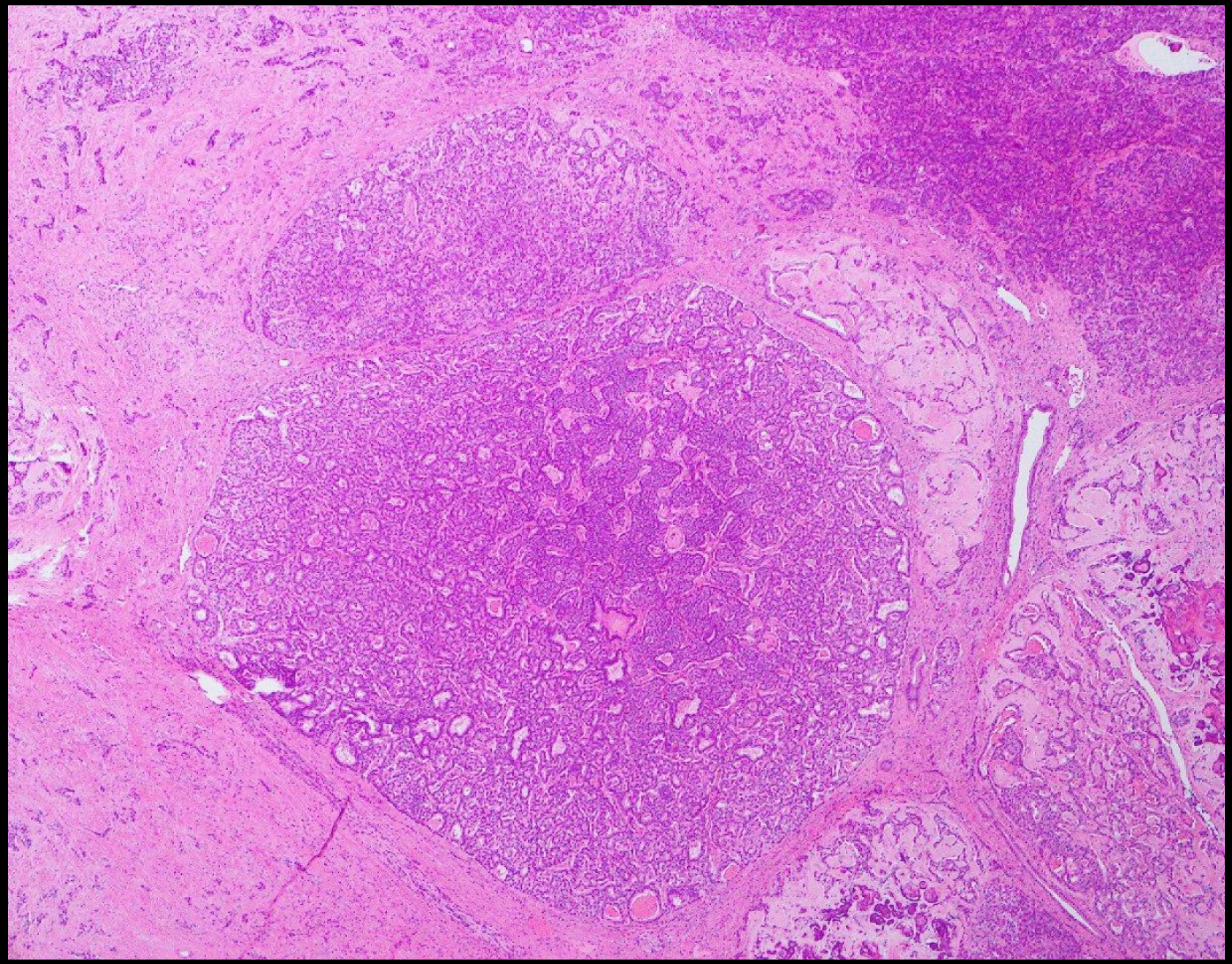


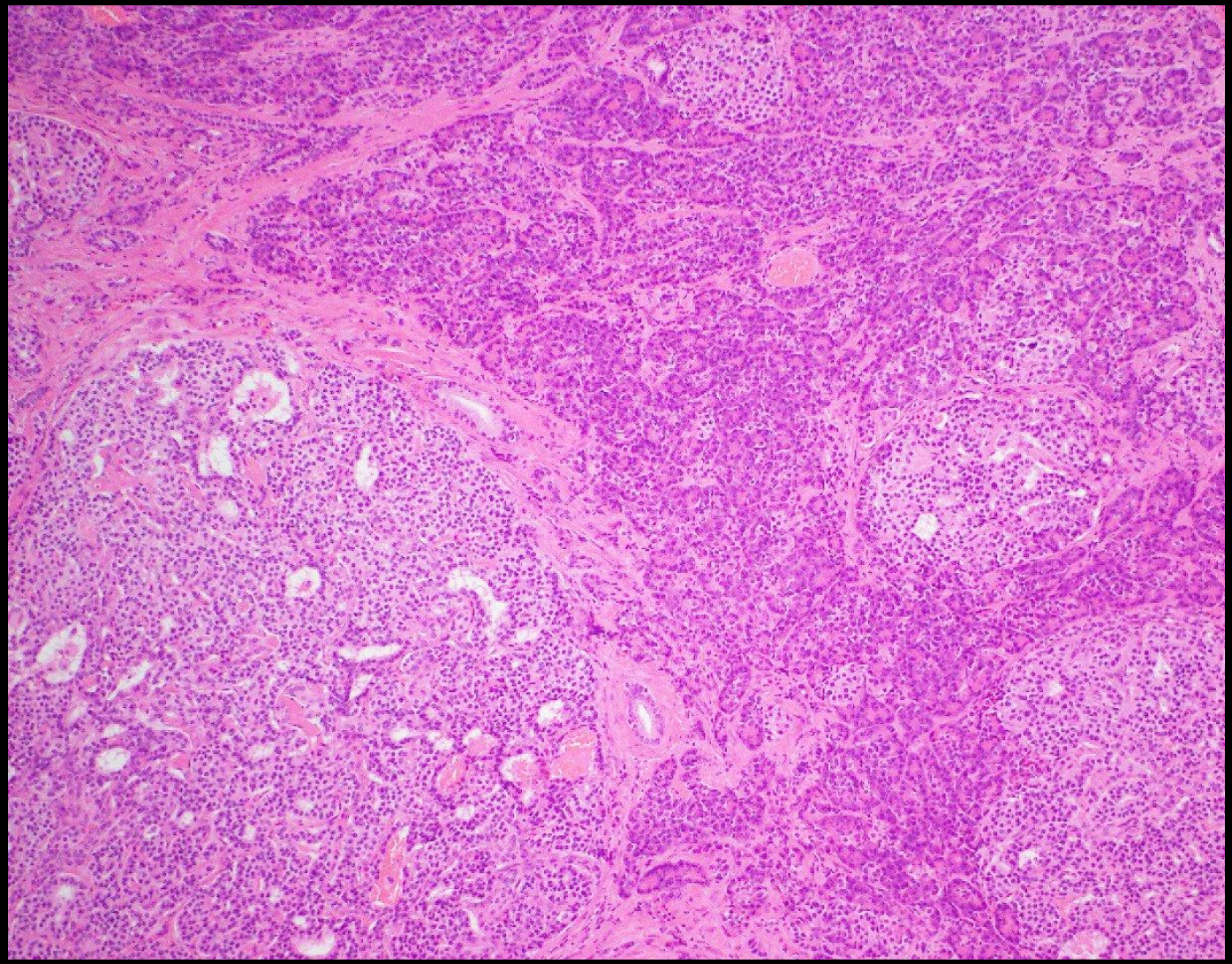


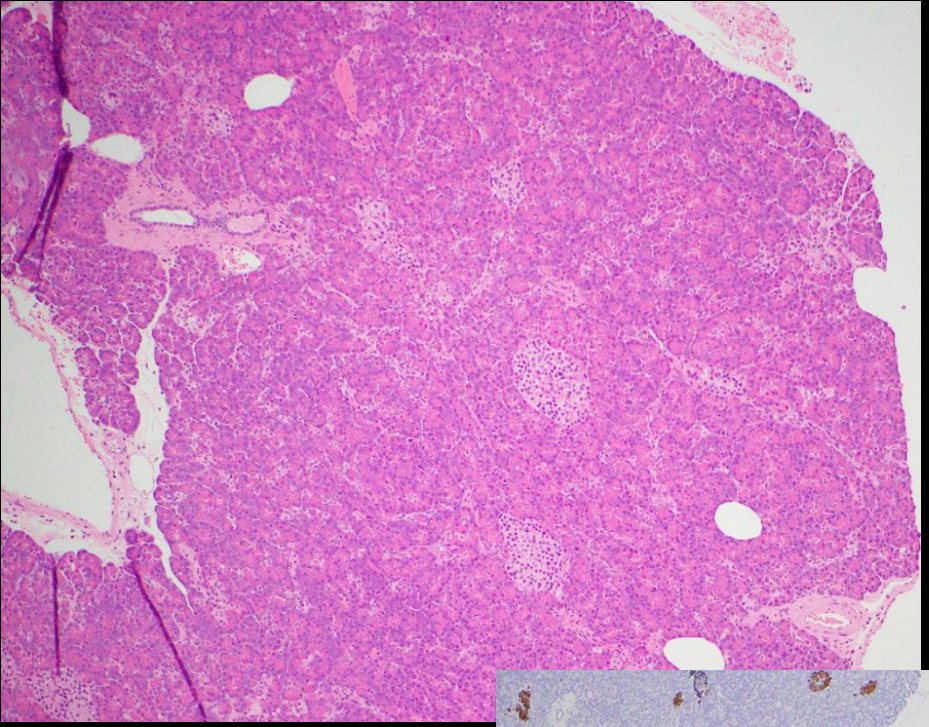


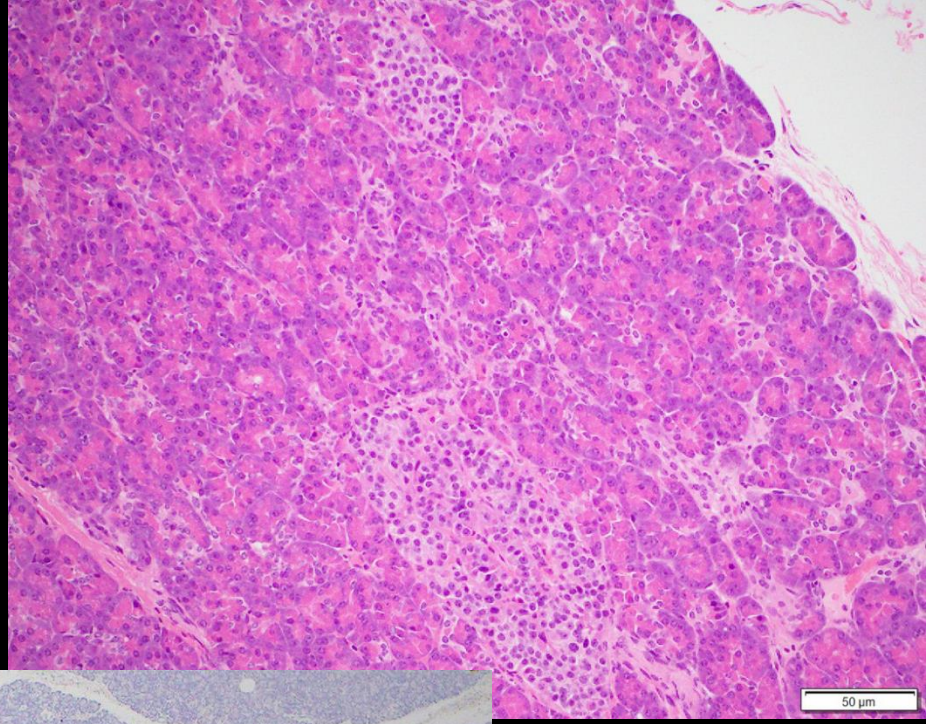


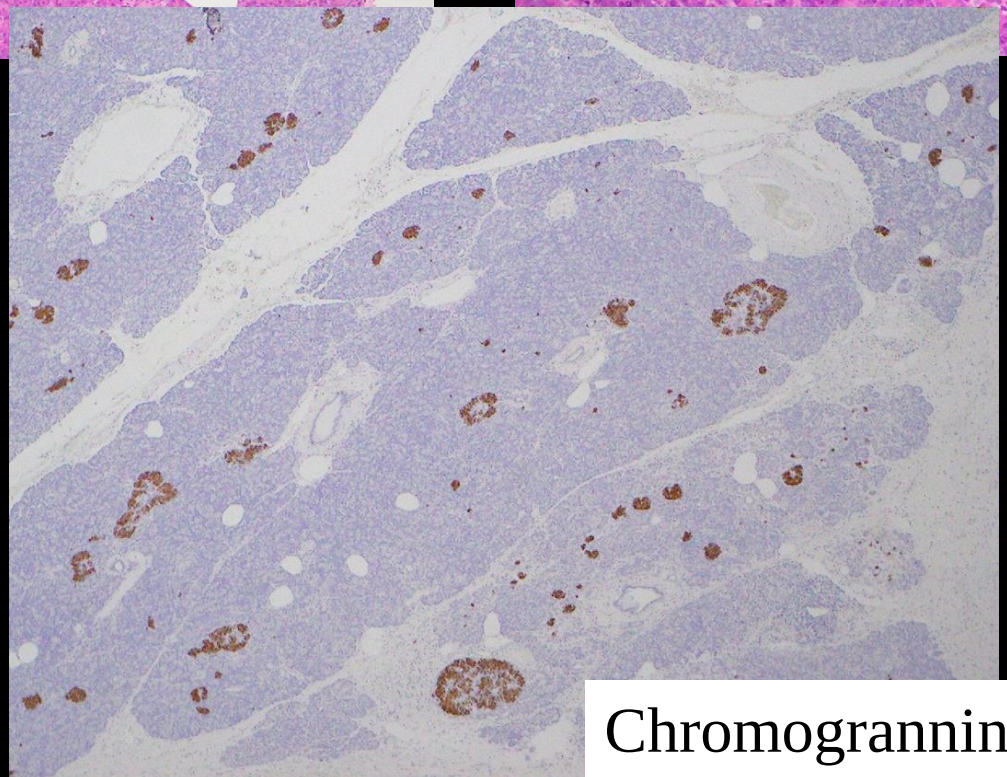




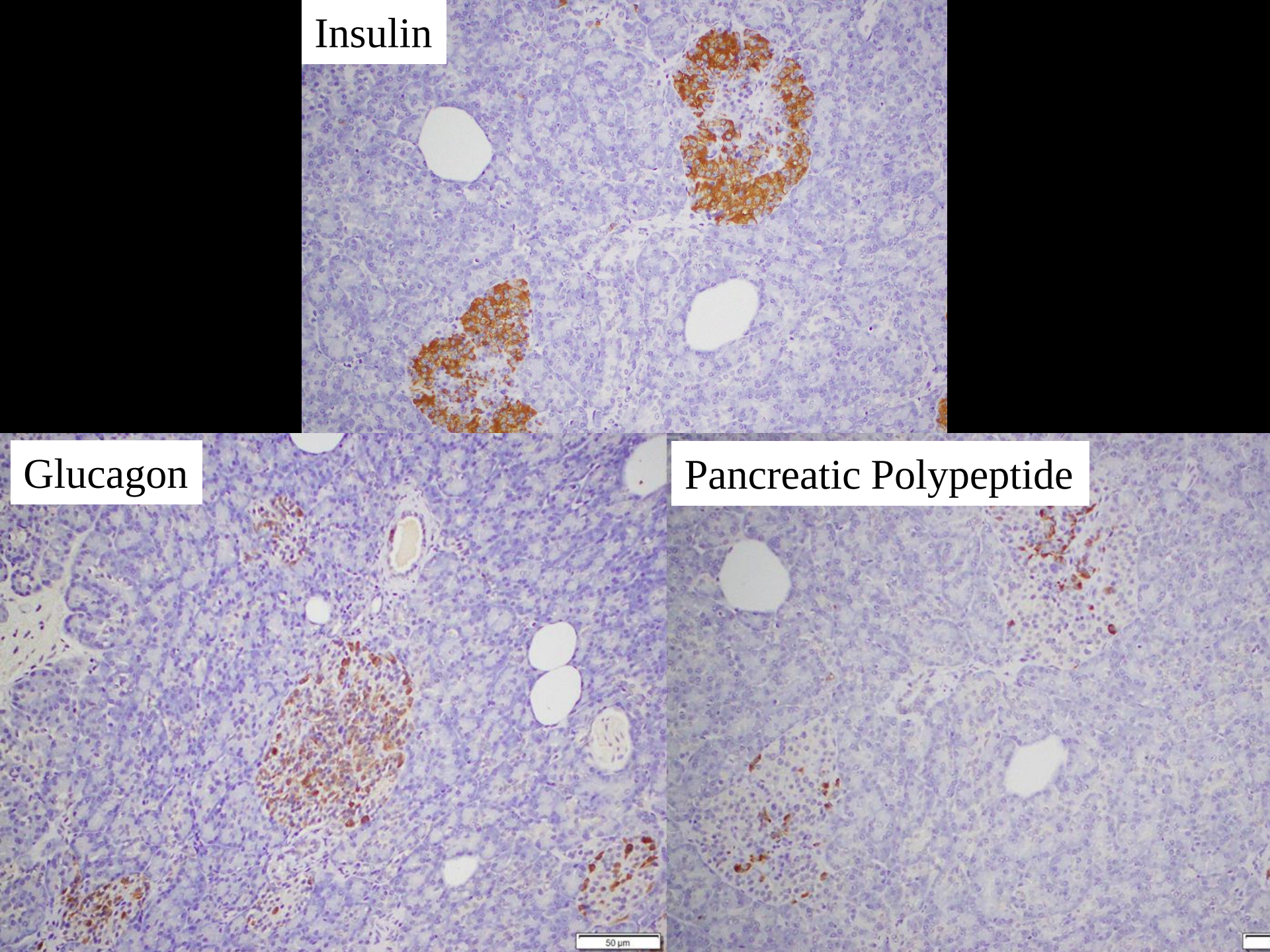




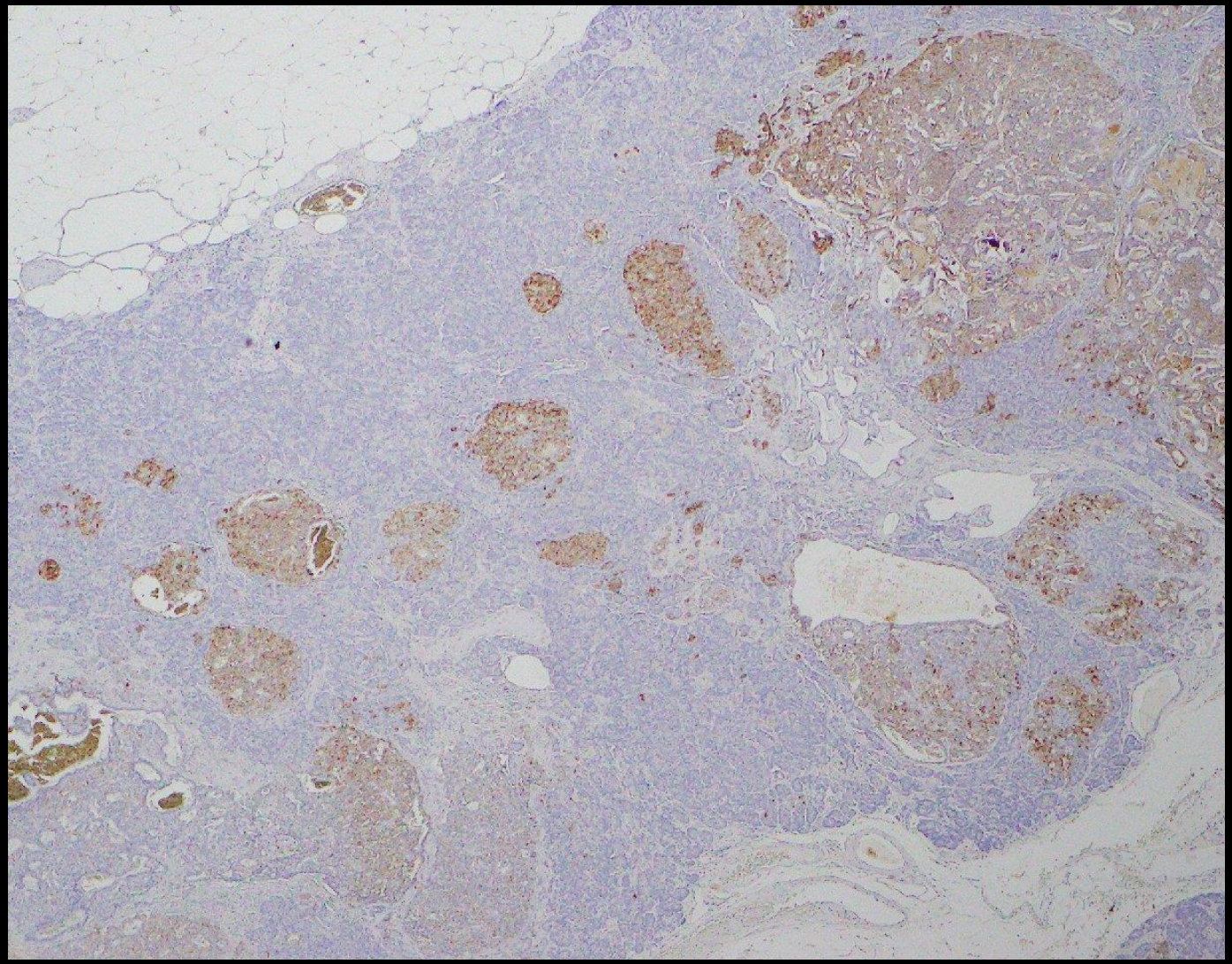




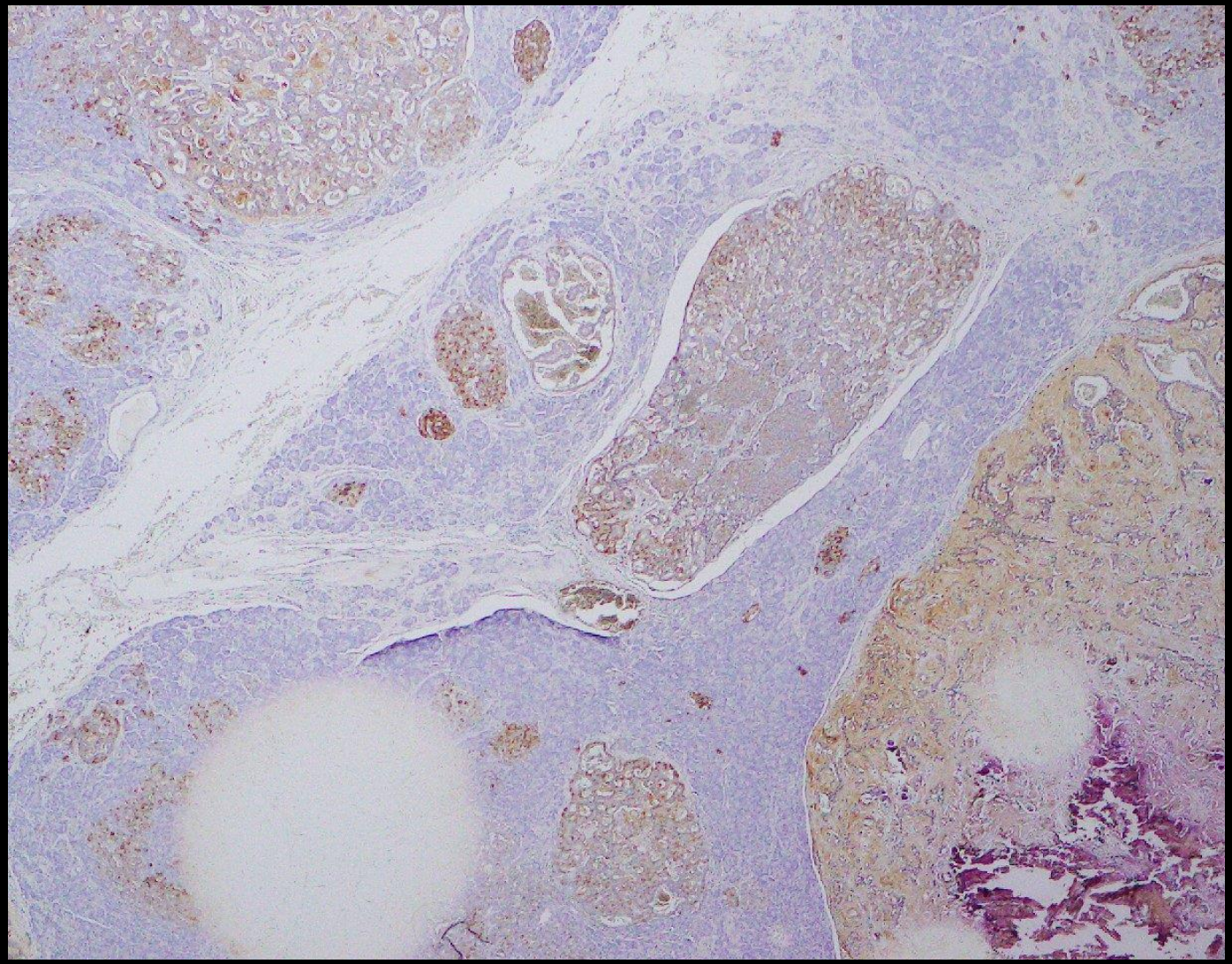
Chromogrannin


Insulin
Glucagon
Pancreatic Polypeptide
50 µm

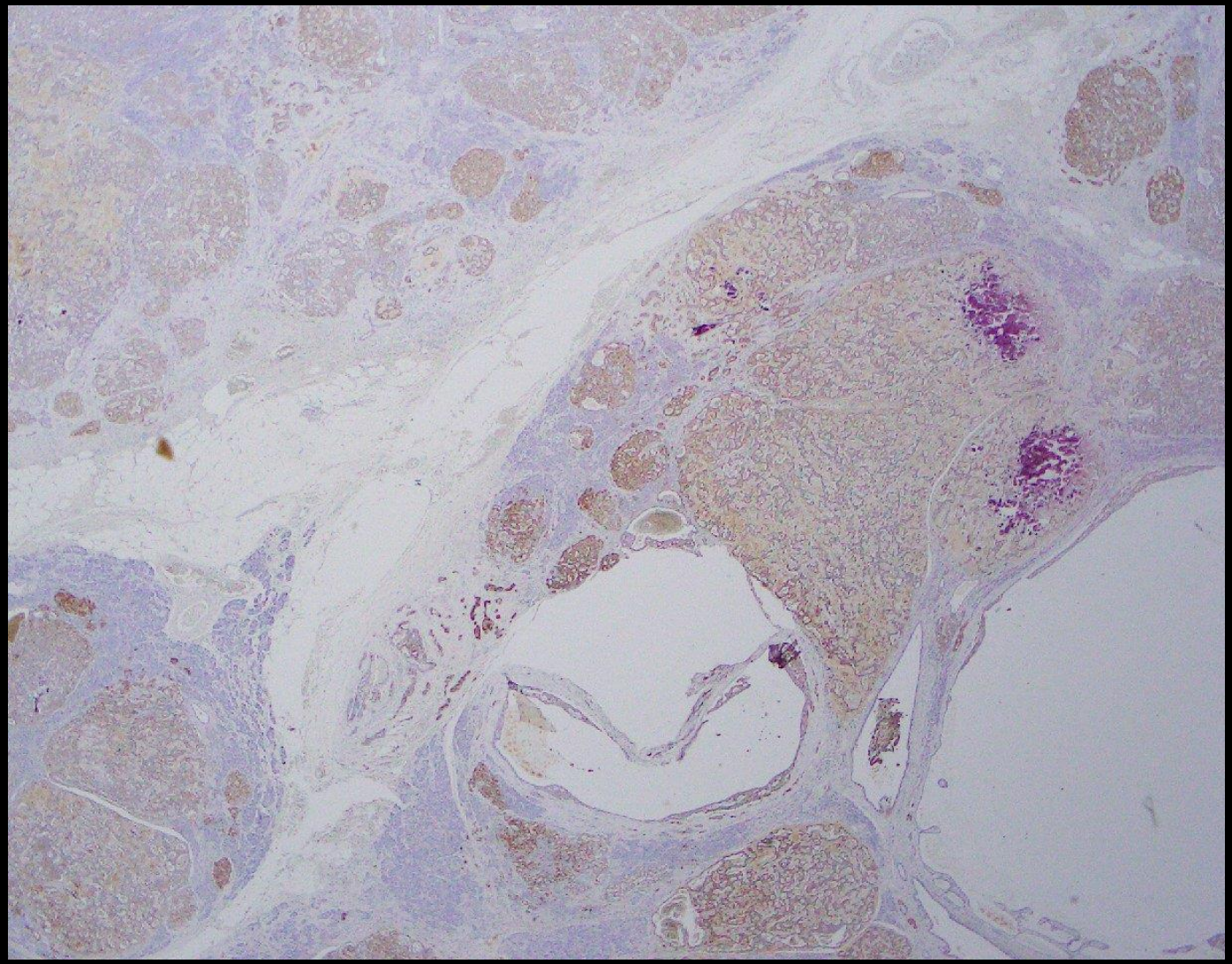
Glucagon



Glucagon

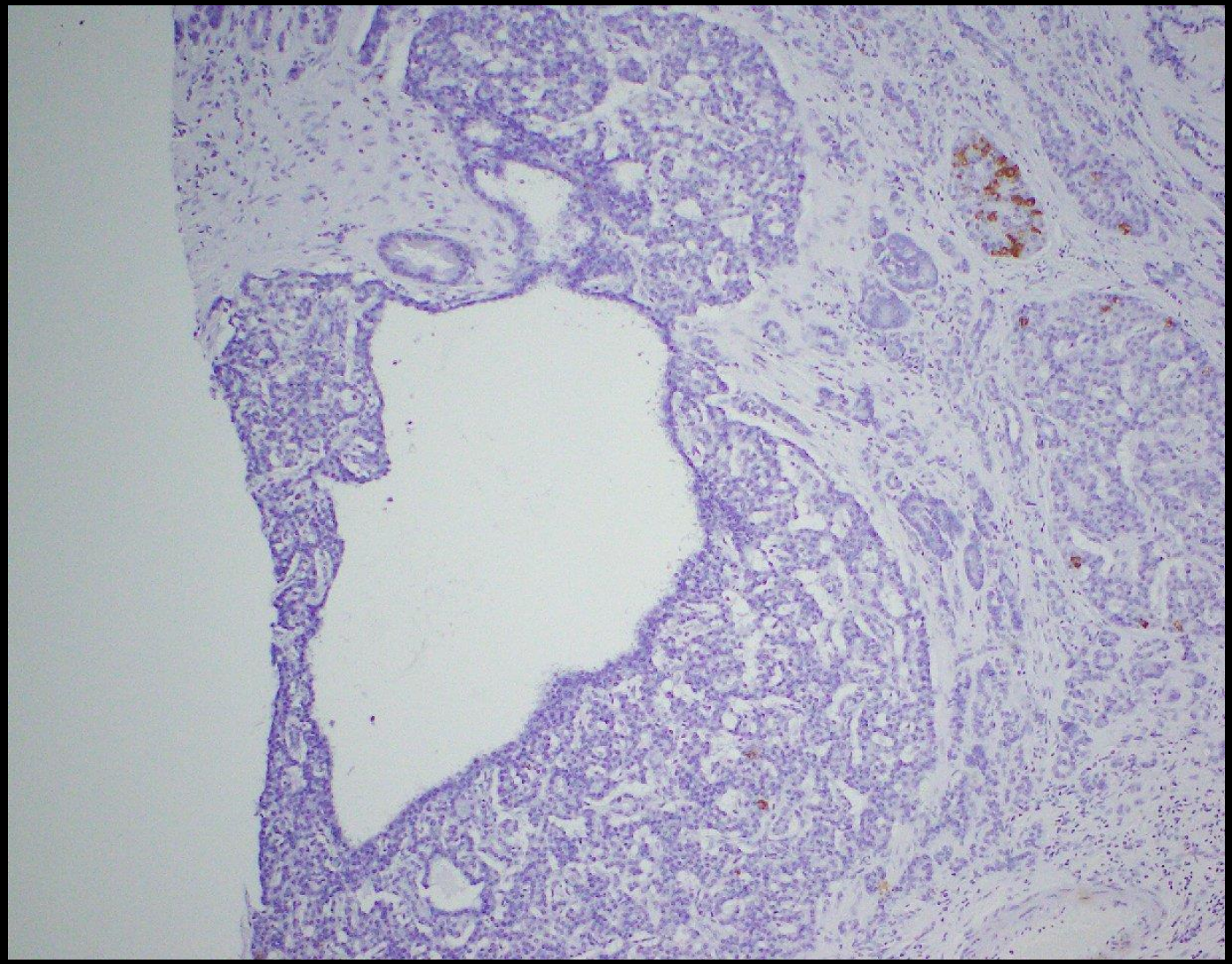


Glucagon

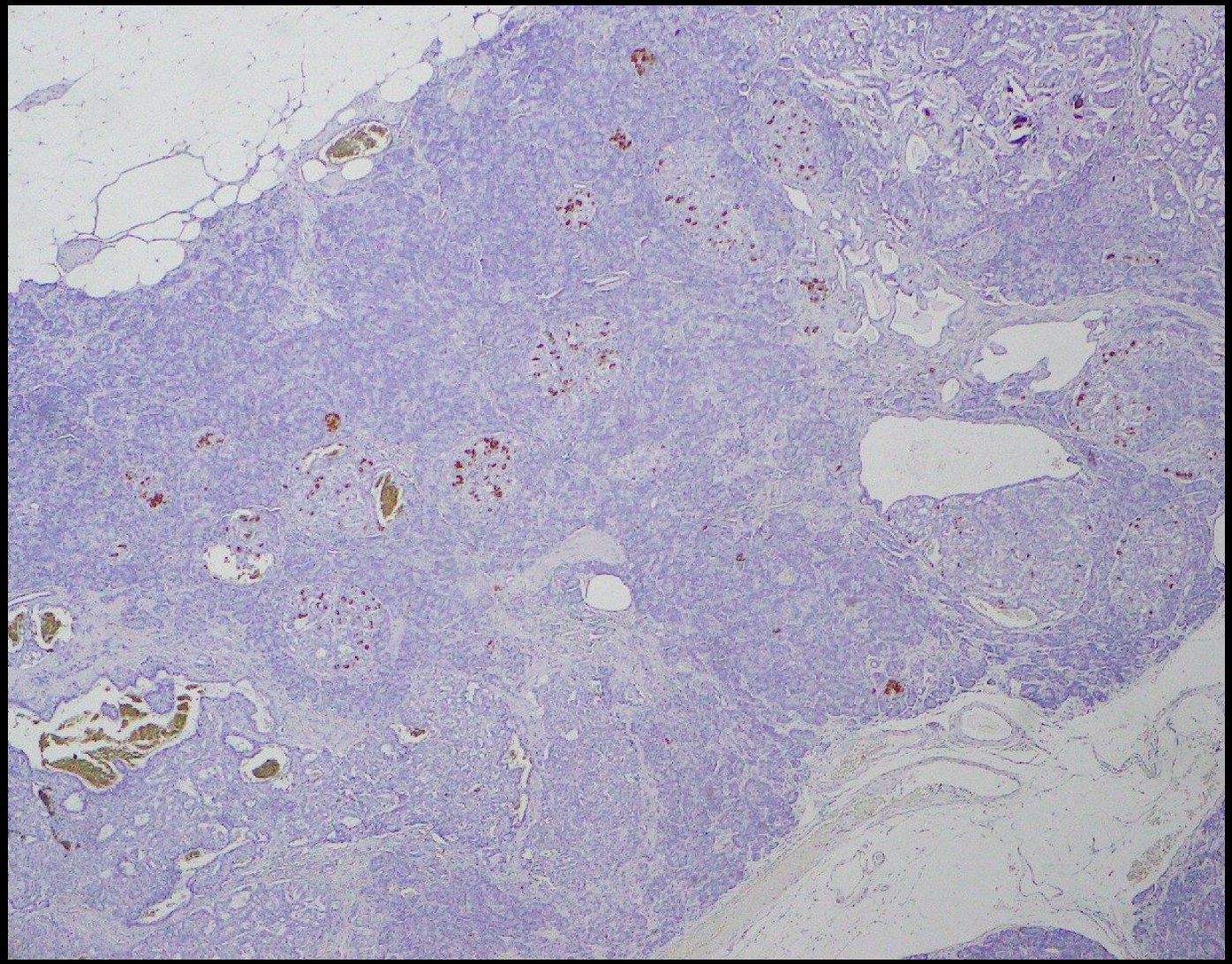



Glucagon

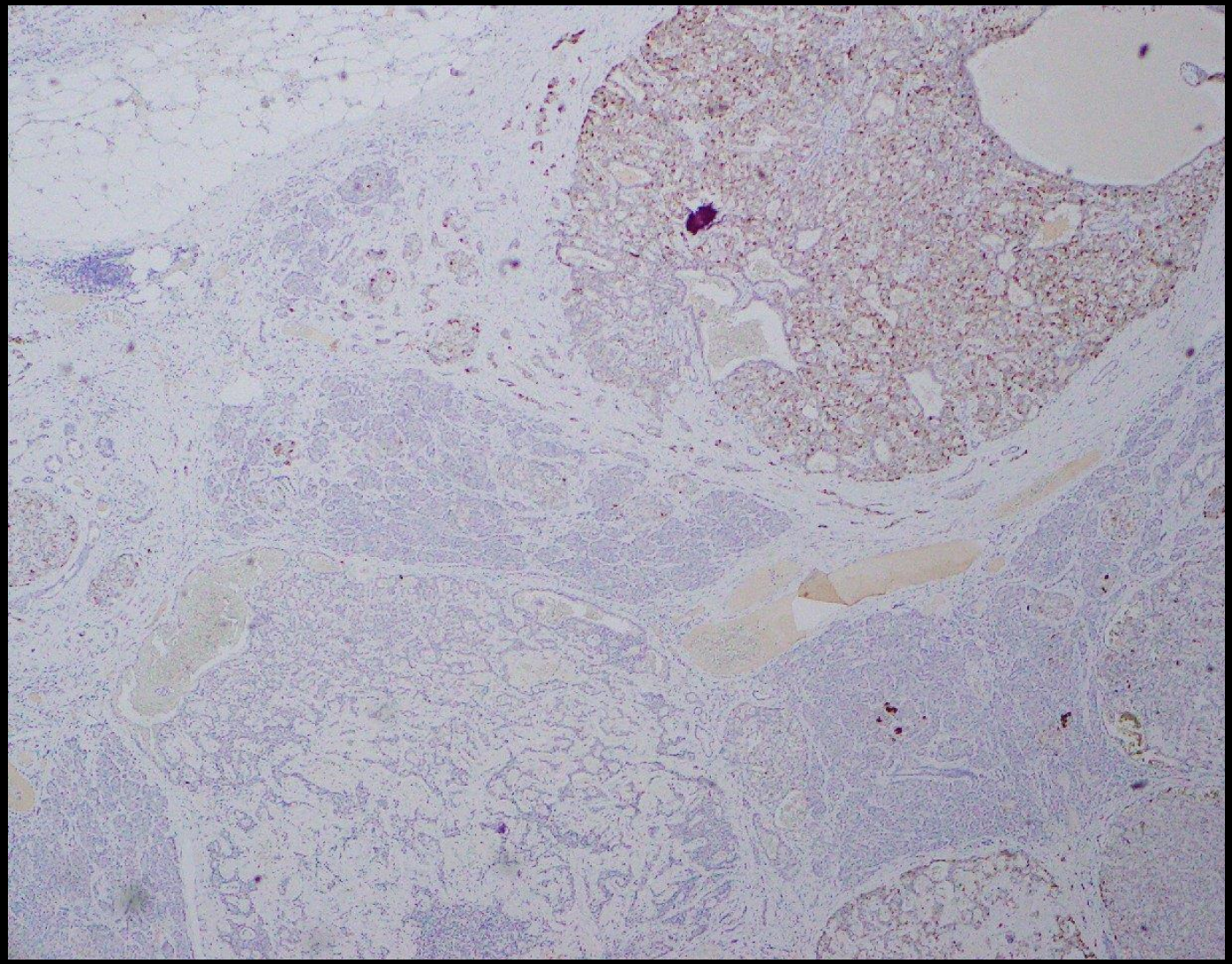
Insulin



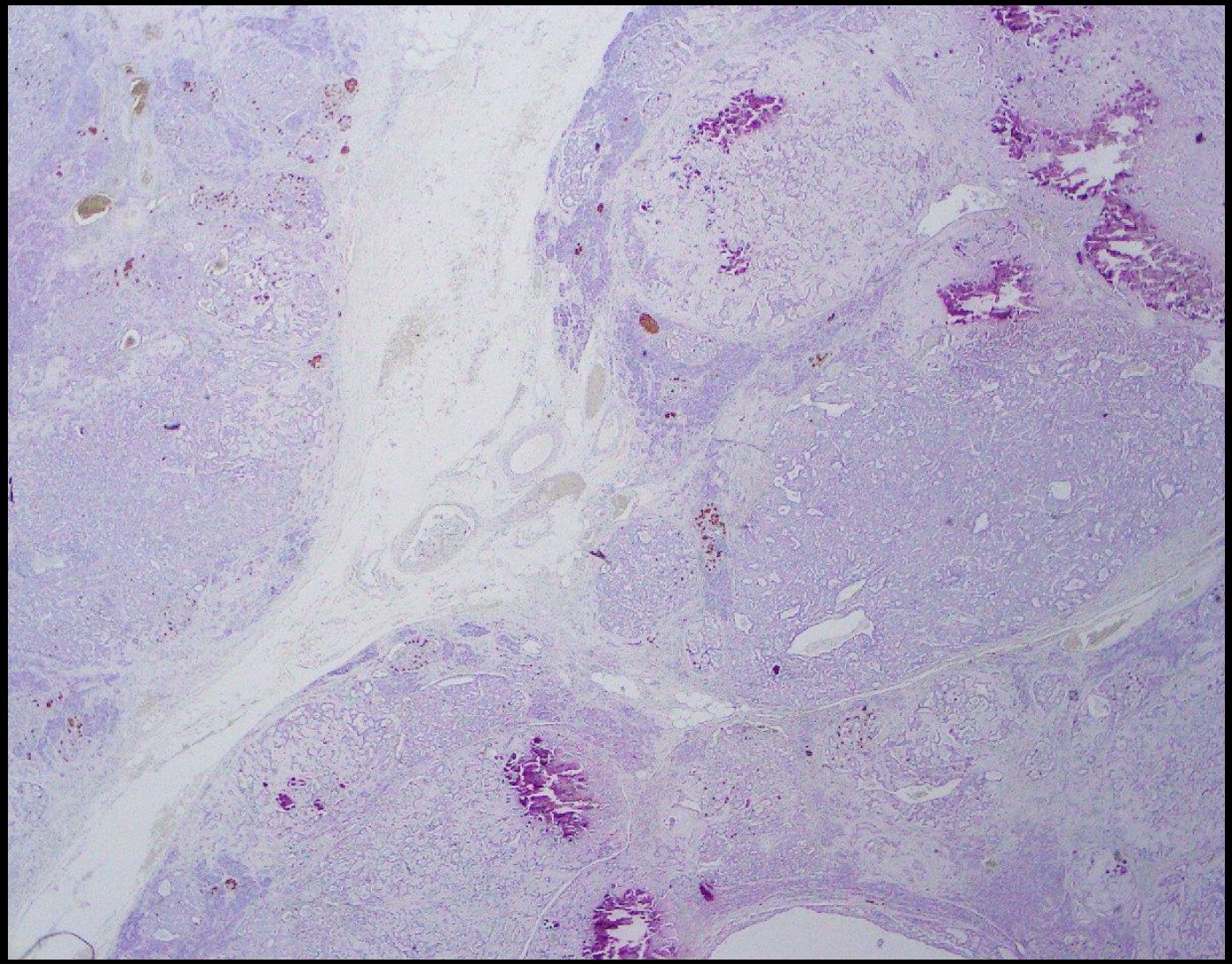
Insulin

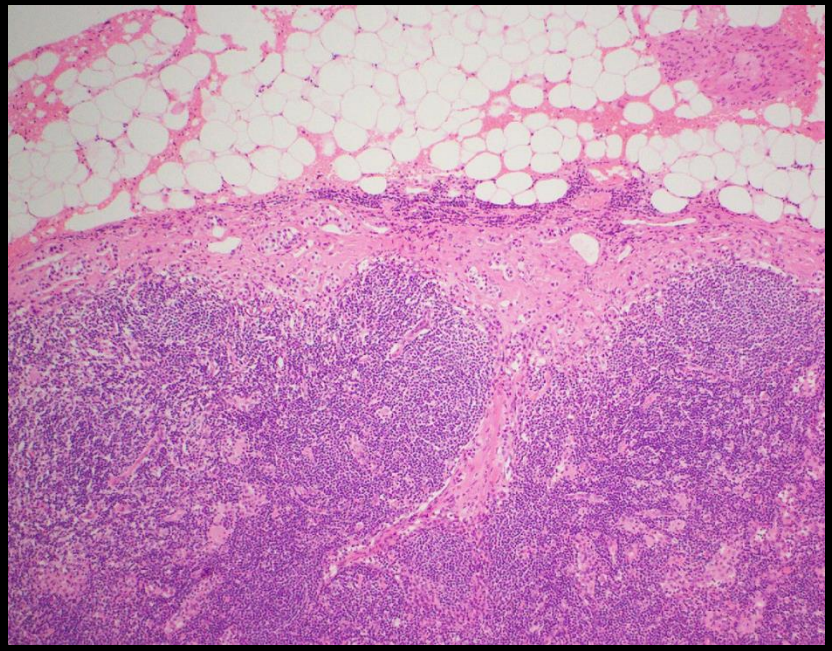


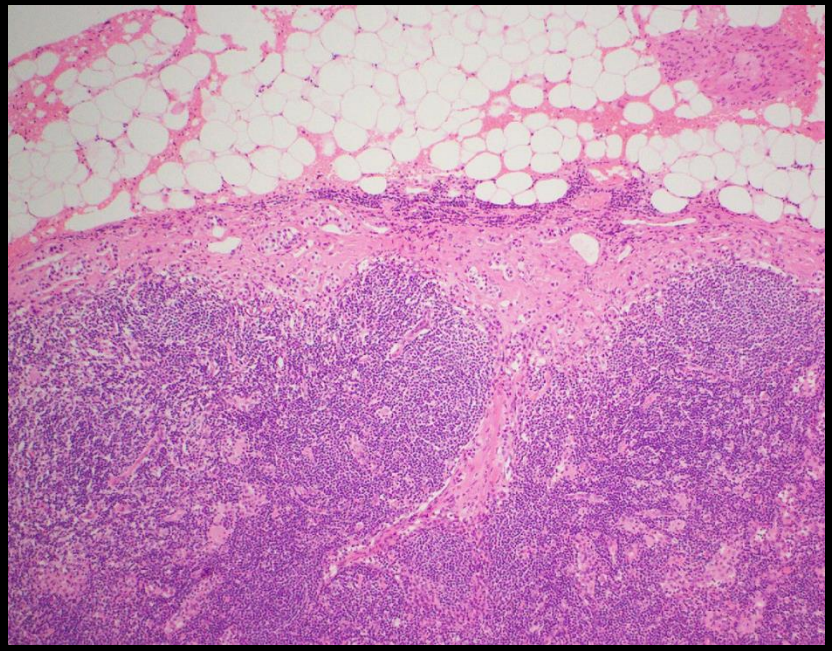
Pancreatic Polypeptide



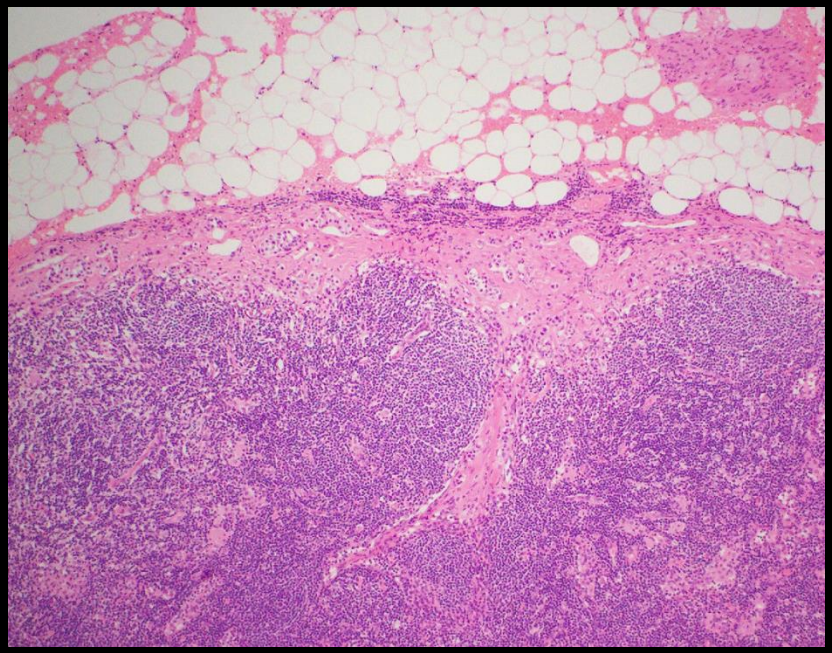
Somatostatin

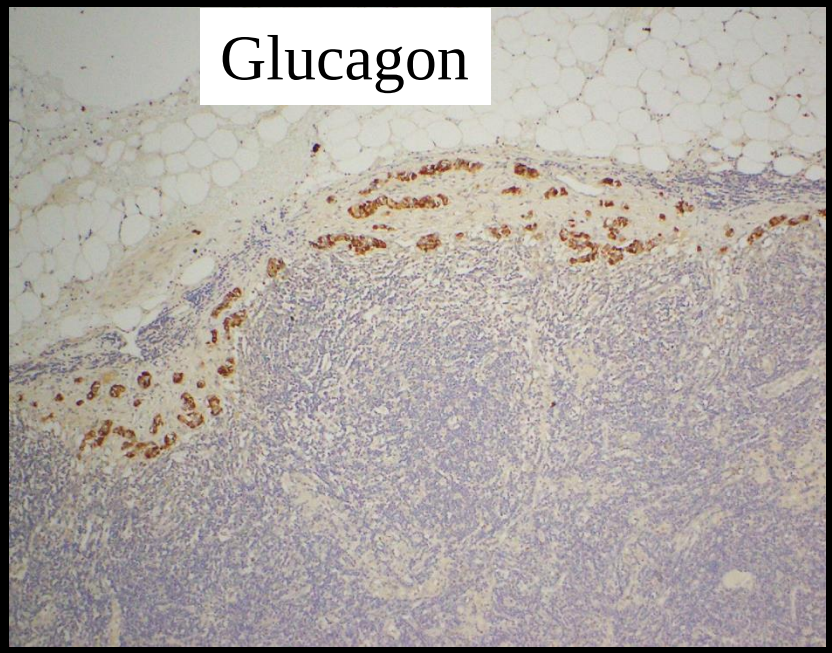


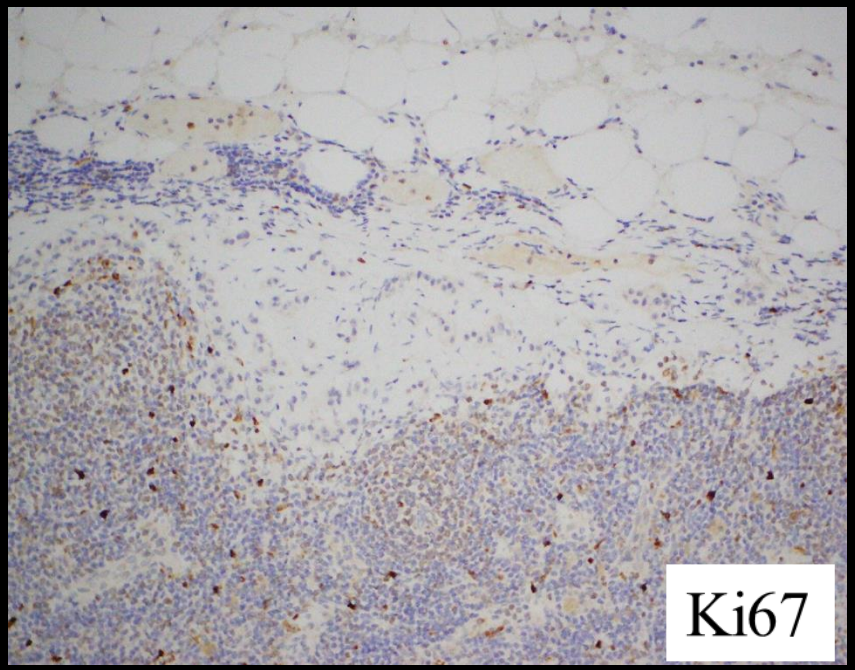


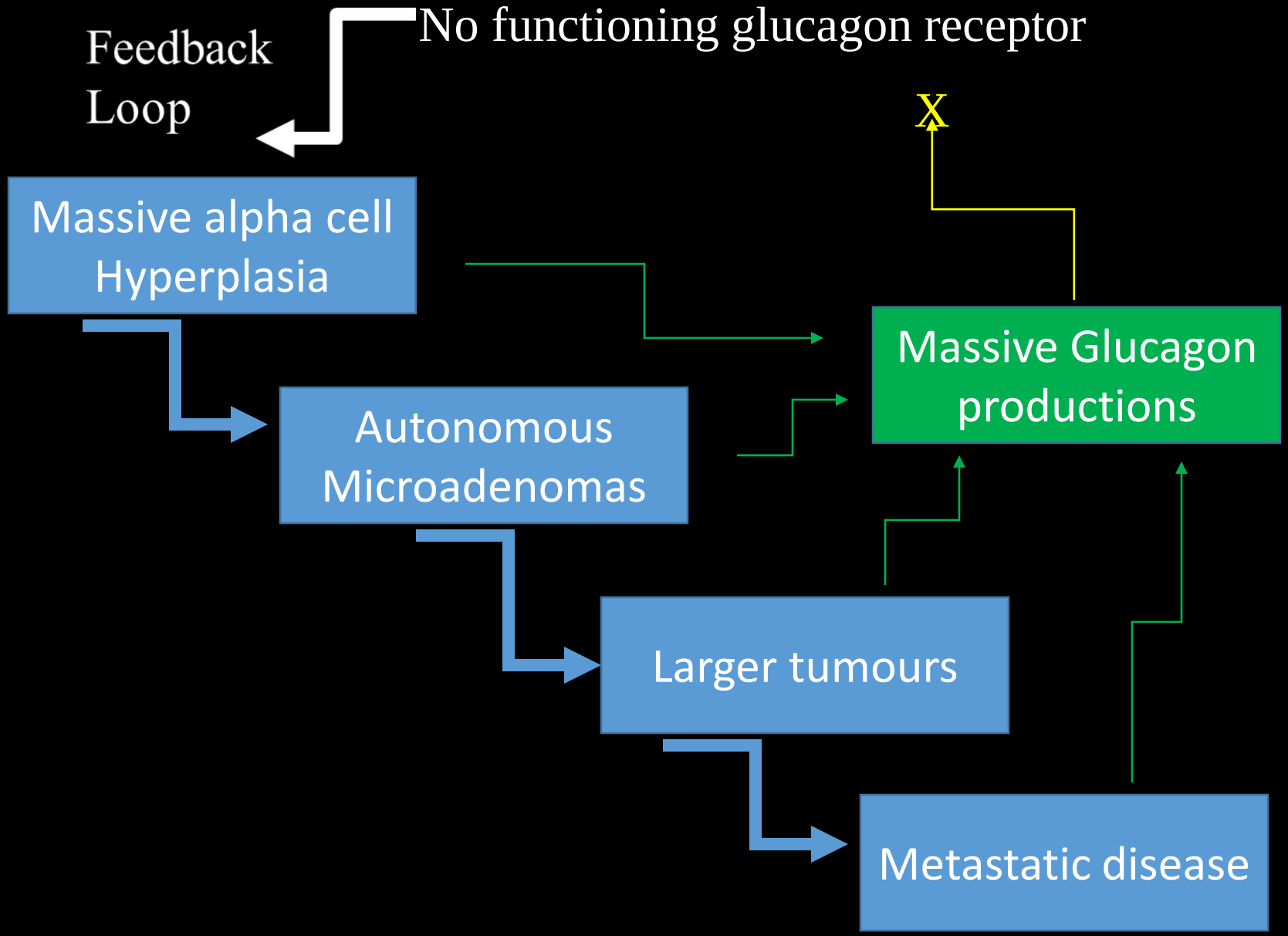



Glucagon




Glucagon


Ki67


Feedback Loop
No functioning glucagon receptor
X
Massive alpha cell Hyperplasia
Massive Glucagon productions
Autonomous Microadenomas
Larger tumours
Metastatic disease

Glucagon cell adenomatosis

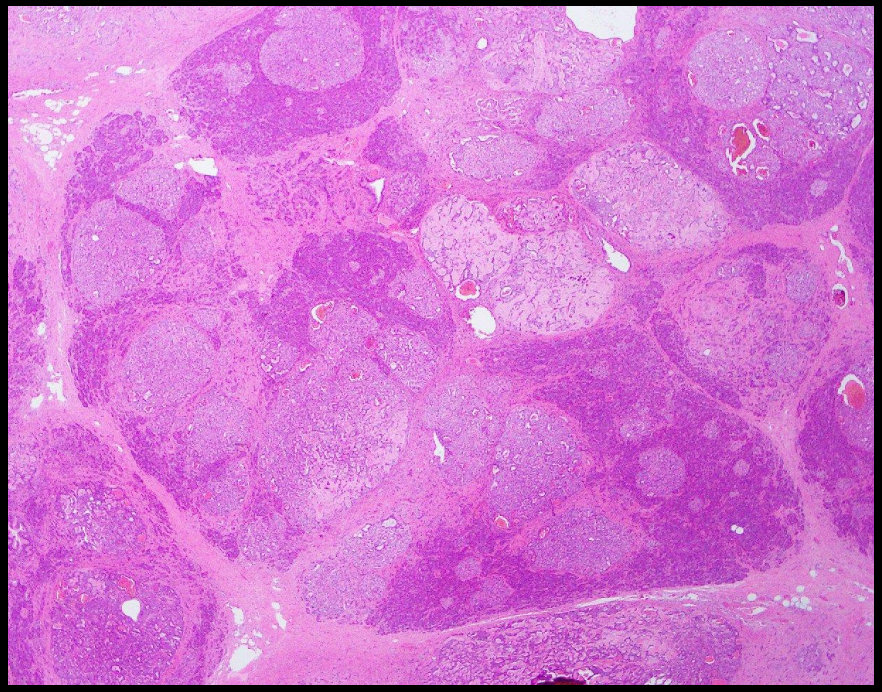
Clinical features

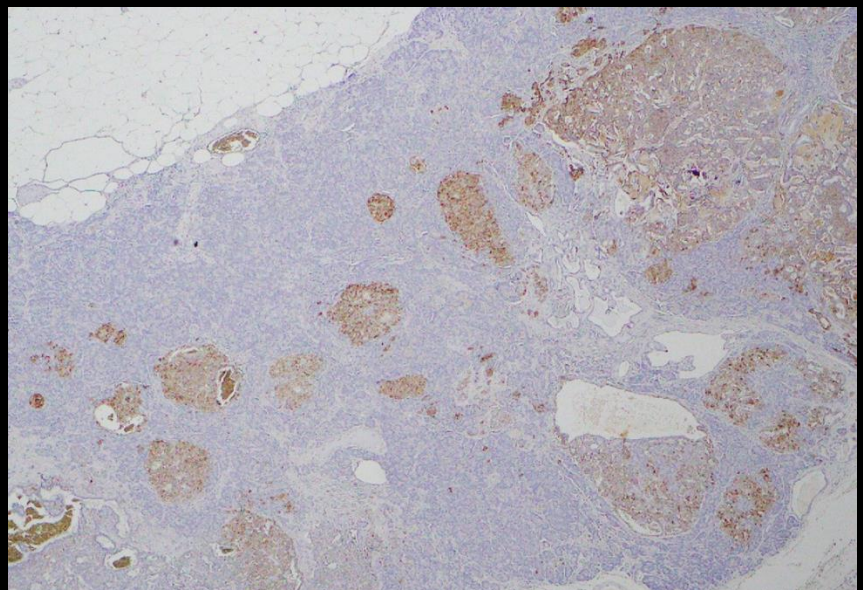
- Massive hyperglucagonemia
- However, no symptoms due to hyperglucagonomemia in fact may develop hypoglycemia

Pathological features

- Multiple (sometimes hundreds) of glucagon producing tumours
- Arise in a background of alpha-cell-hyperplasia progressing to neoplasia
- Glucagon IHC is definitive (panc polypeptide may also be produced)
- Although metastasis occurs commonly, ki67 index is very low

Glucagon cell adenomatosis





Consider whenever multiple glucagon producing tumours or widespread hyperplasia and not MEN1

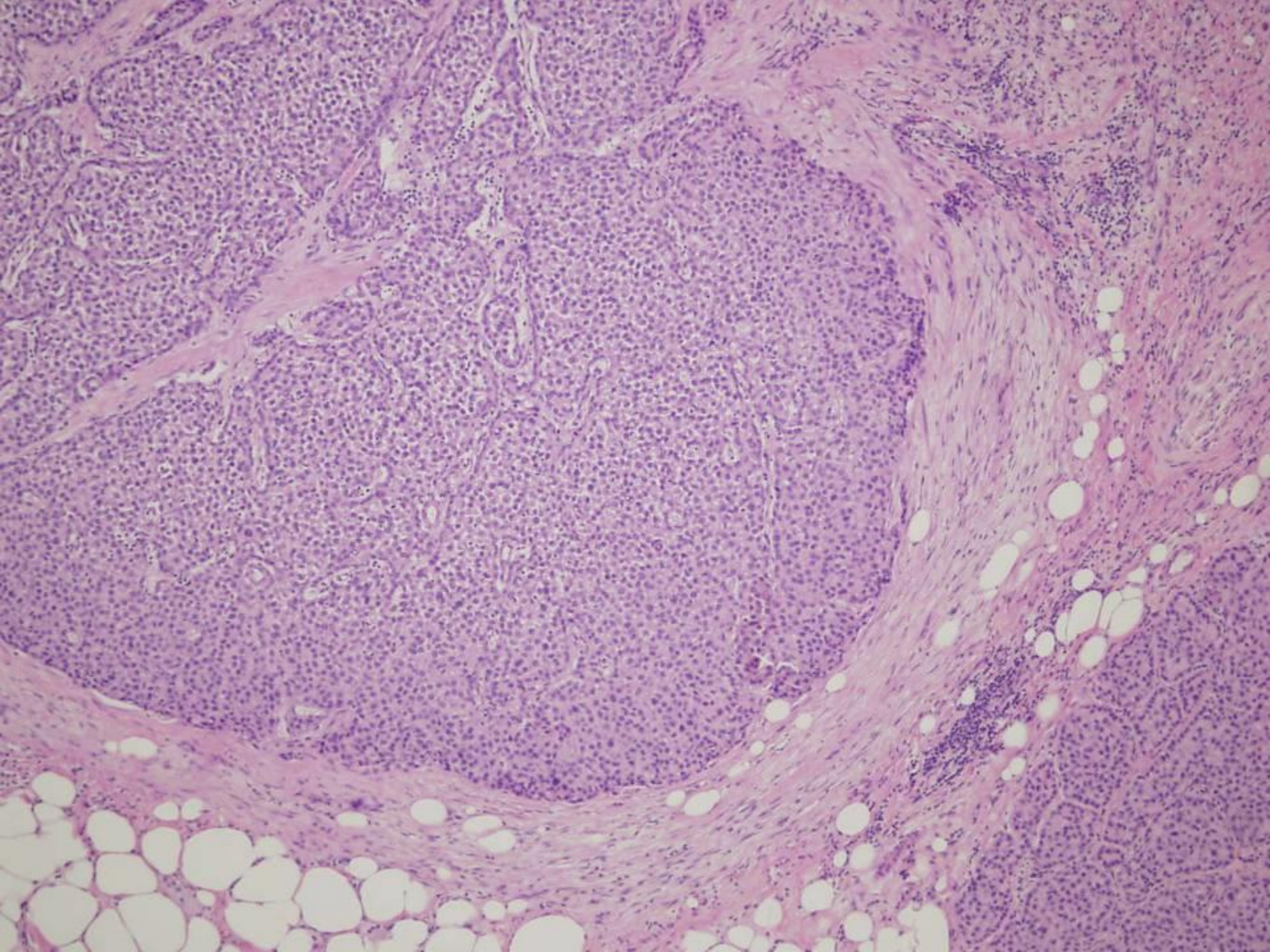
Acinar Cell Carcinoma

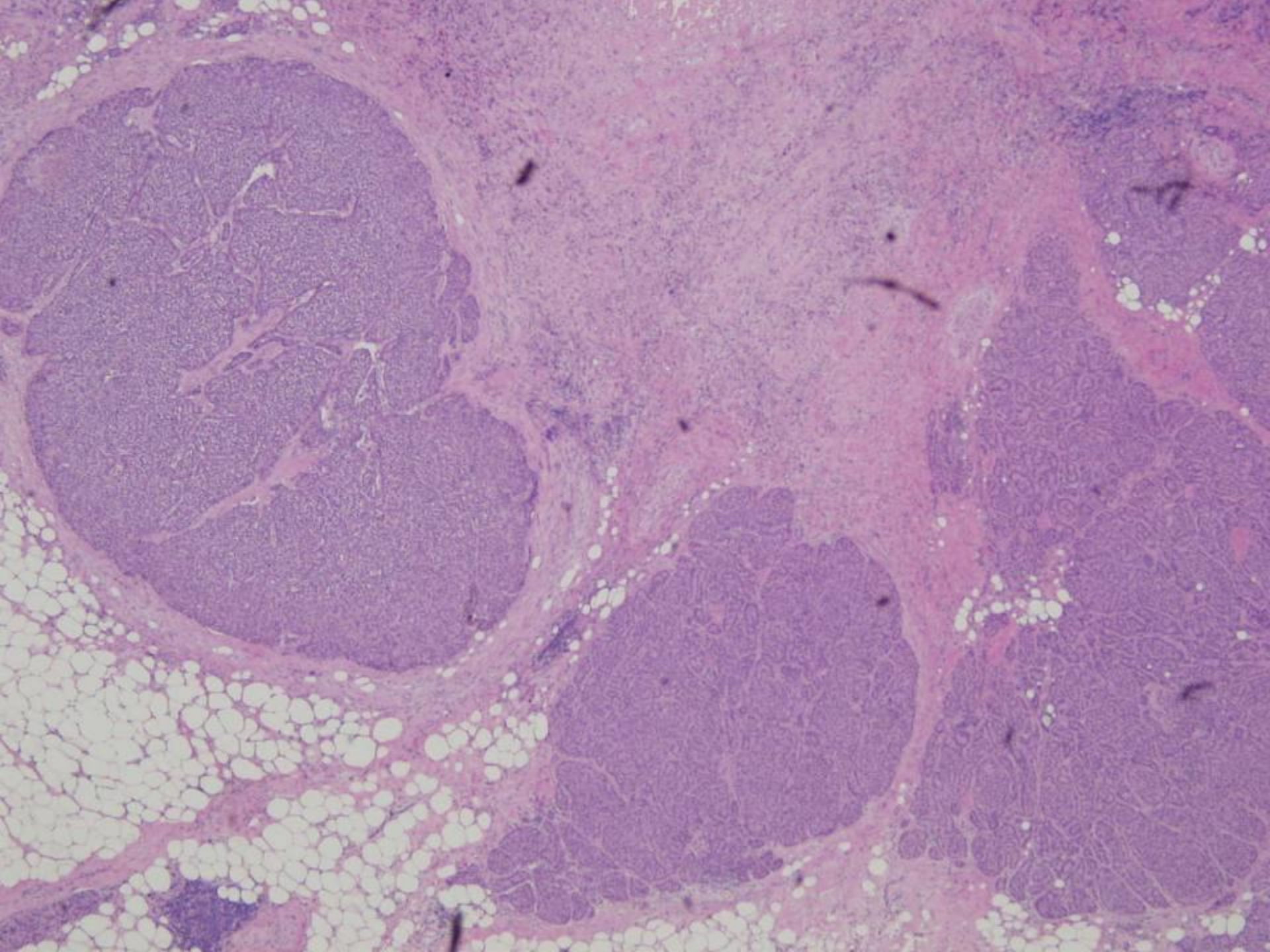
2% of ICGC pancreatic cancer cases

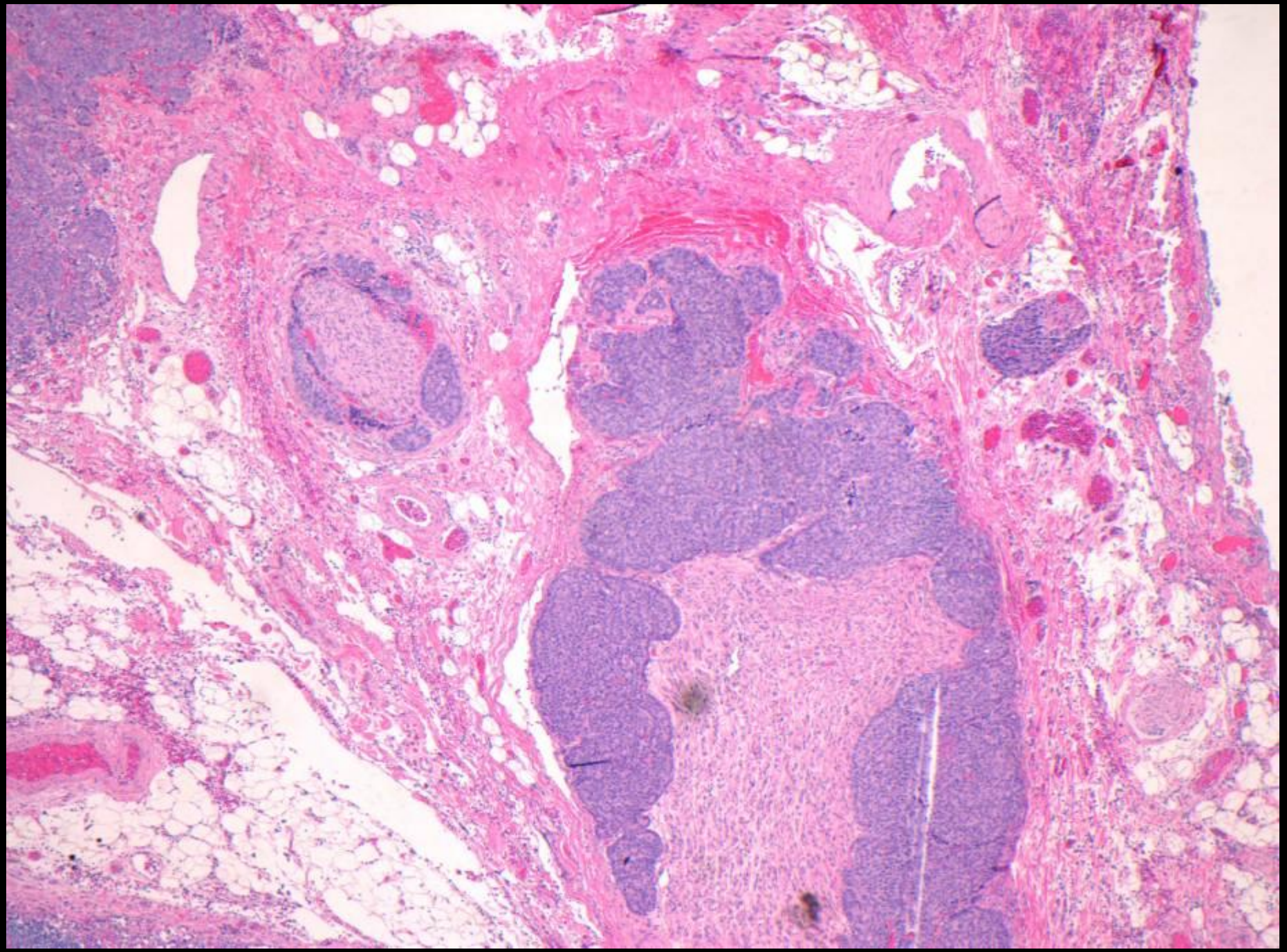
Commonly presents as a tumour which looks like a NET but is negative for chromogrannin

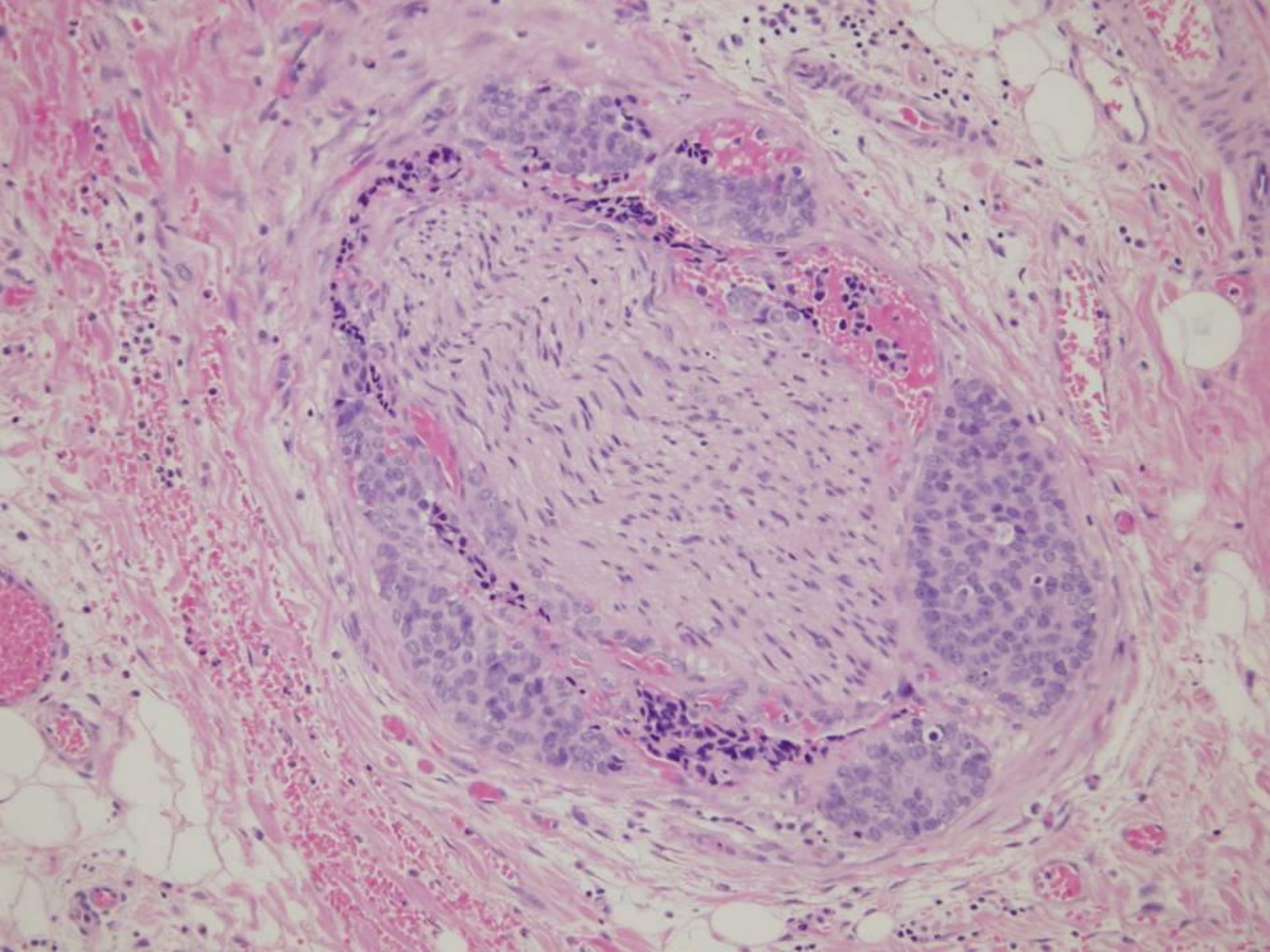
MICROSCOPIC FEATURES

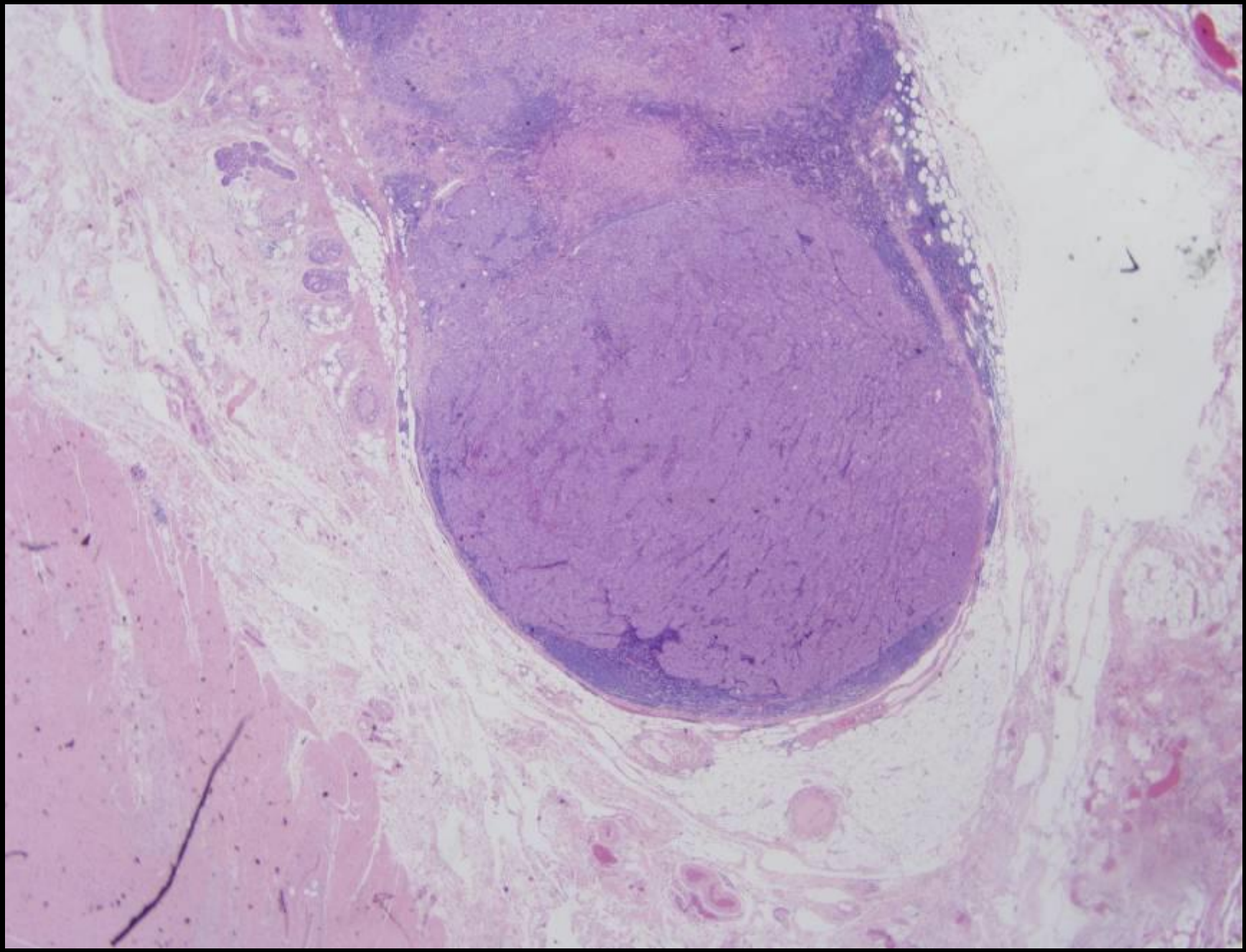
- Solid to trebecular arrangement of cells with acinar formation.
- The cells have abundant eosinophilic cytoplam, round to oval nuclei and prominent nucleoli.
- Not much pleomorphism.
- Infitrative borders.
- Rare mitoses

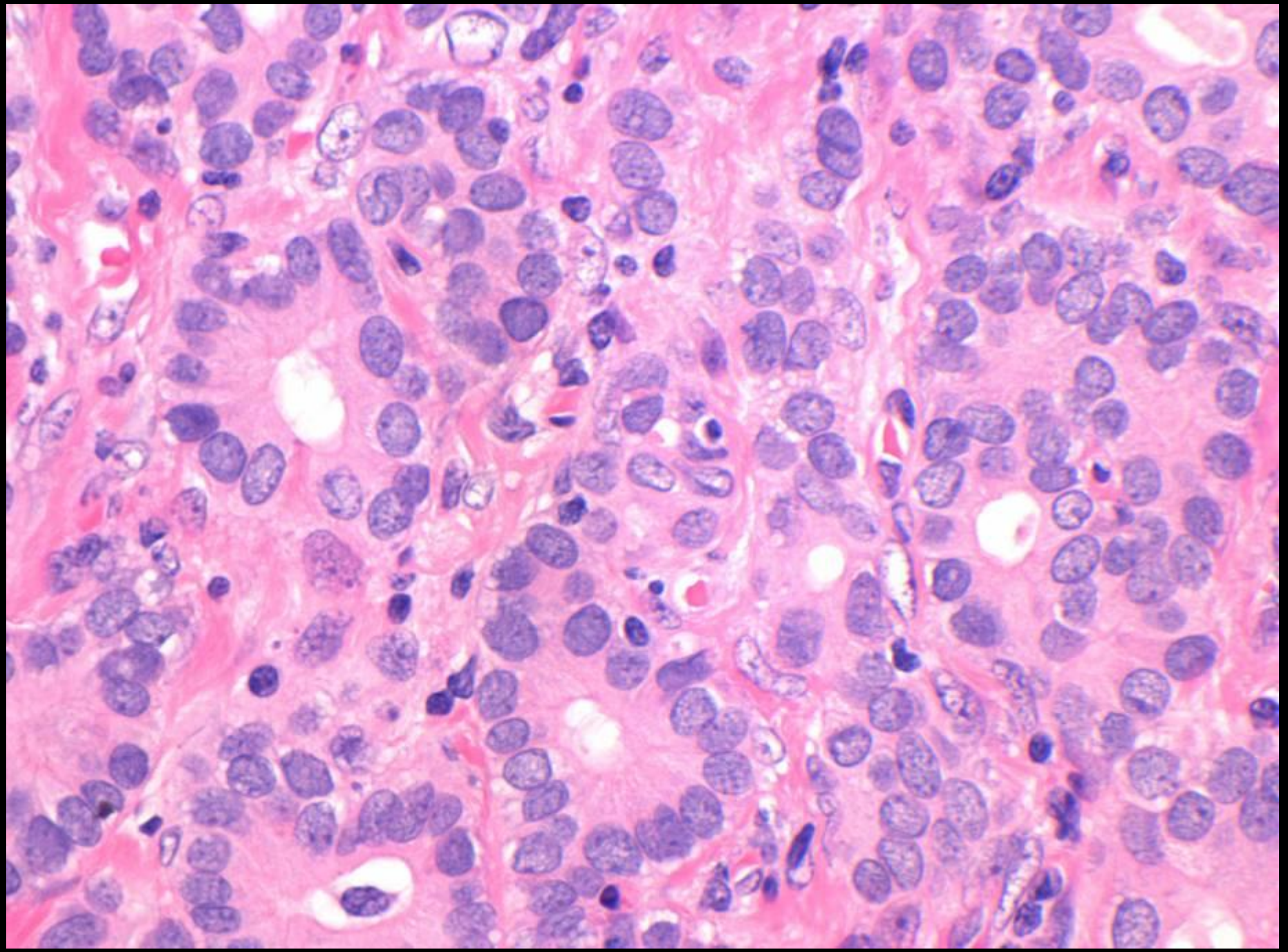


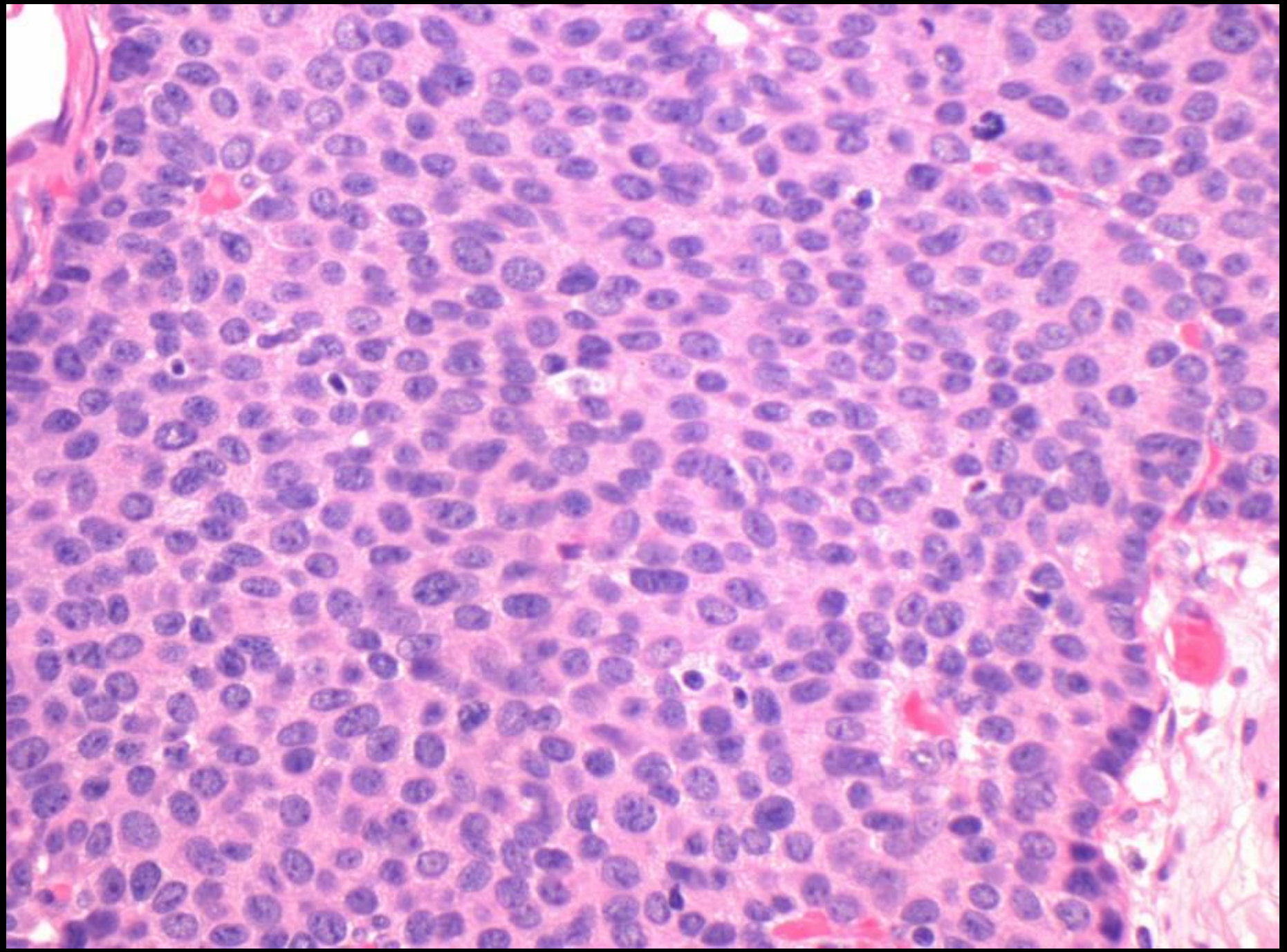


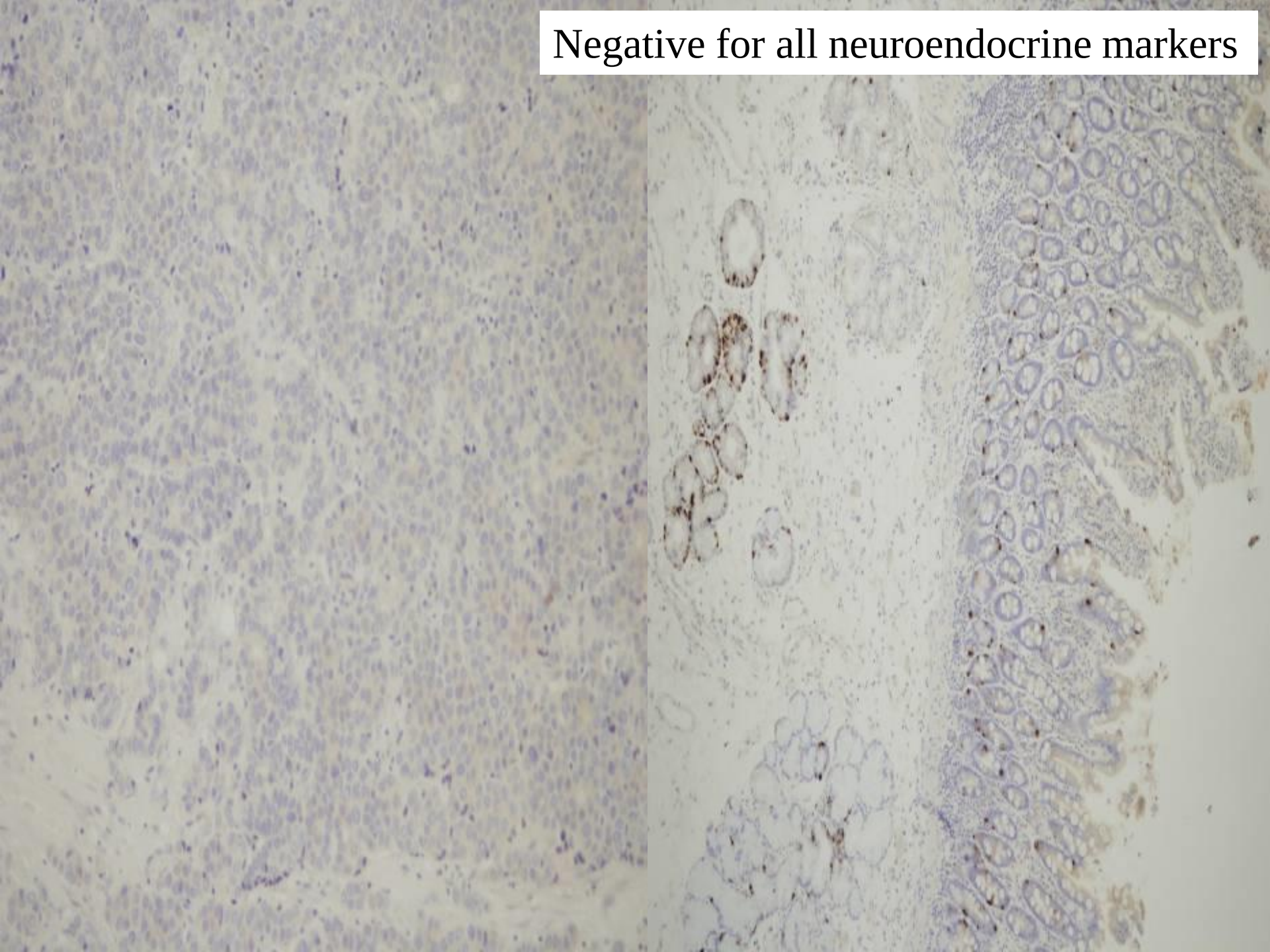


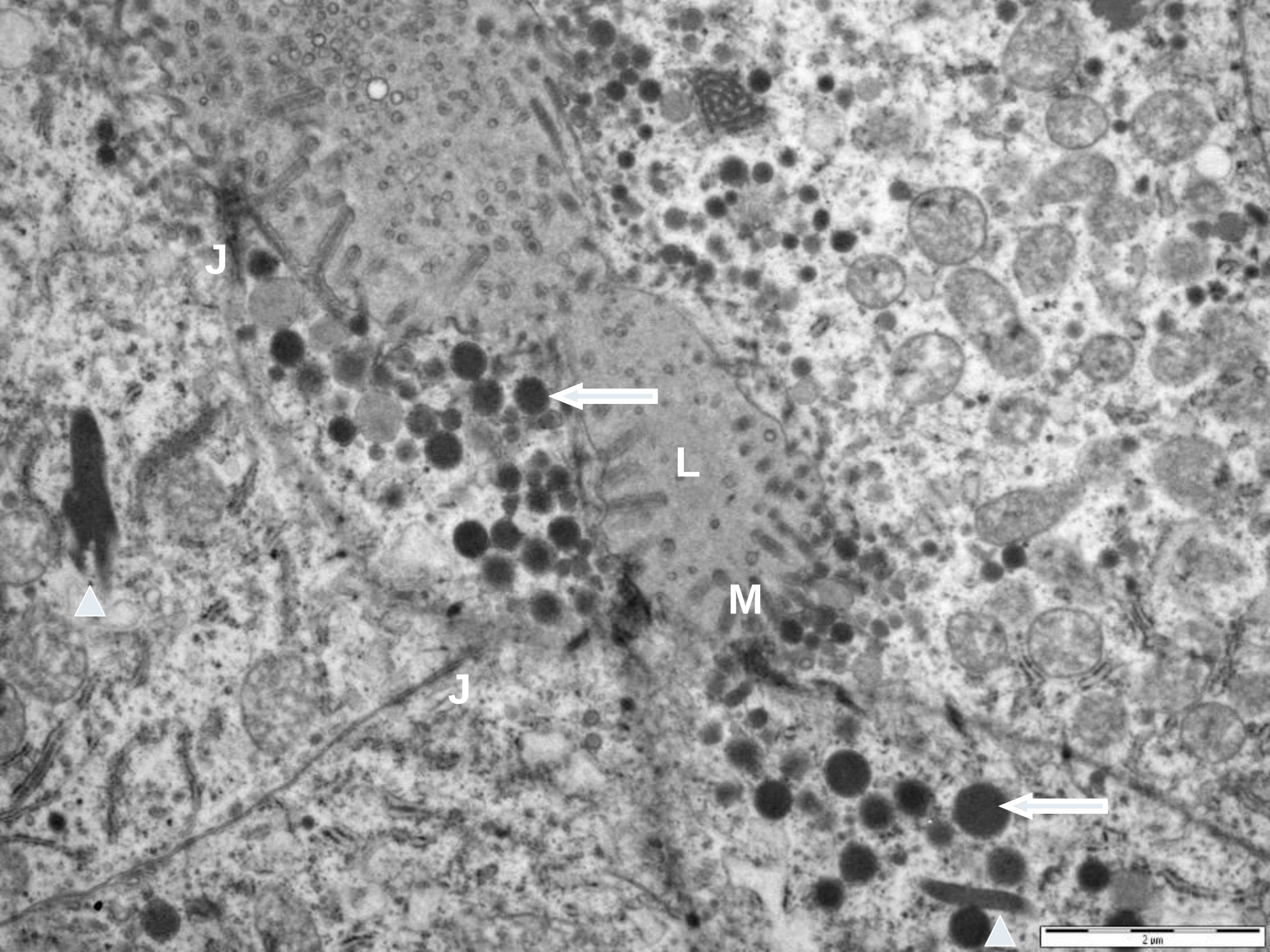


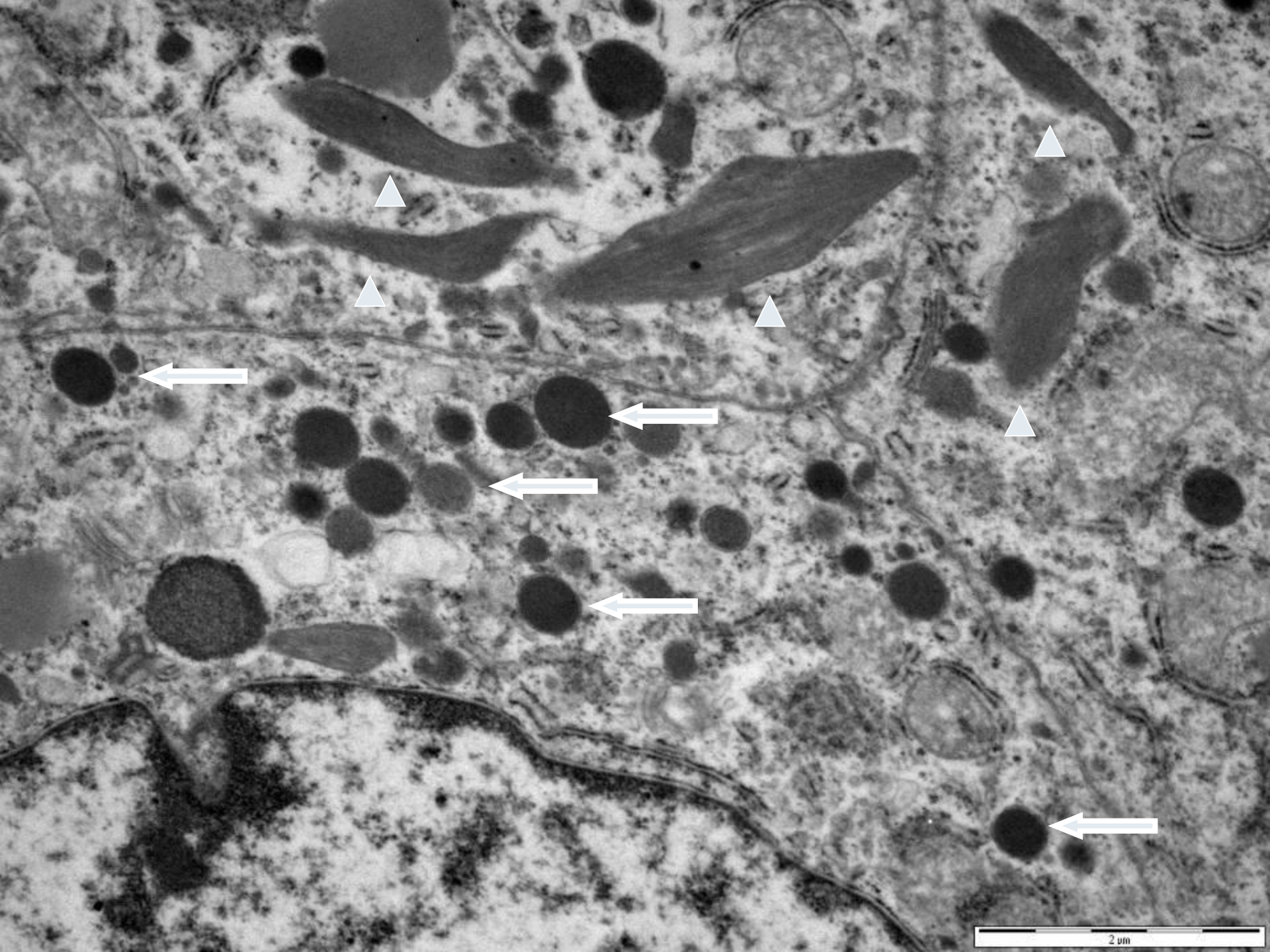


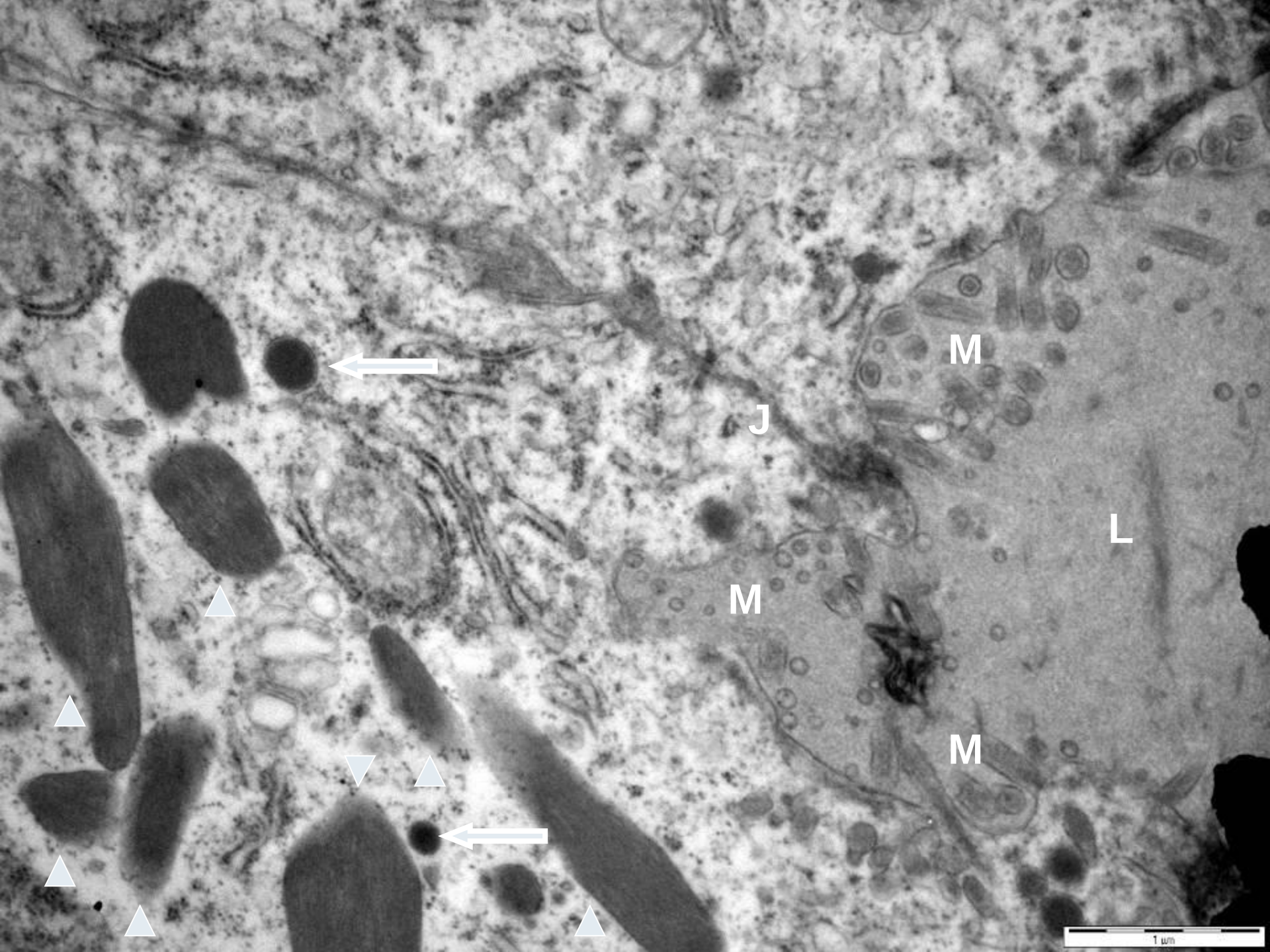




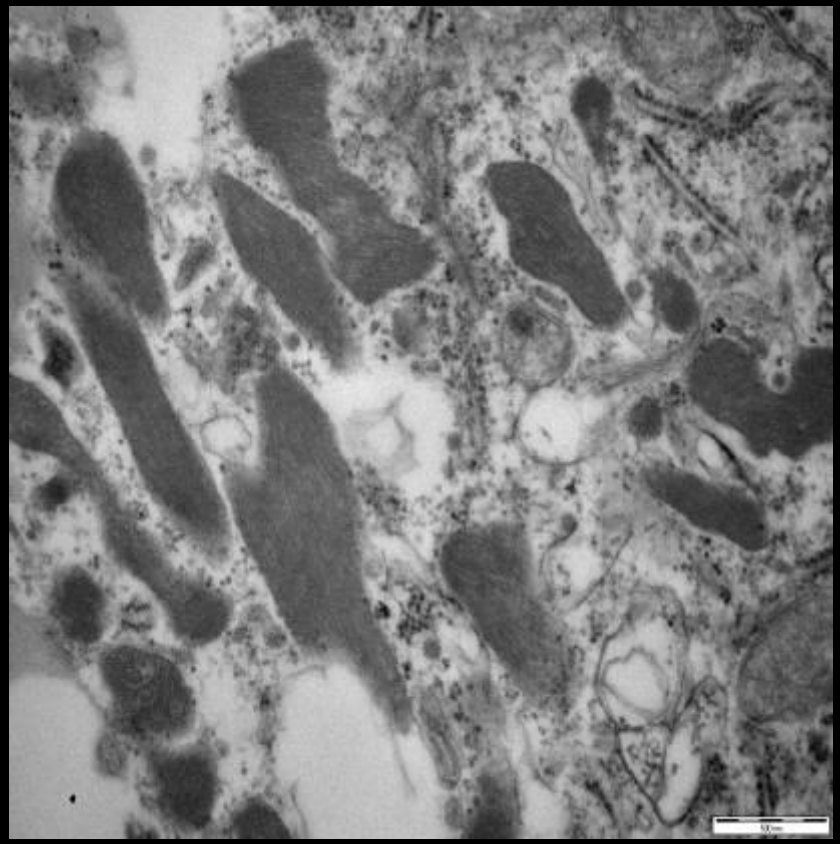

Negative for all neuroendocrine markers

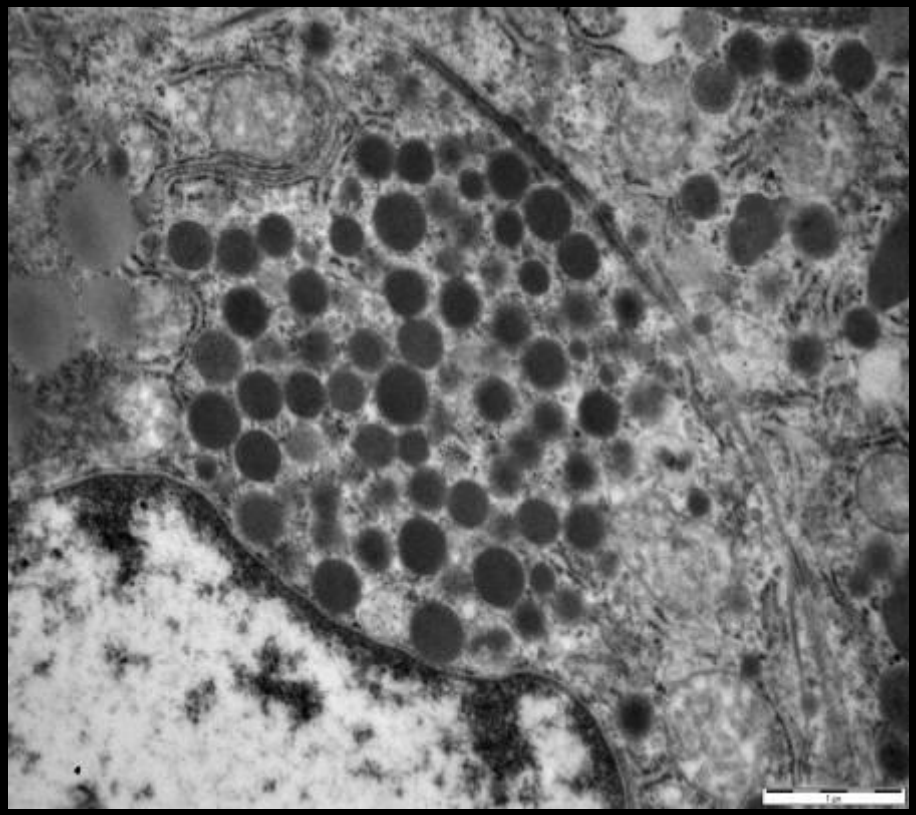

J
L
M
J
2 µm

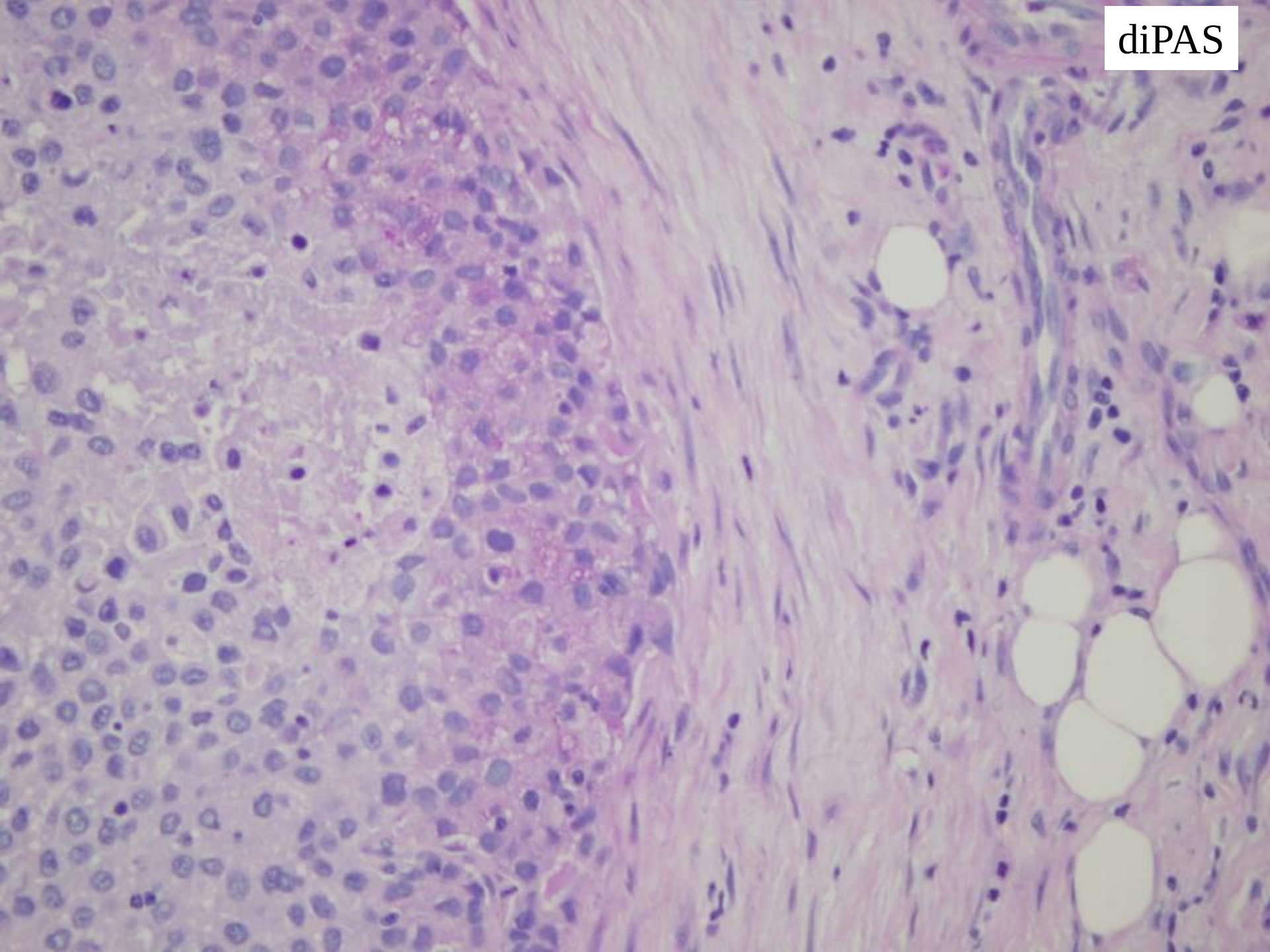

2 µm

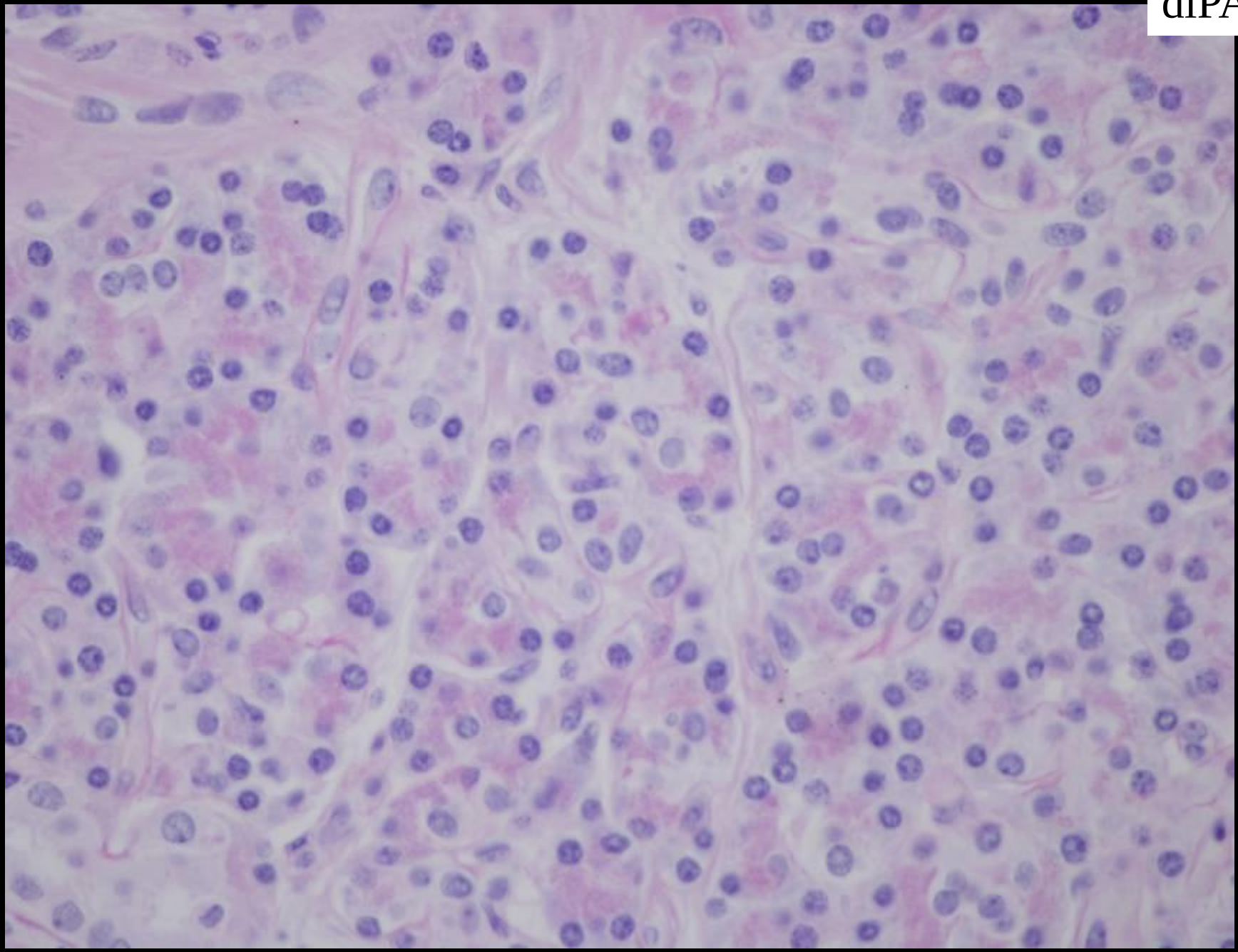

M
J
L
M
M
1 µm

Filamentous inclusions

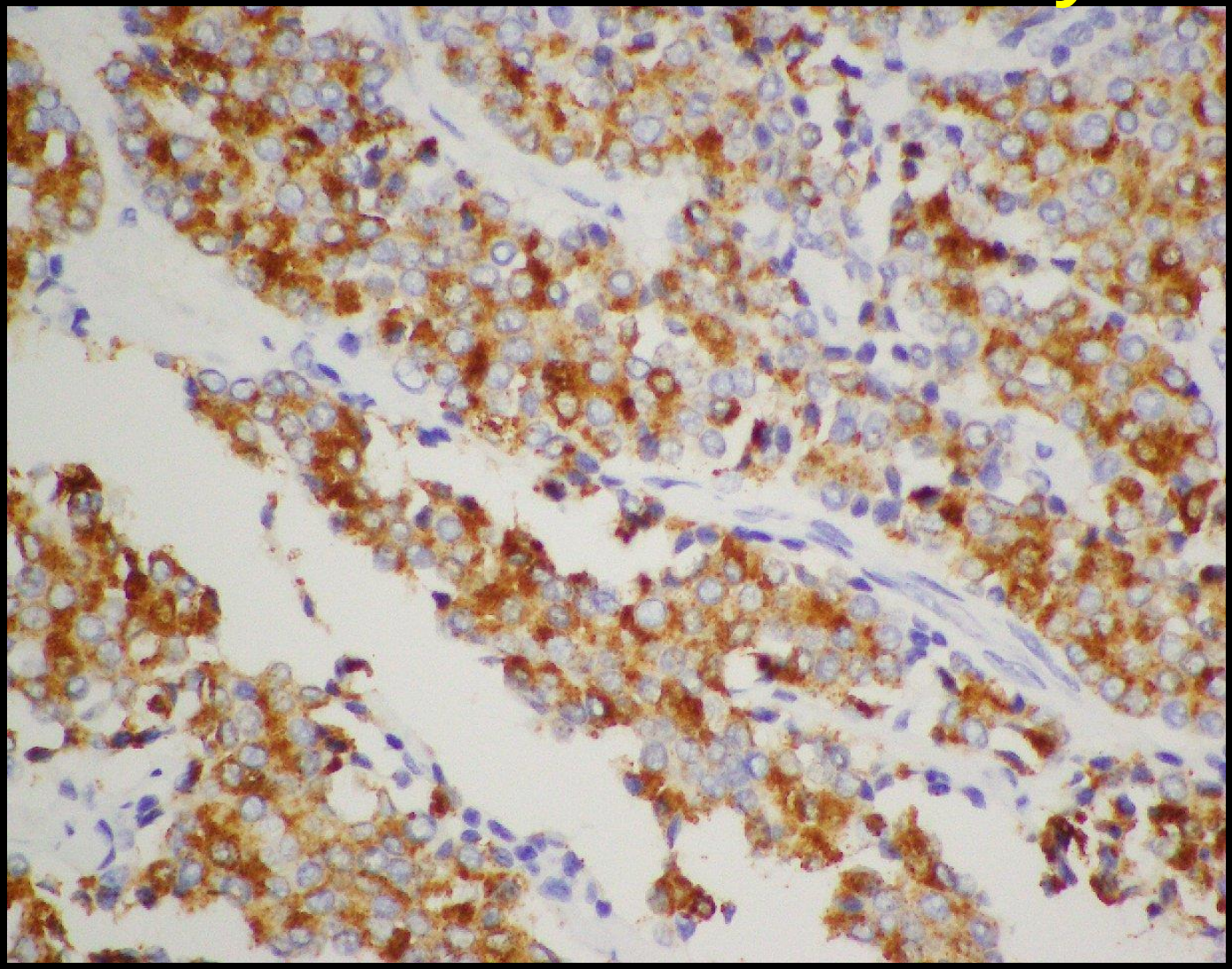




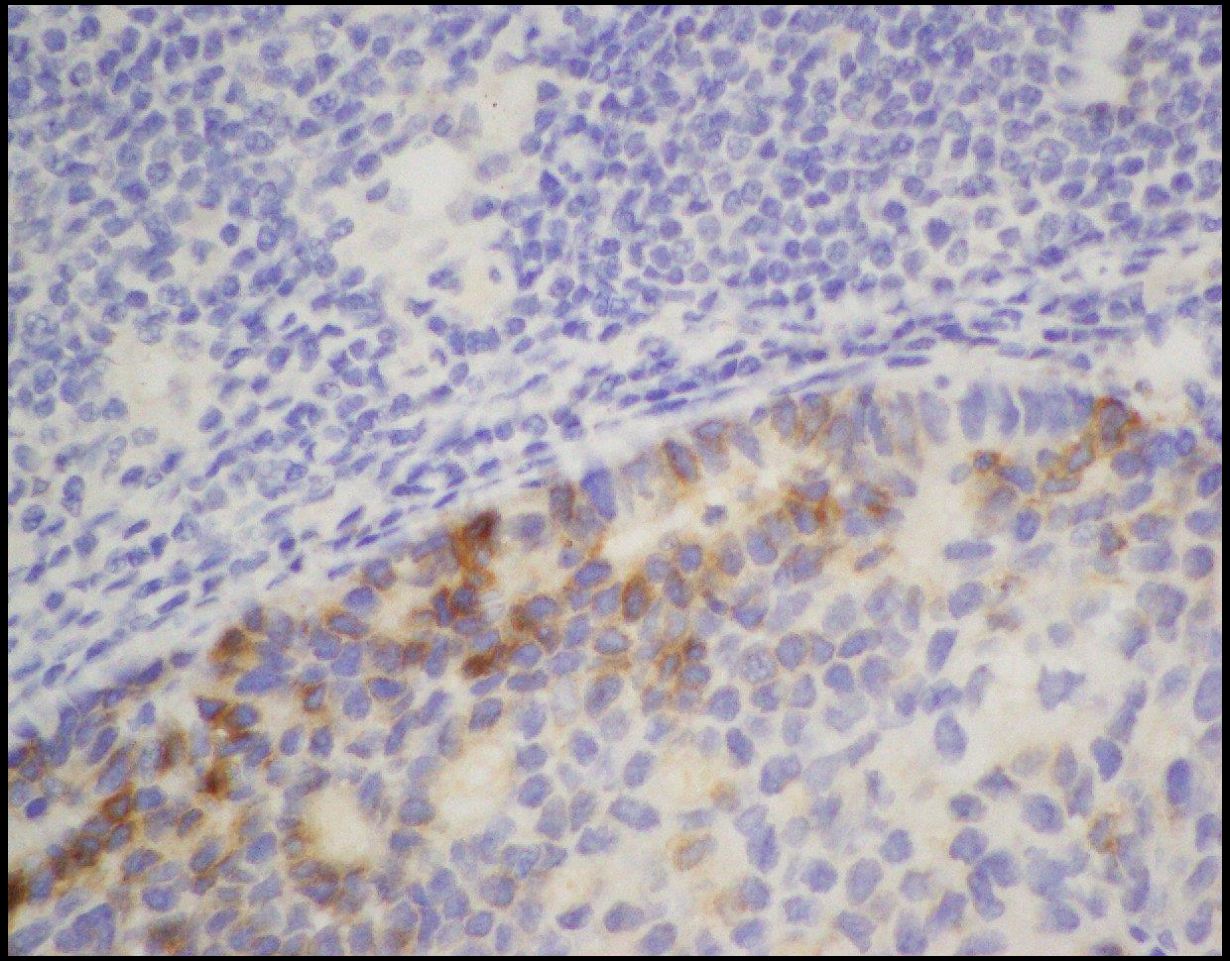

diPAS


diPAS

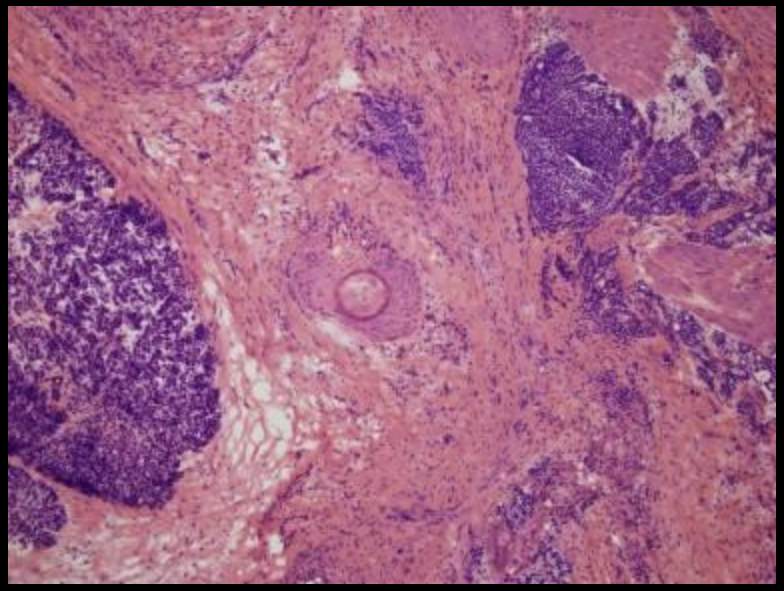
BCL10 and trypsin immunohistochemisry

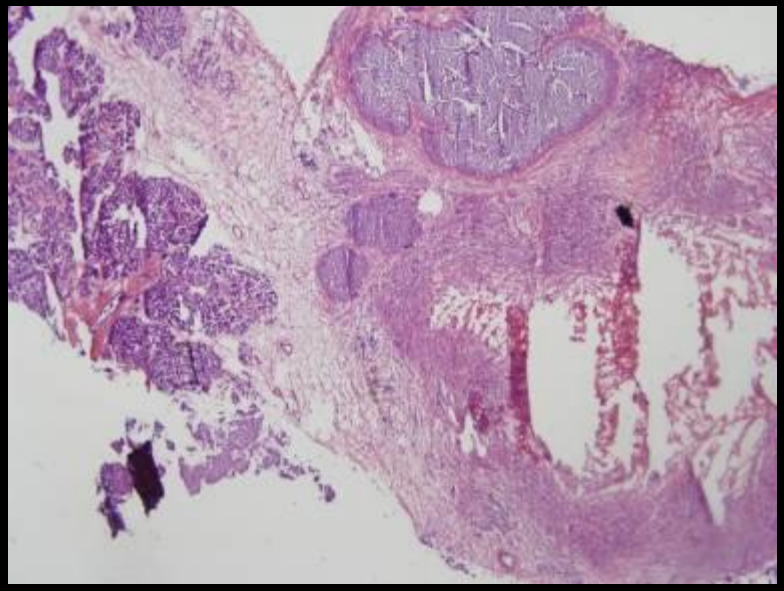


BCL10 and trypsin immunohistochemisry



FROZEN SECTION





Pancreatic Acinar cell Carcinoma

- Incidence : varies in the literature, ranging between 1 to 13%
  -At present 1 to 2%

Age : more common during 5th through 7thdecade

- **Symptoms**
- Most common: weight loss, abdominal pain and nausea and vomiting.
- "Lipase hypersecretion syndrome": Subcutaneous fat necrosis or panniculitis as a result of increase levels of lipase (10-15%)
- Syndrome-polyarthritis, subcutaneous fat necrosis, or panniculitis and eosinophilia

MOLECULAR GENETICS

- KRAS, p53, SMAD4, CDKN2A mutations very rare.
- 25% have beta-catenin/APC loss and may show abnormal nuclear staining for beta-catenin

Outcome

Poor prognosis but still better than stage matched pancreatic cancer

Not graded

5 year survival 25-50%

Patients with elevated levels of serum lipase had worse prognosis (hepatic metastasis)

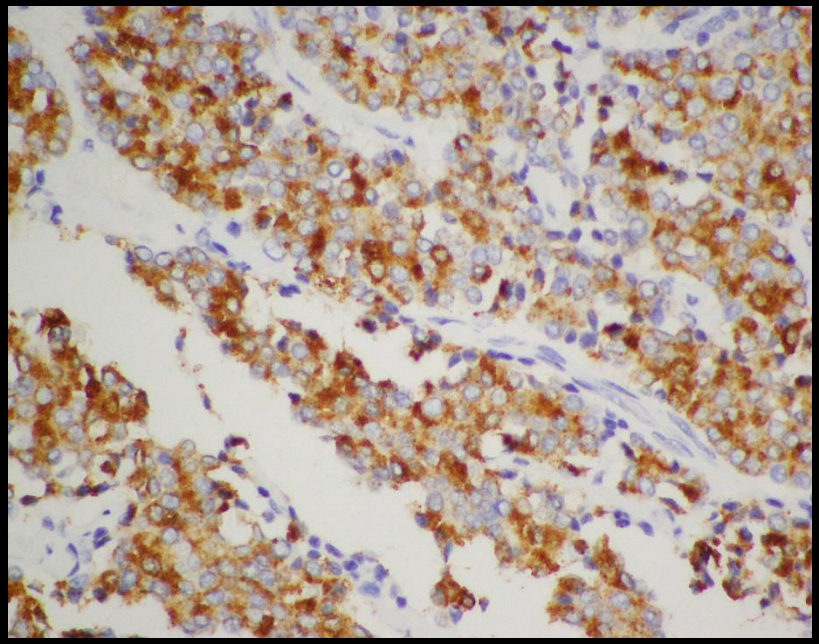
VARIANTS

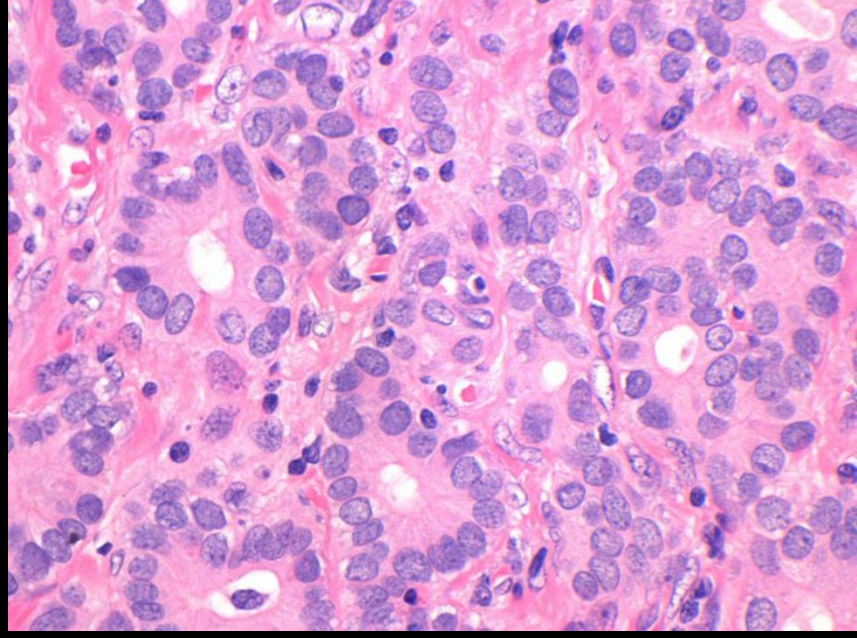
Acinar cell cystadenoma

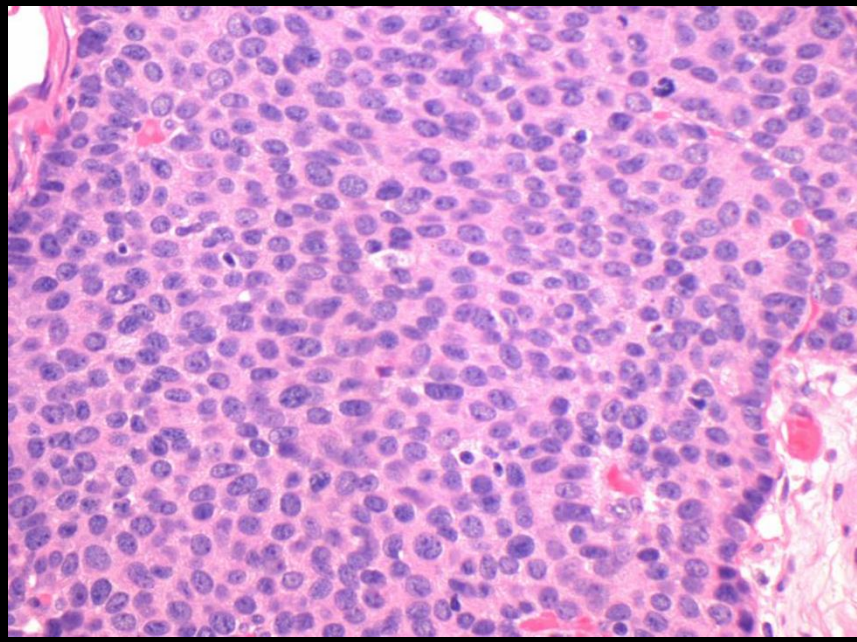
Acinar cell cystadenocarcinoma

Mixed acinar cell carcinoma (mixed-ductal; mixed acinar-neuroendocrine)

Acinar cell carcinoma







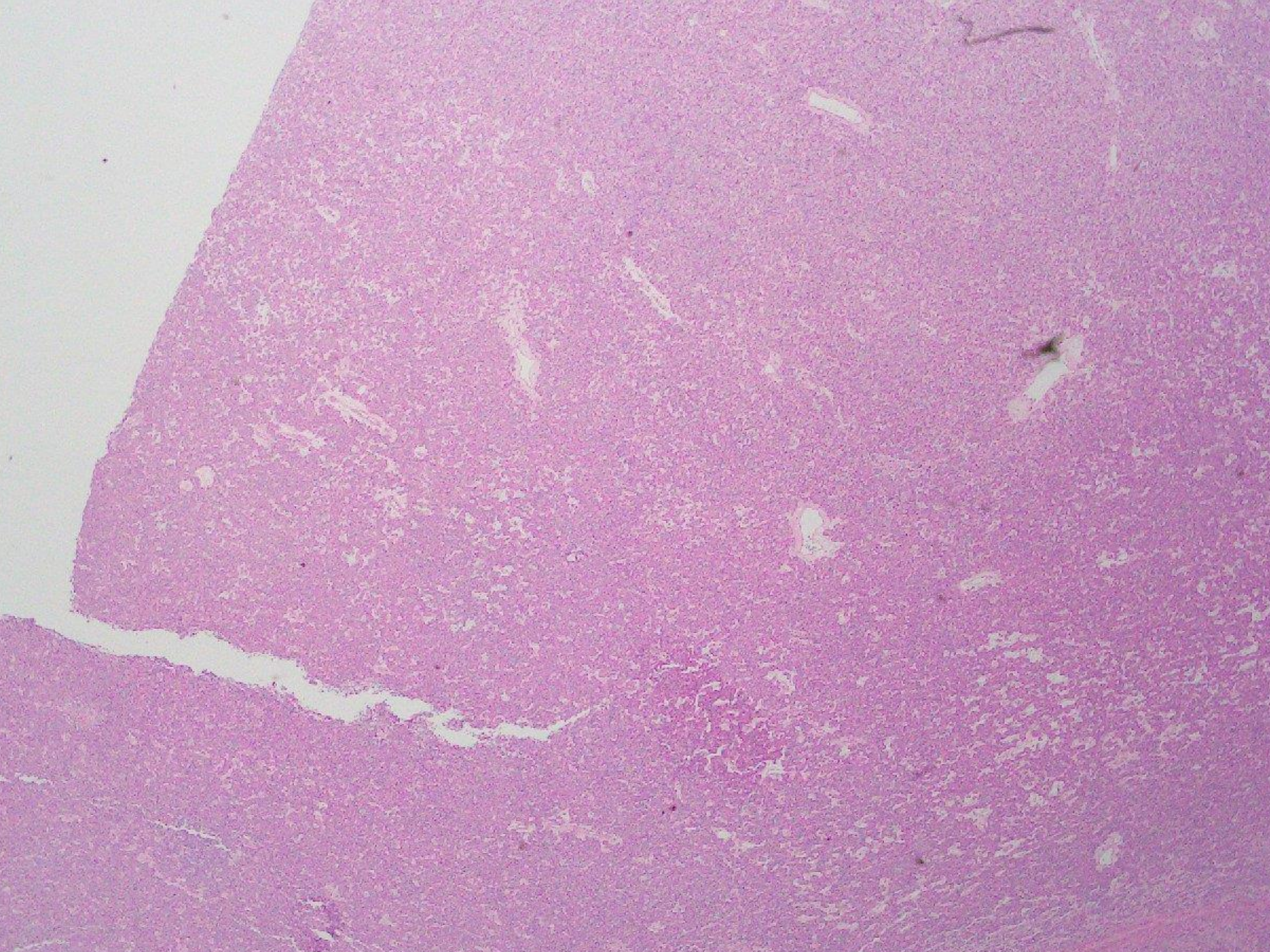
Best markers are BCL10 and Trypsin
Looks like a PNET but negative for chromogranin

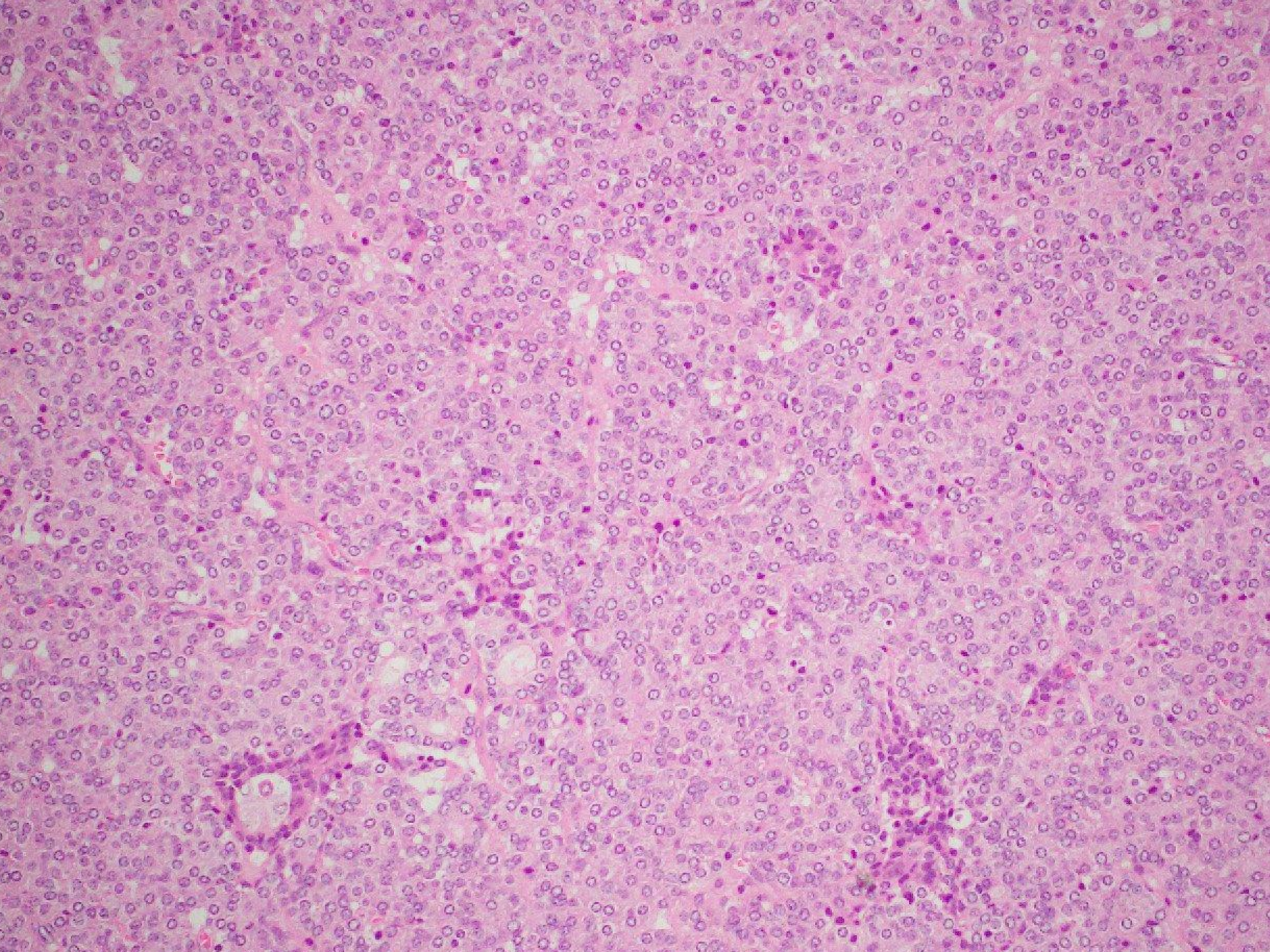
Traps are:
May be mixed (MiNEN)
May have nuclear beta-catenin staining

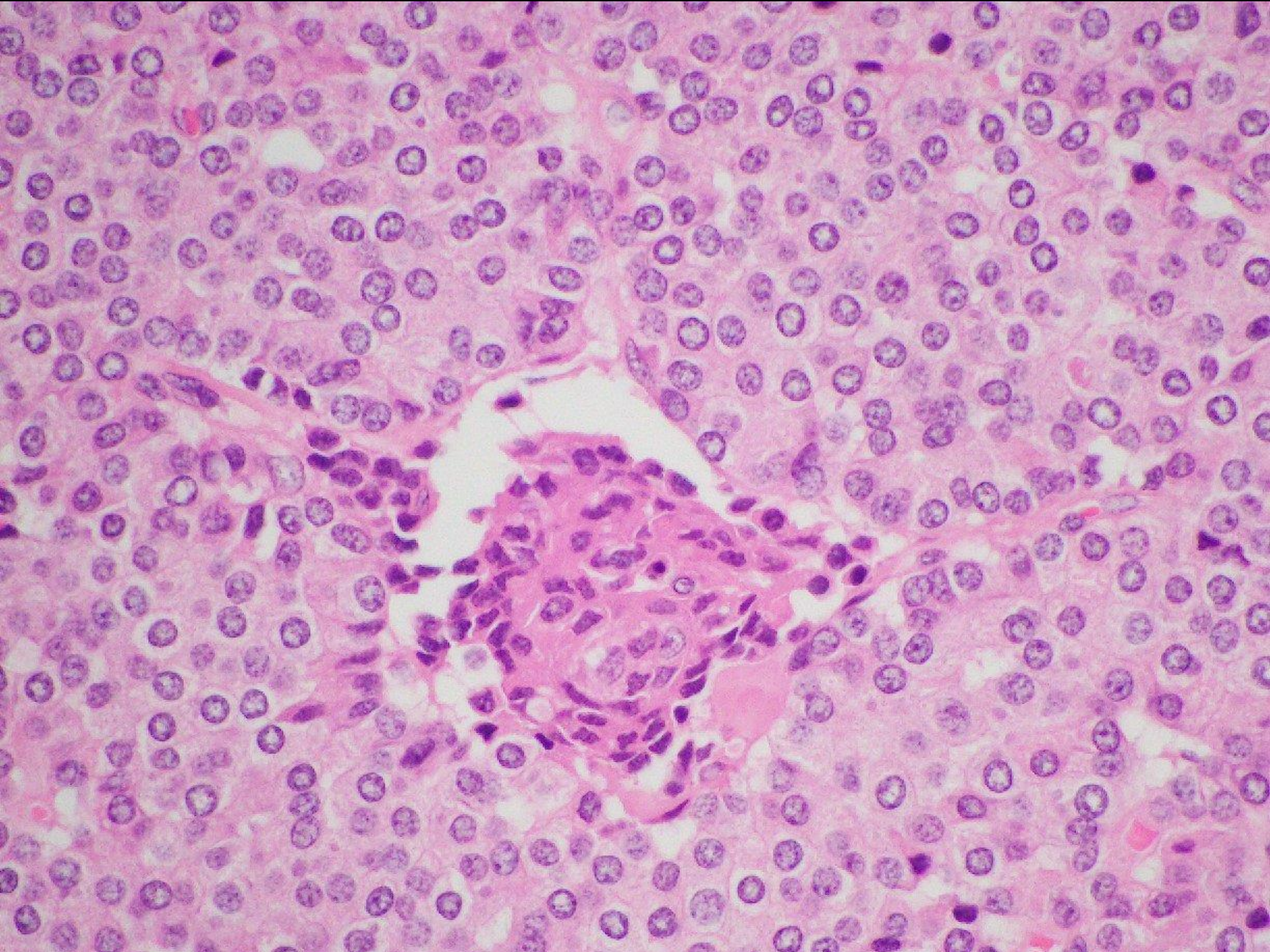
Pancreatoblastoma

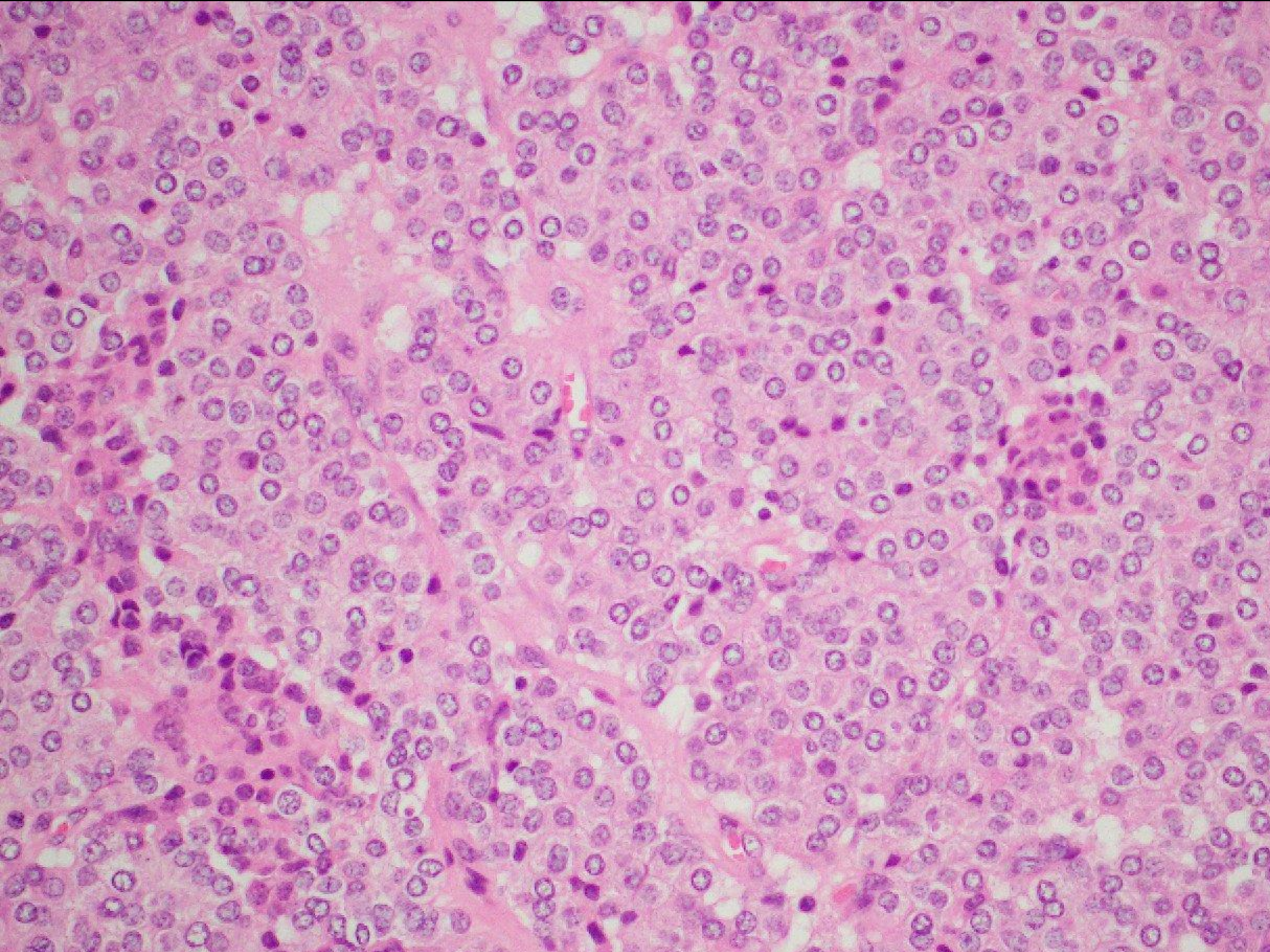
0.5% of ICGC pancreatic cancer cases

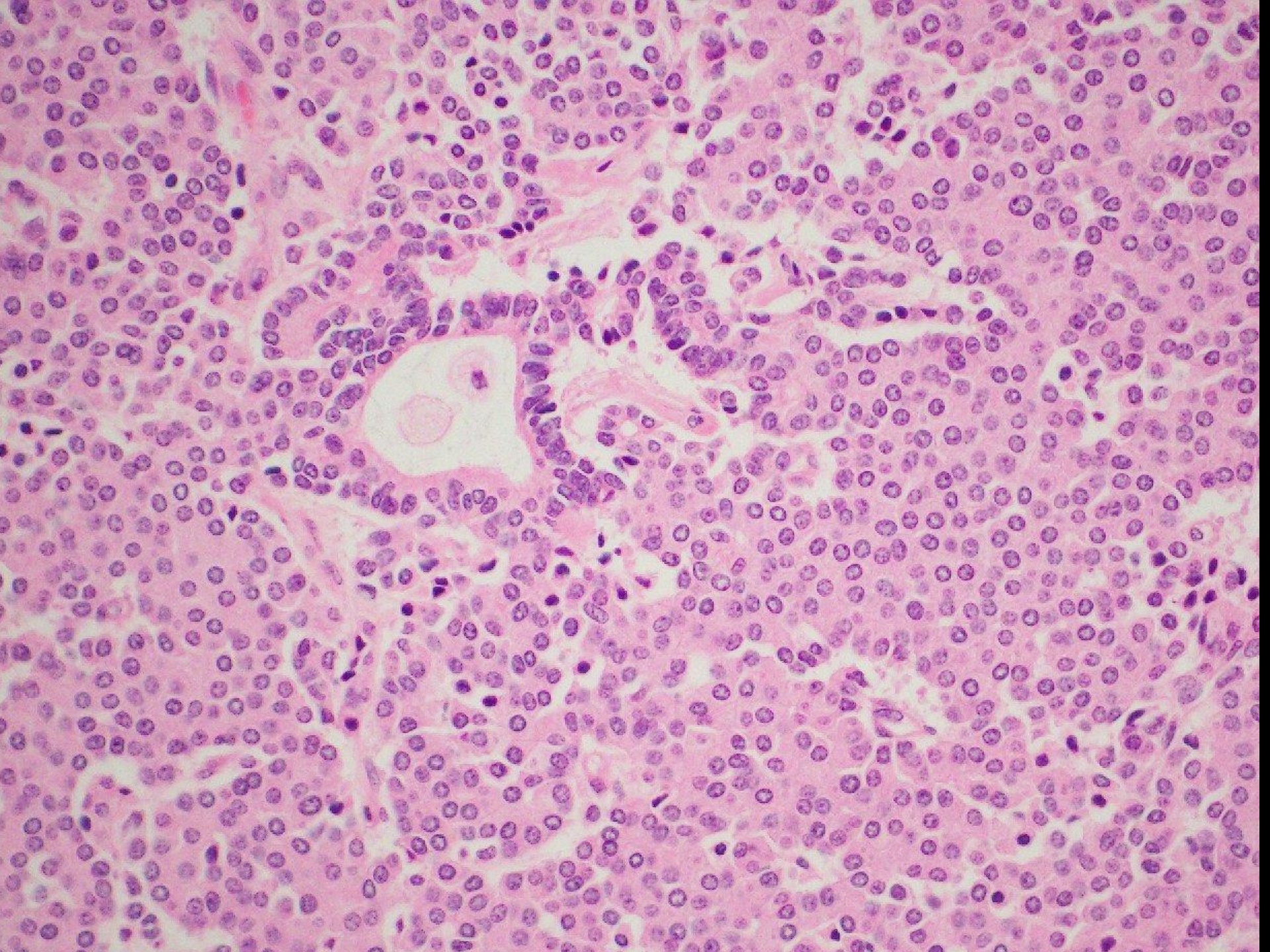
May show trilineage differentiation (squamous, NET, acinar)

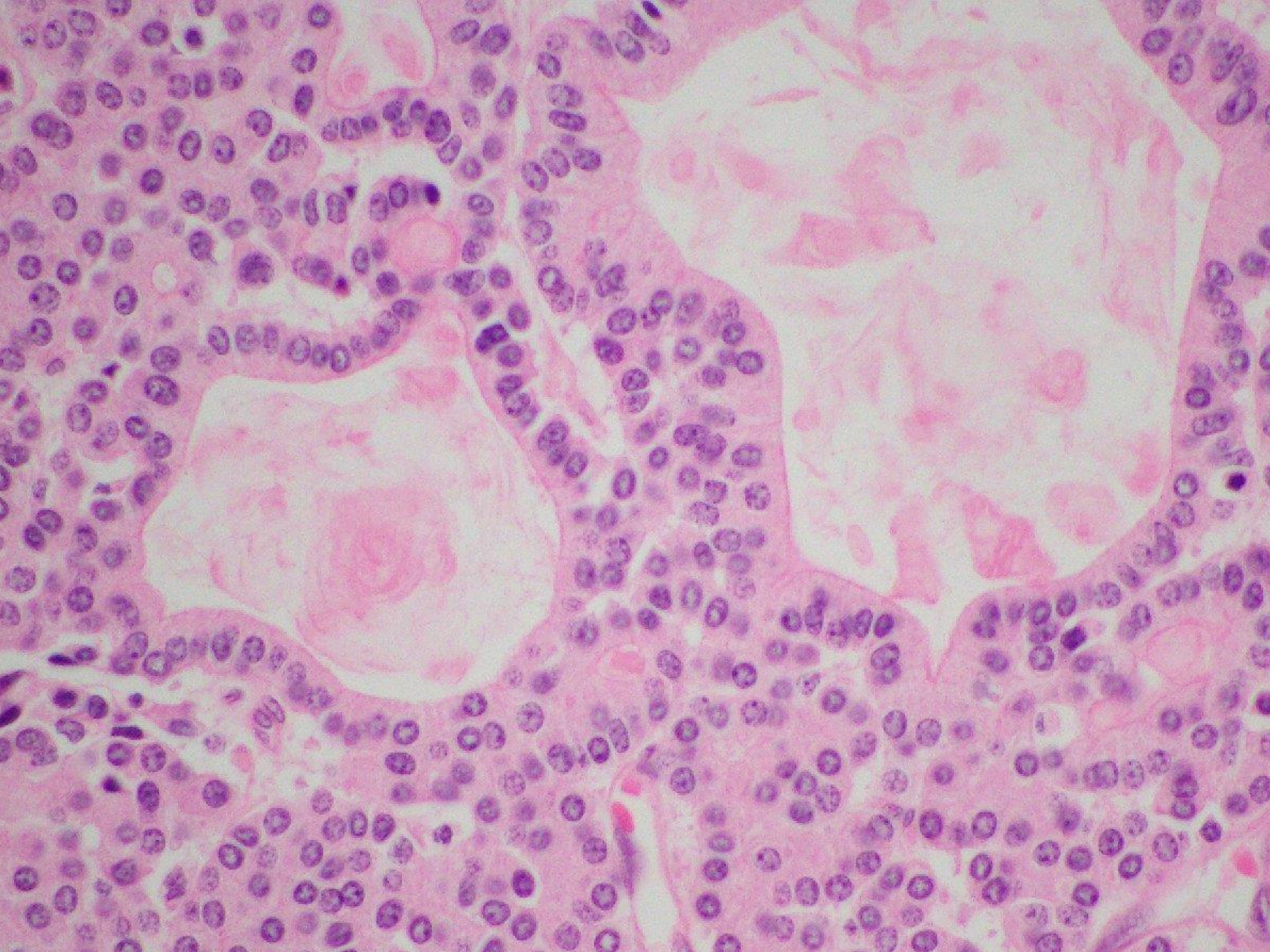


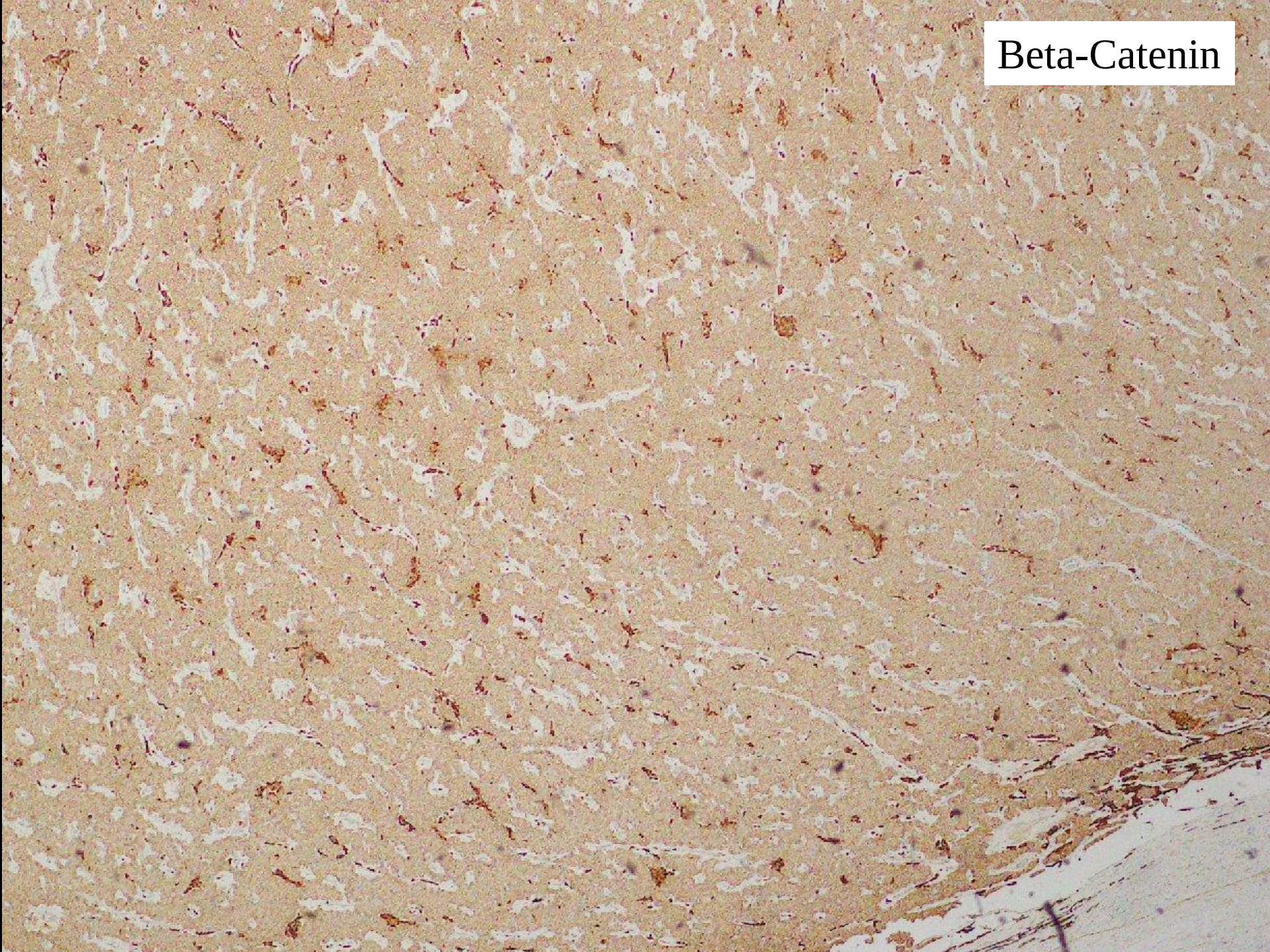


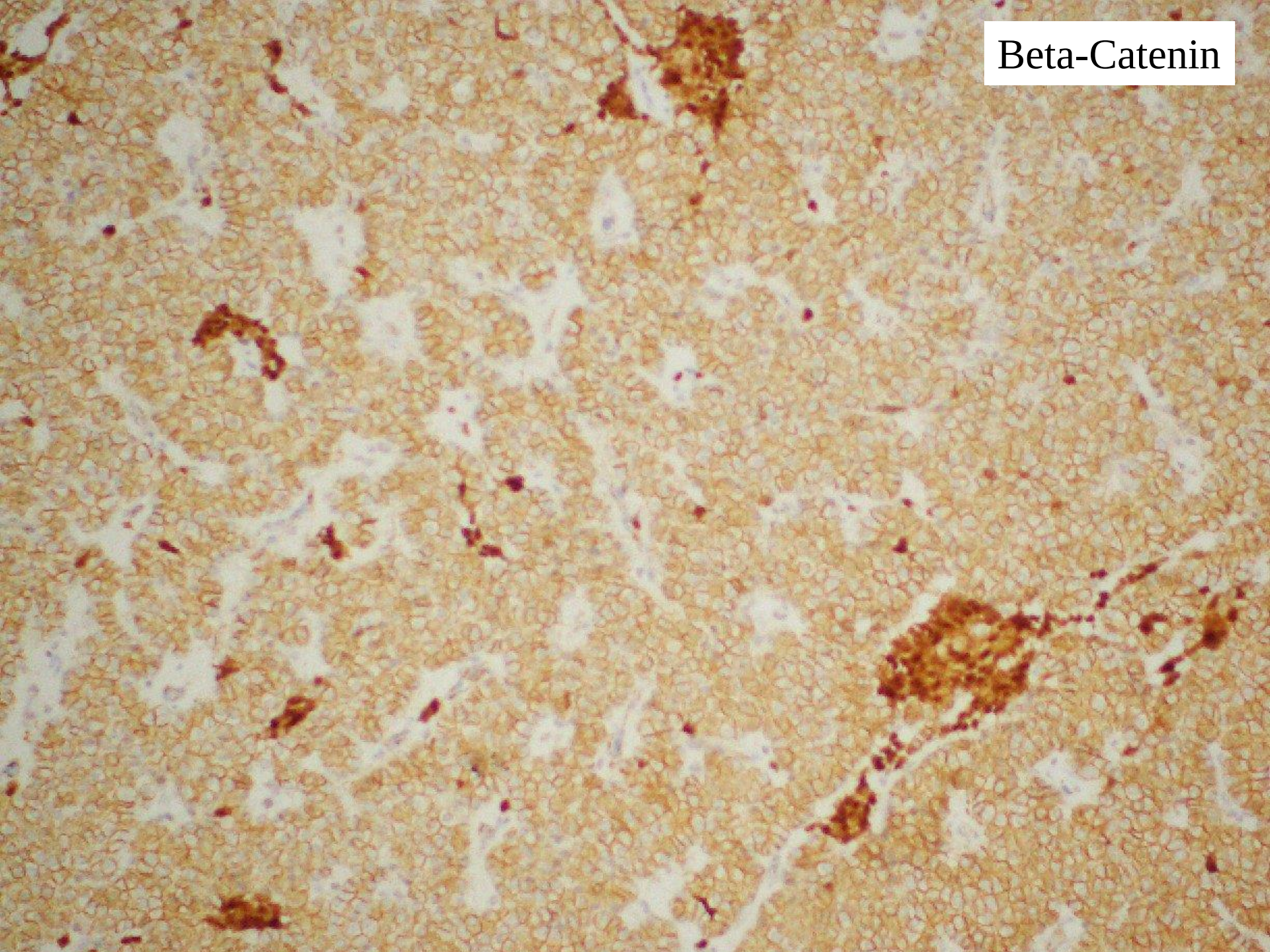









Beta-Catenin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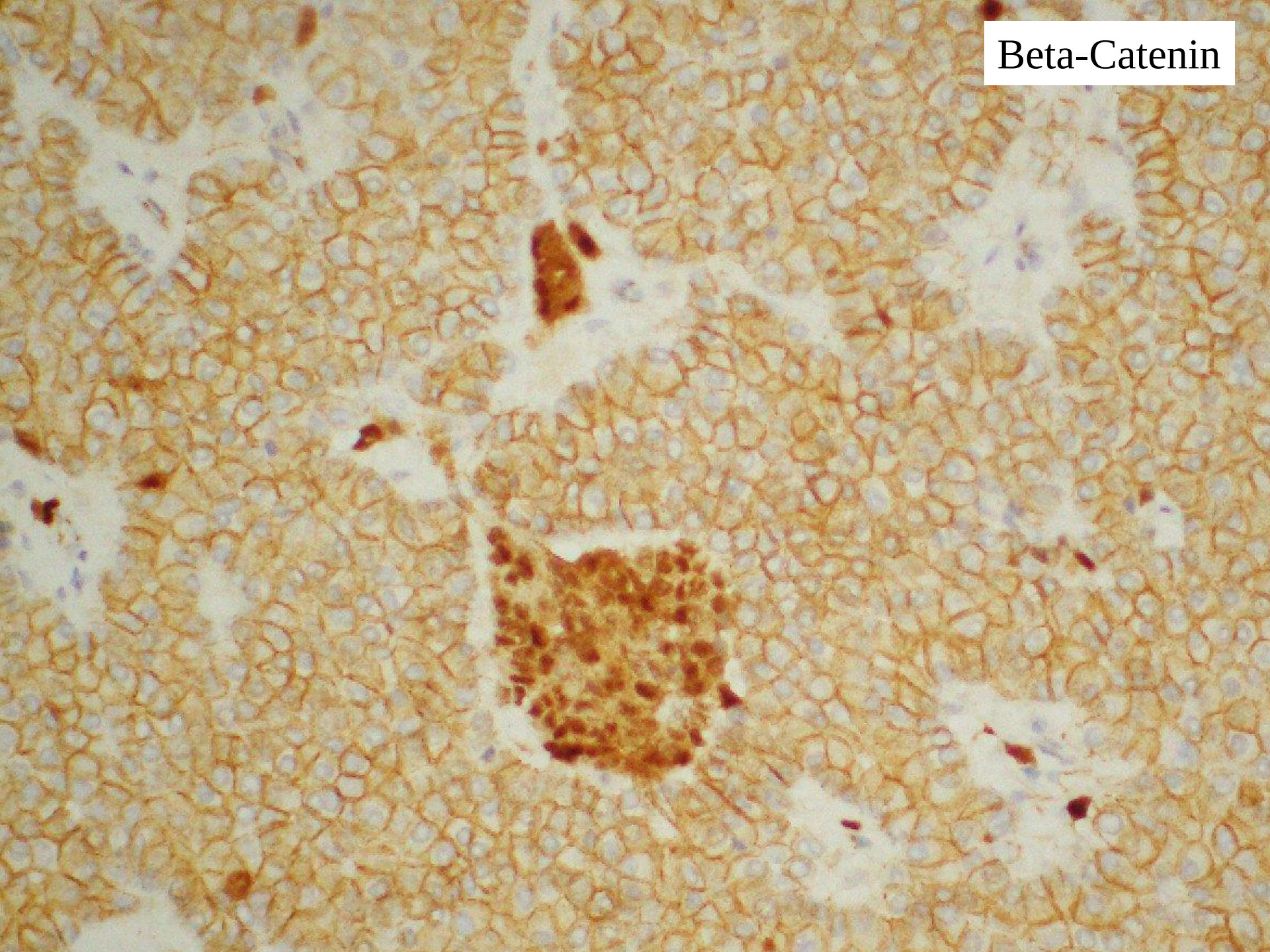
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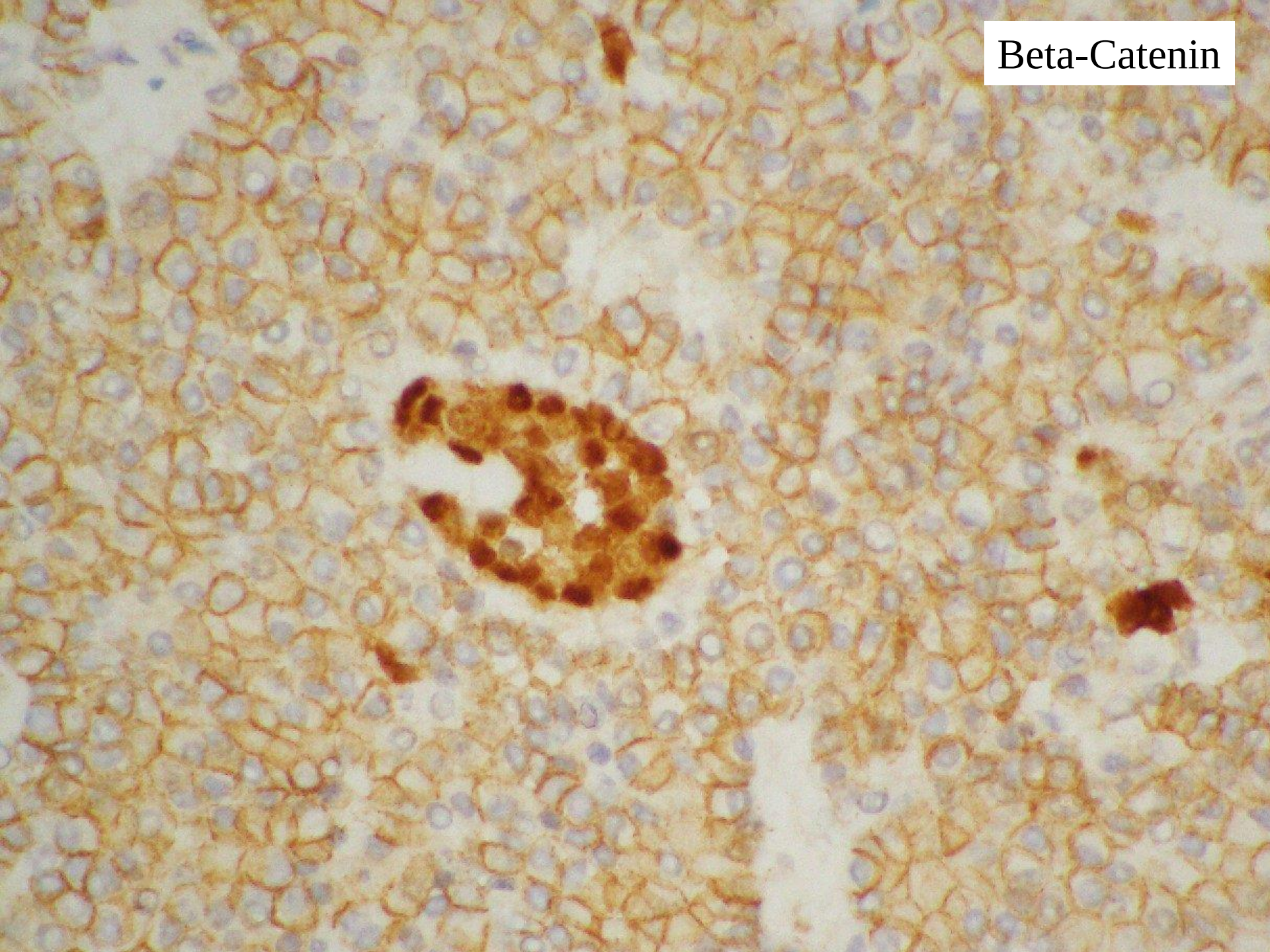
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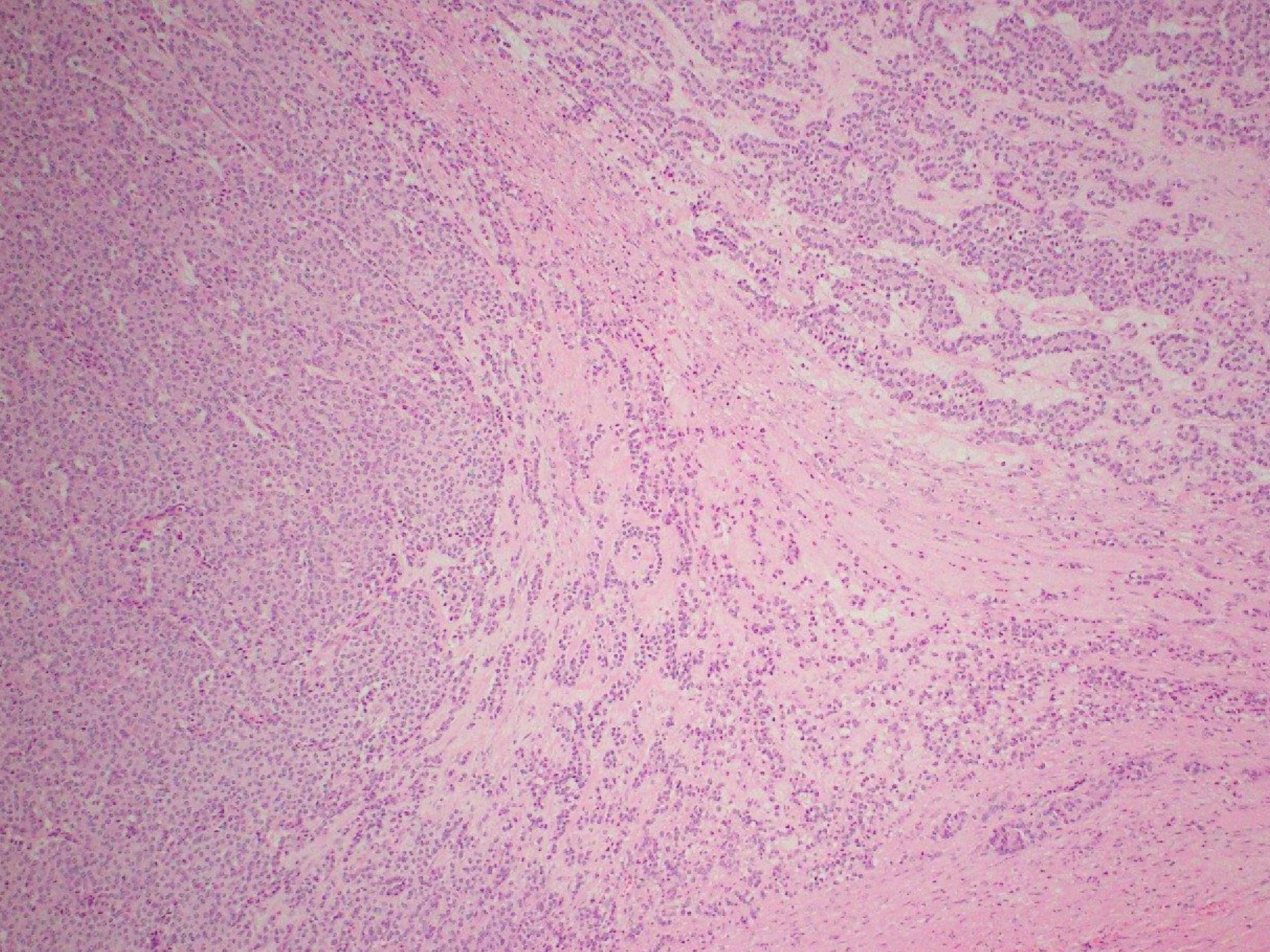

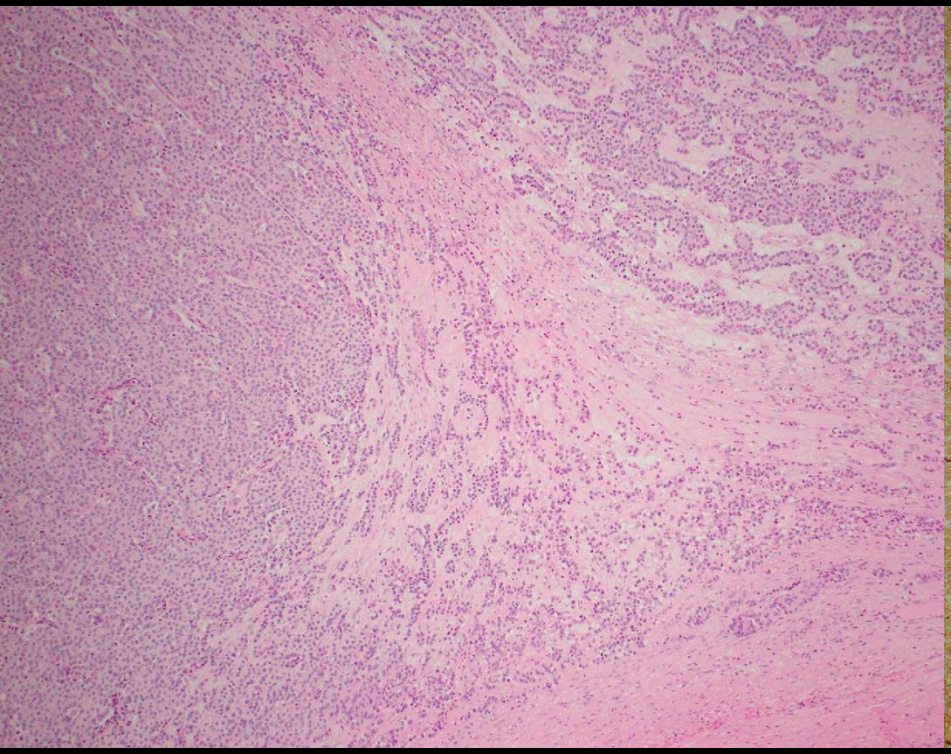

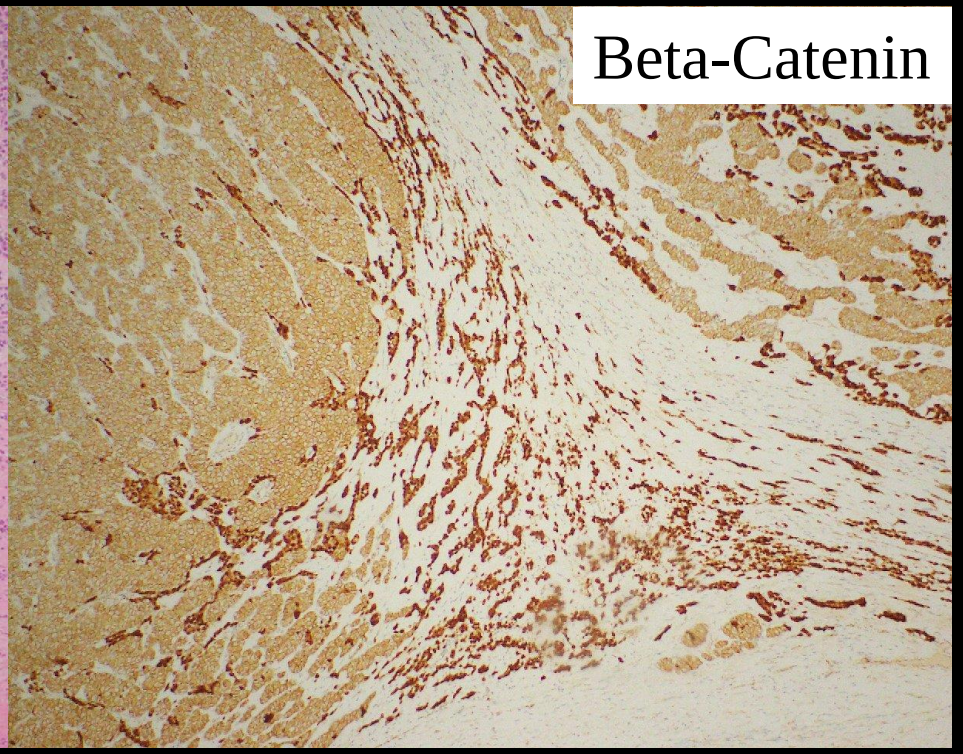
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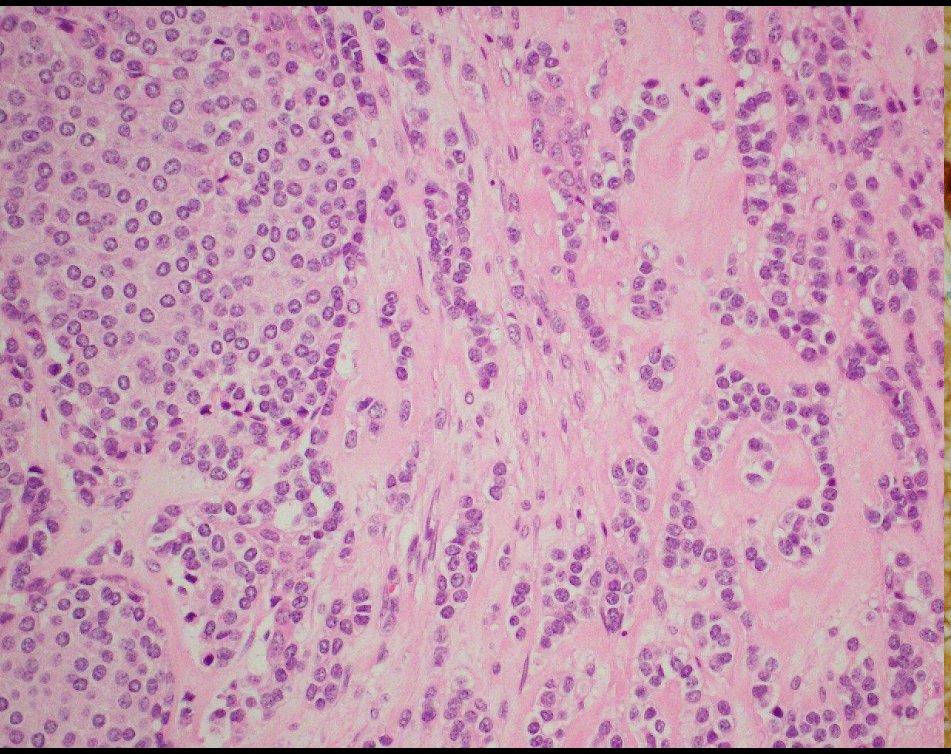

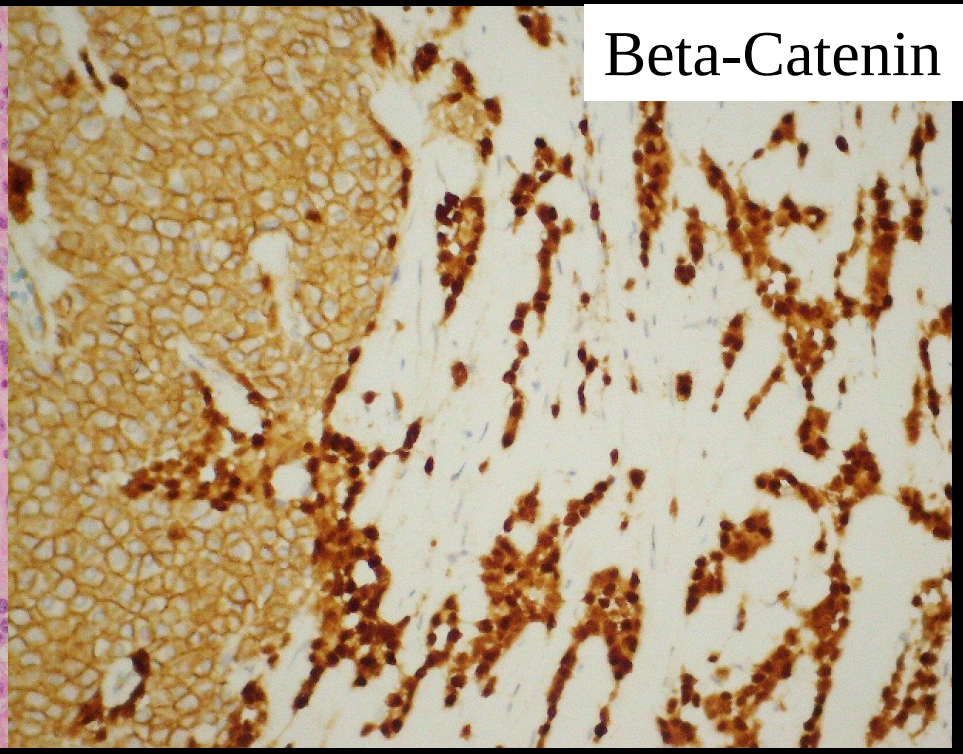
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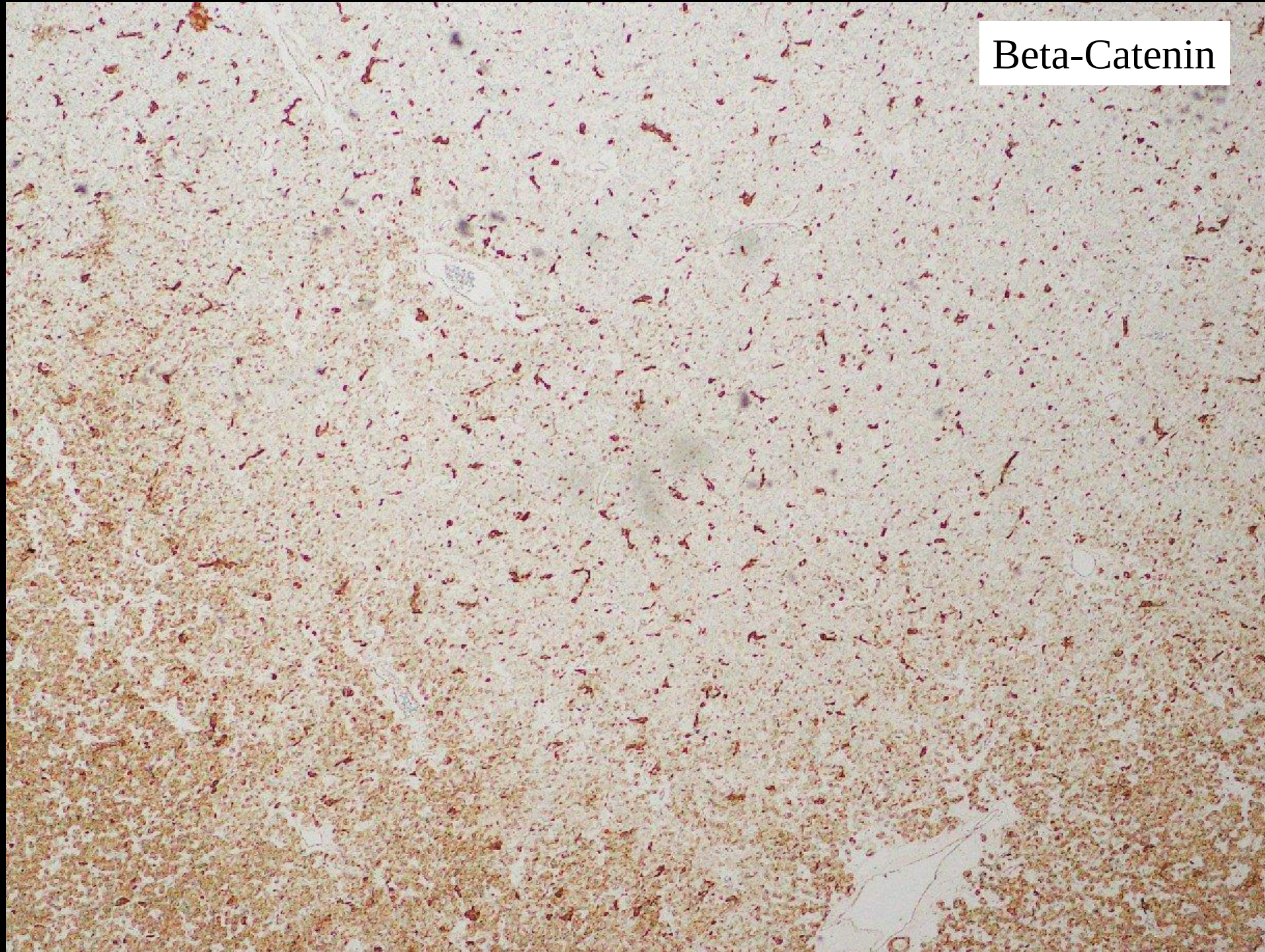
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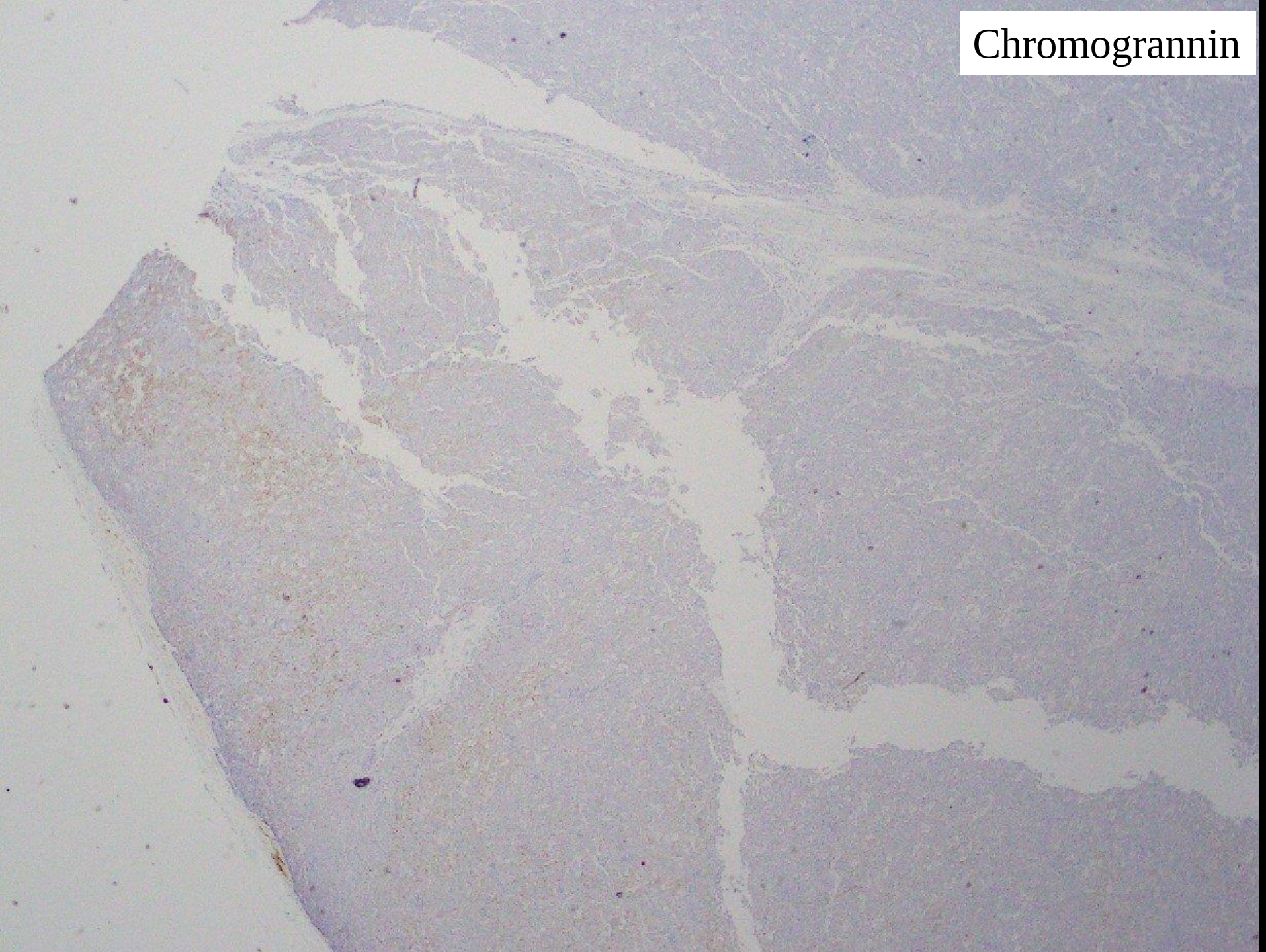
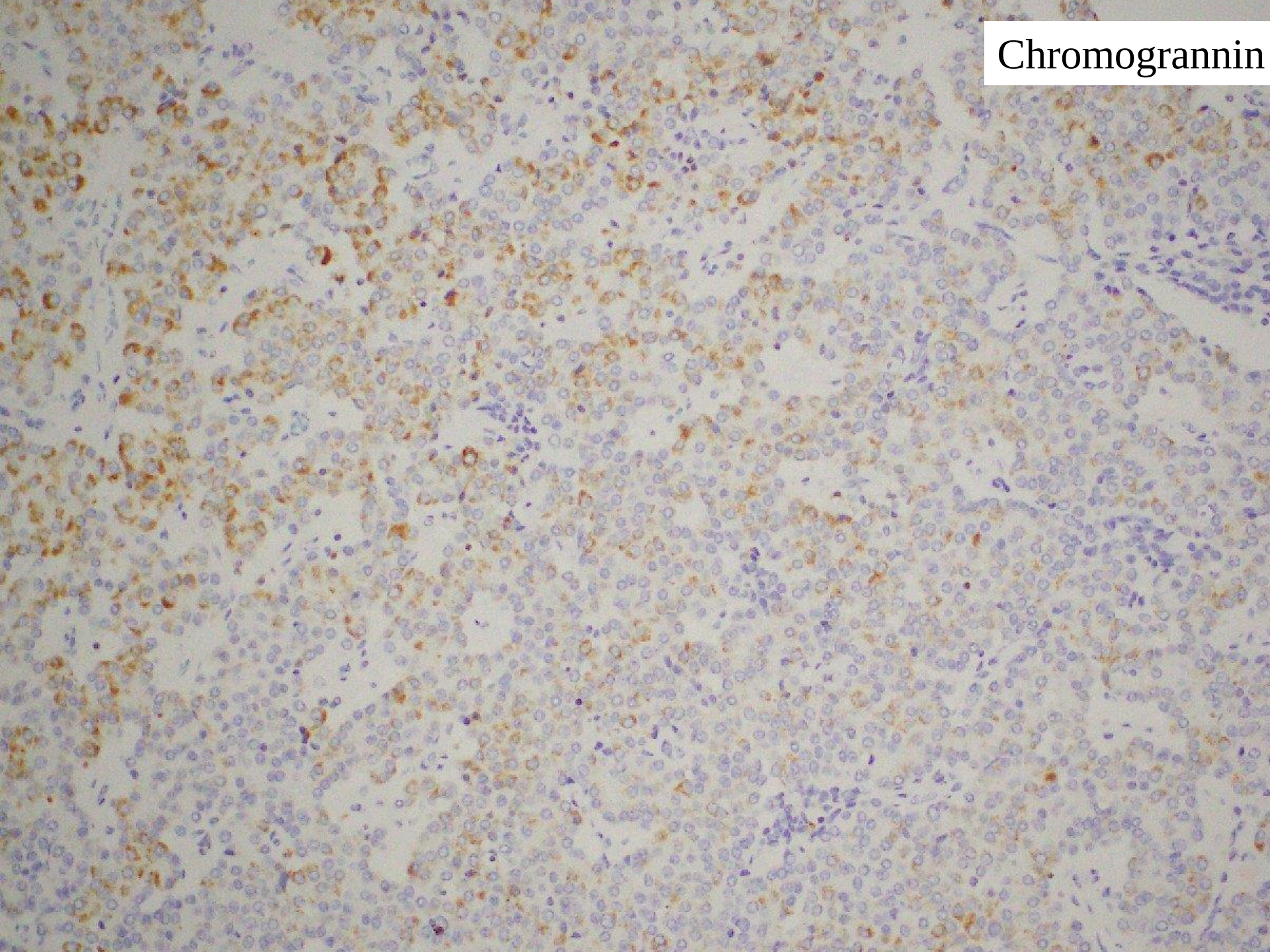

Chromogrannin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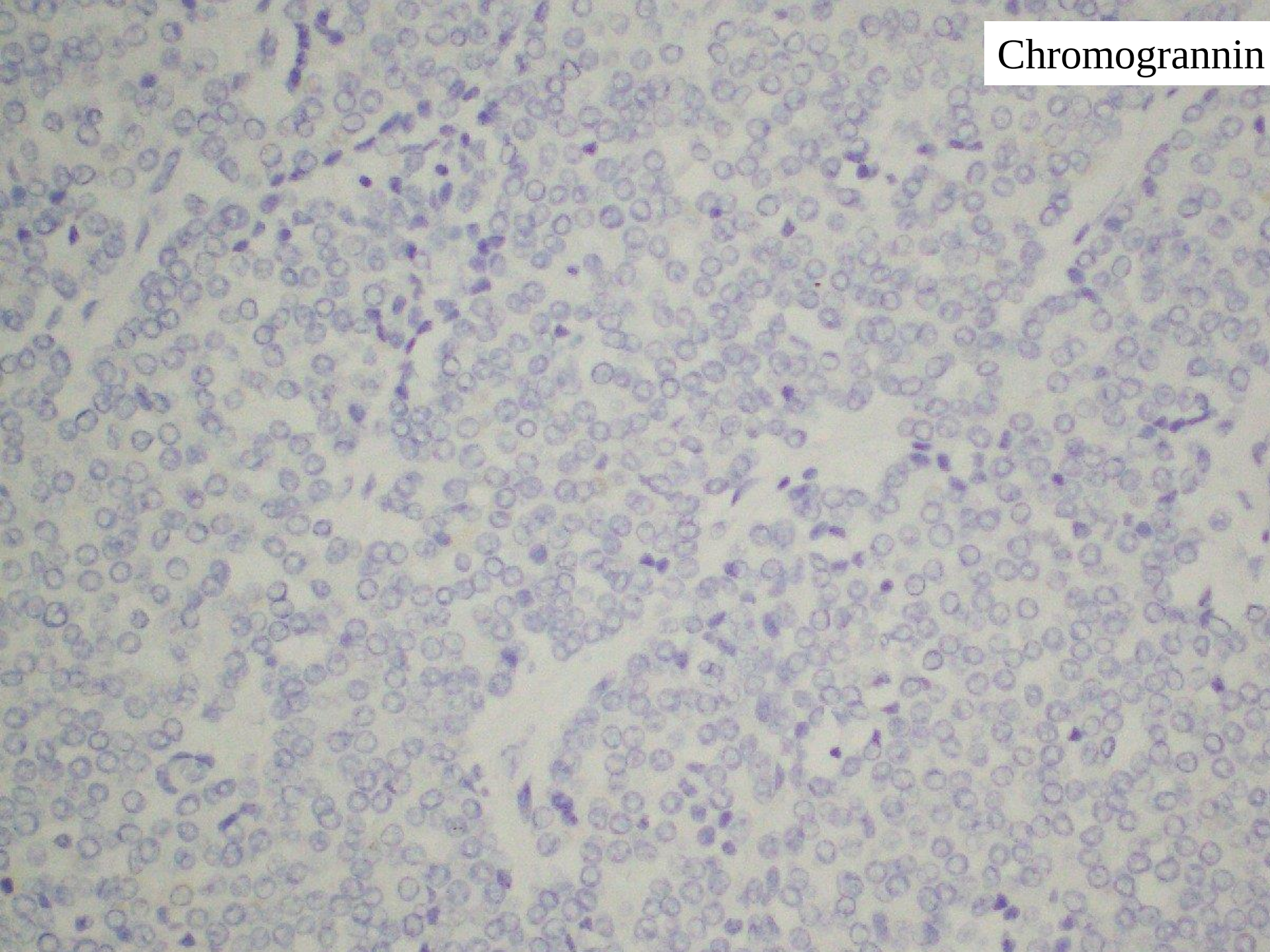
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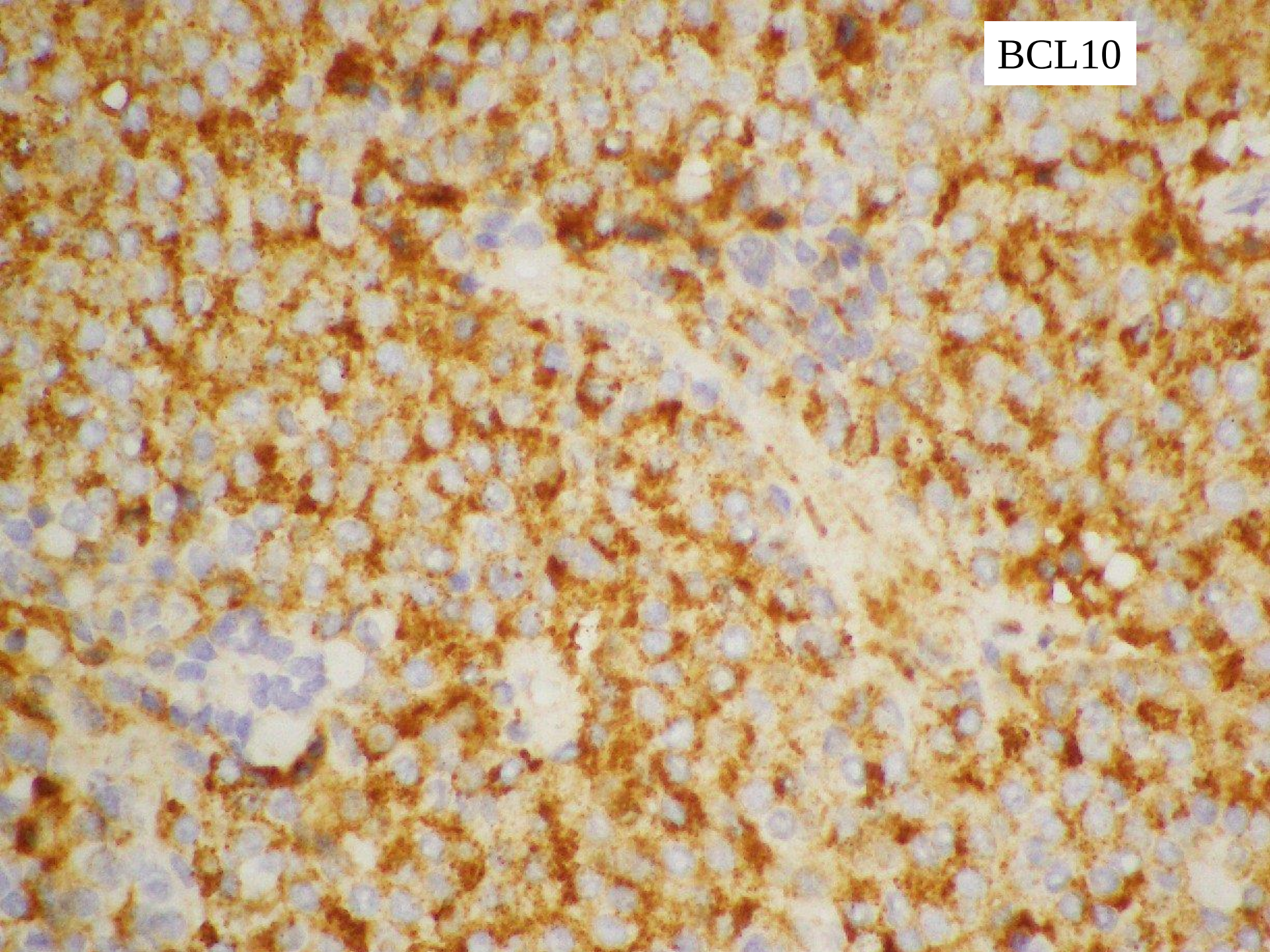
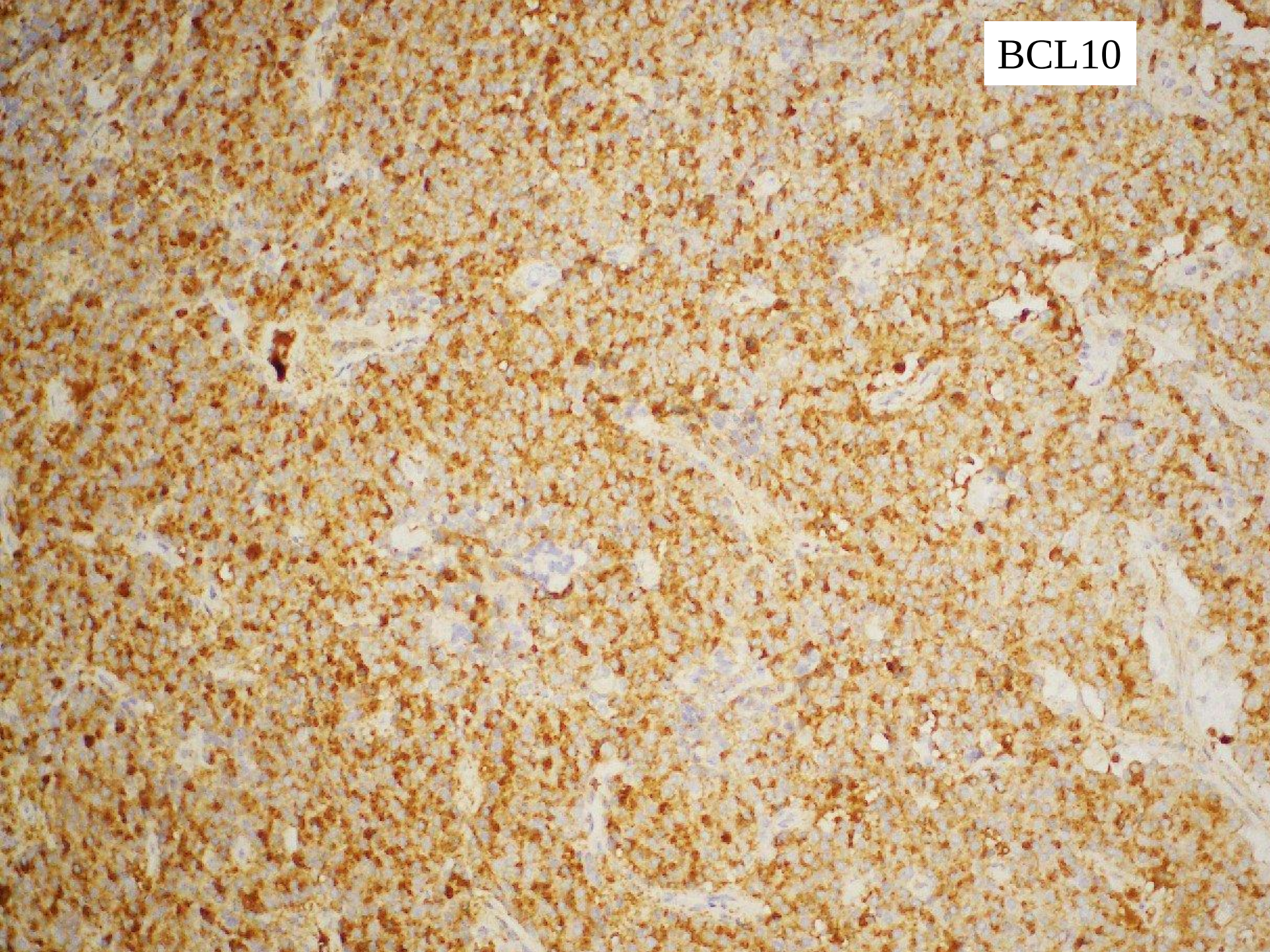
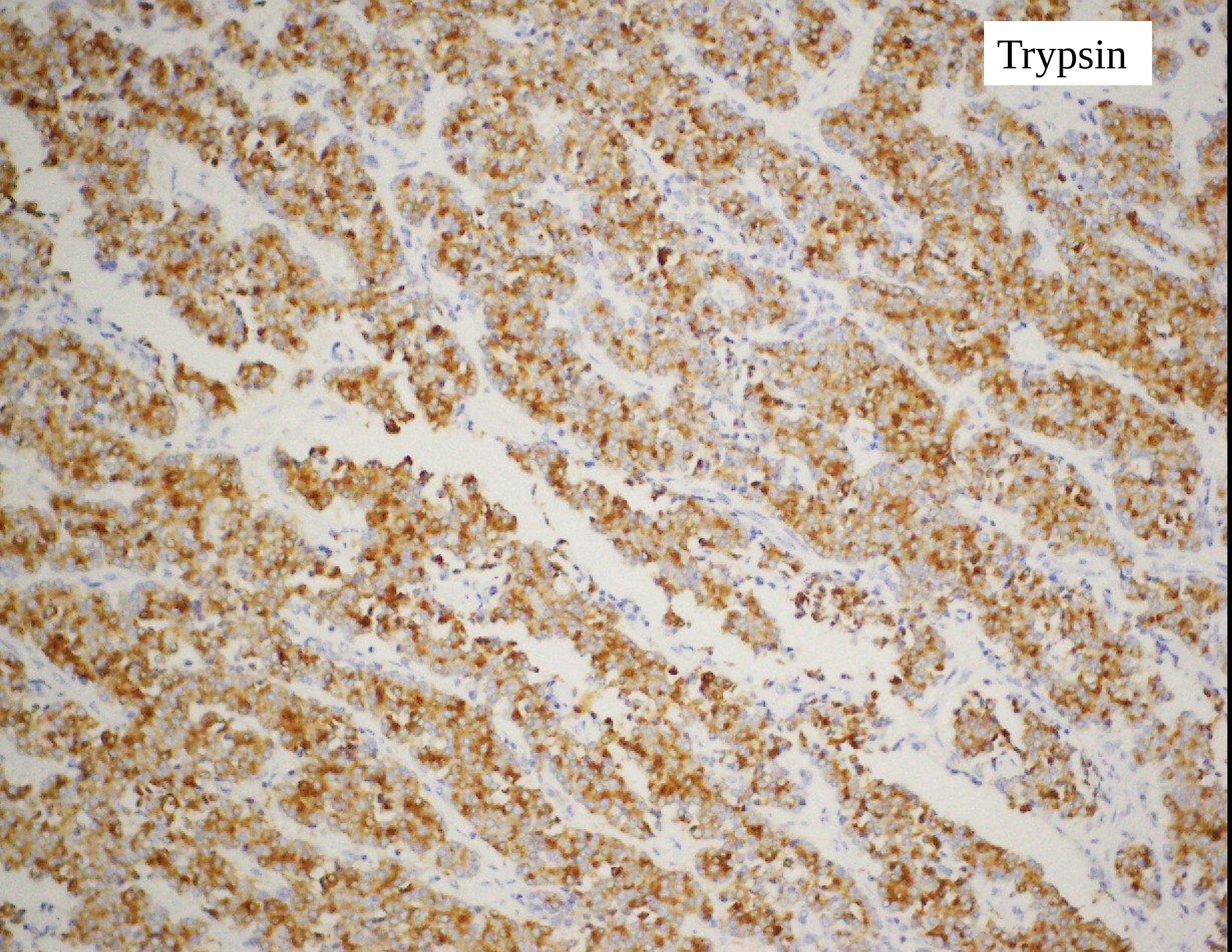

BCL10


BCL10


Trypsin

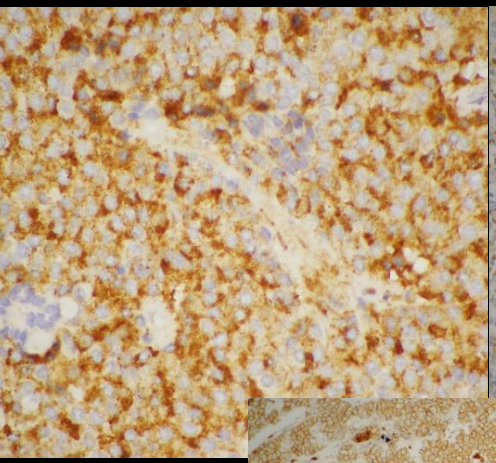
Outcome

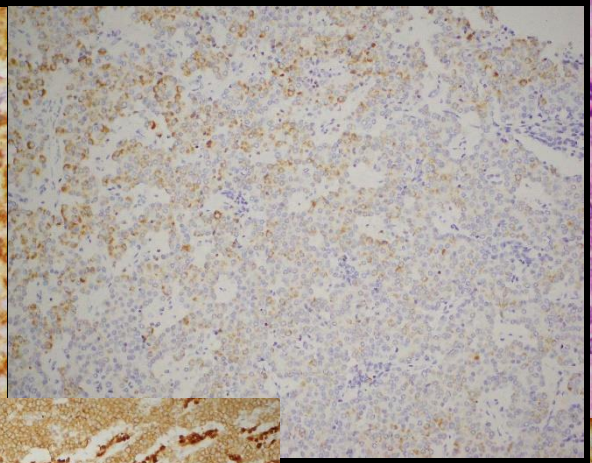
Outcome is better than pancreatic cancer, 5year survival for resected patients 50-65%

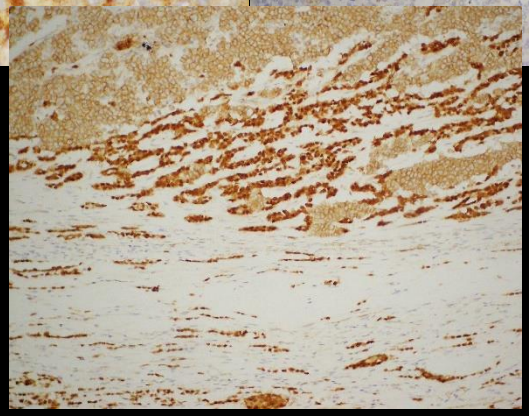
Children may have better outcome than adults

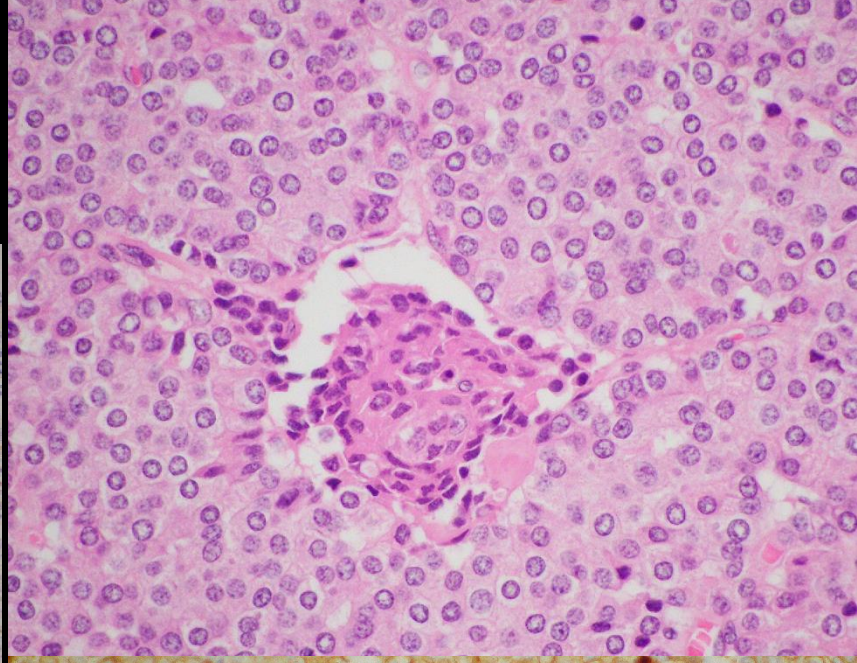
Cases reported in association with Beckwith-Widemann syndrome and FAP

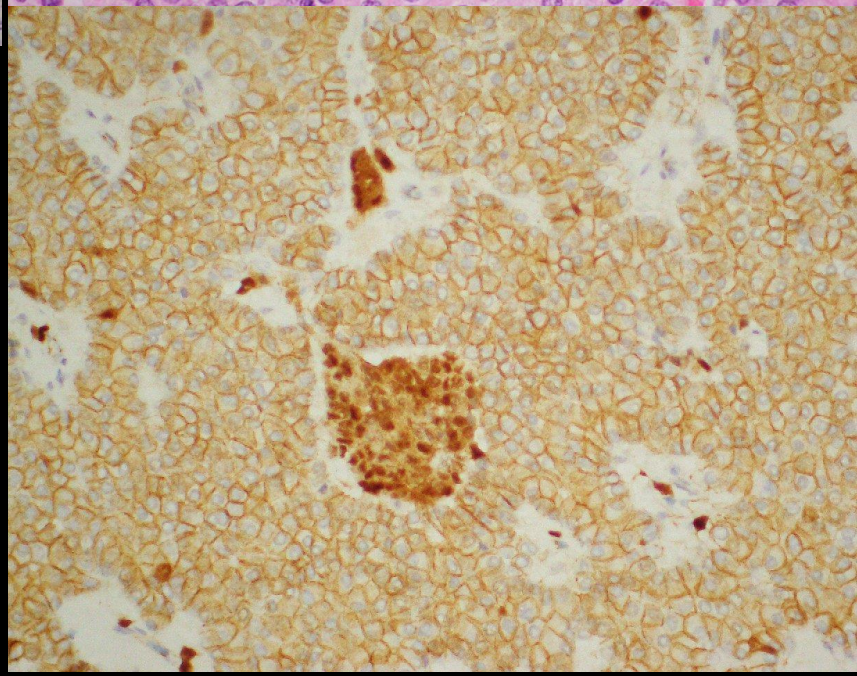
Pancreatoblastoma











Clues are squamous morules

Mosaic beta-catenin pattern is key!!

Traps are:

Not all morules obvious

Trilineage expression (nets,acinar)

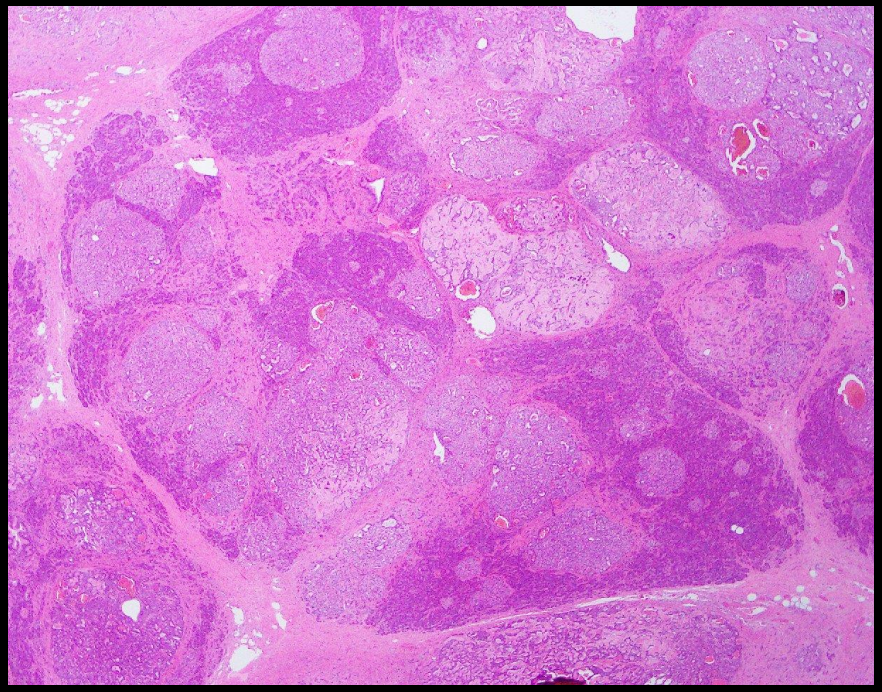
Three commonly missed pancreatic pathologies that are NOT simple neuroendocrine tumours

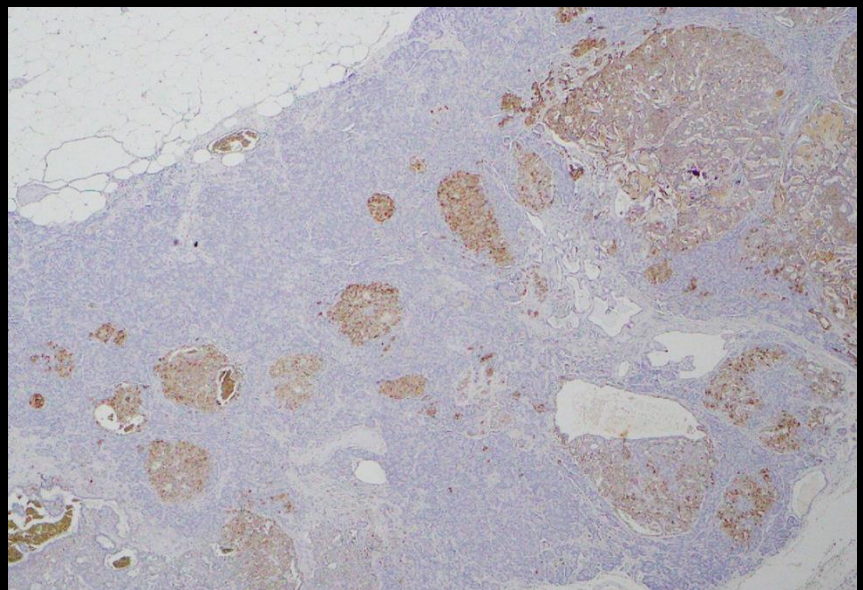
Glucagon cell adenomatosis (germline glucagon receptor mutation)

Pancreatic acinar cell carcinoma

Pancreatoblastoma

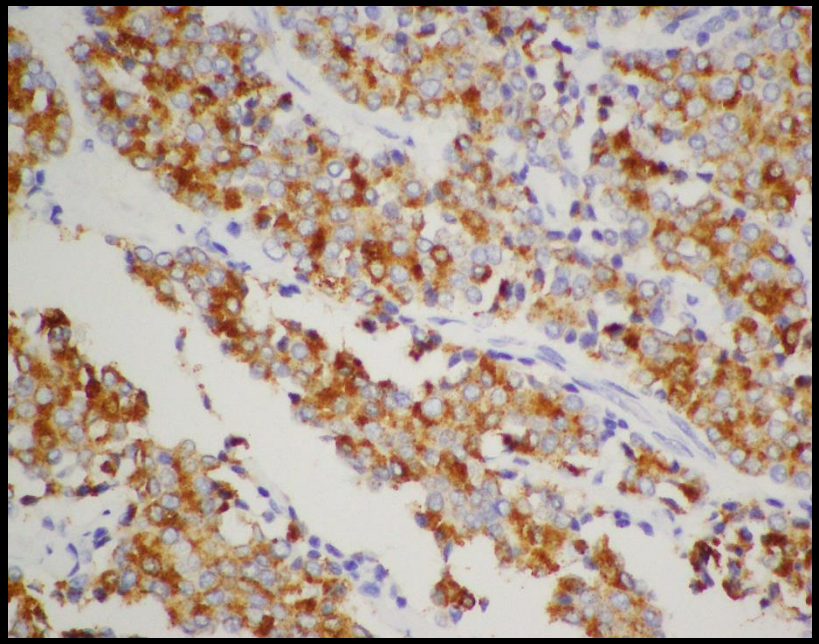
Glucagon cell adenomatosis

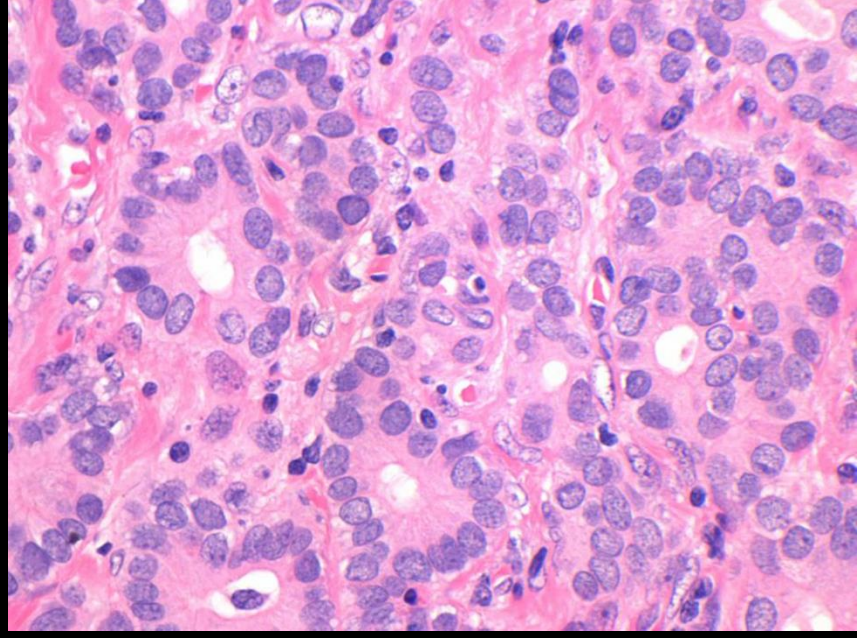


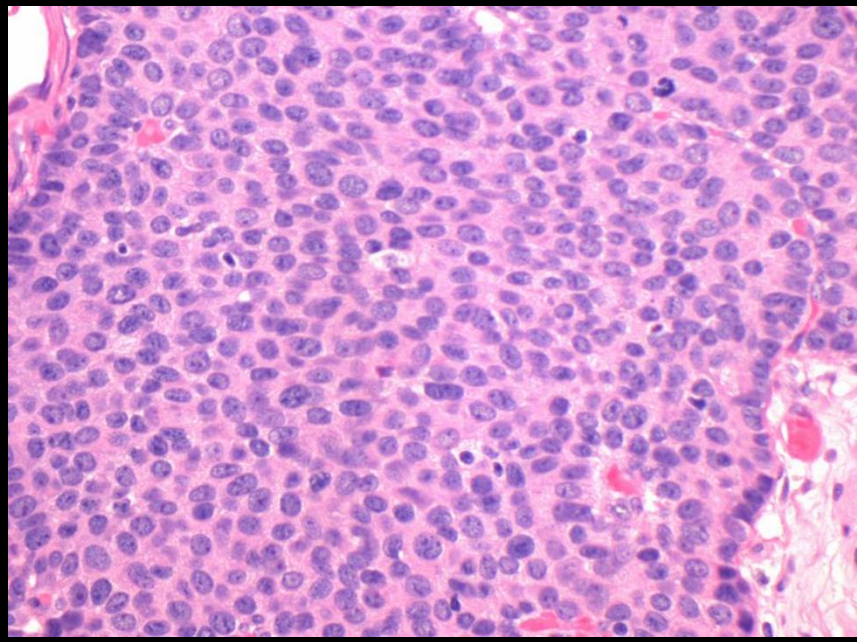


Consider whenever multiple glucagon producing tumours or widespread hyperplasia and not MEN1

Acinar cell carcinoma



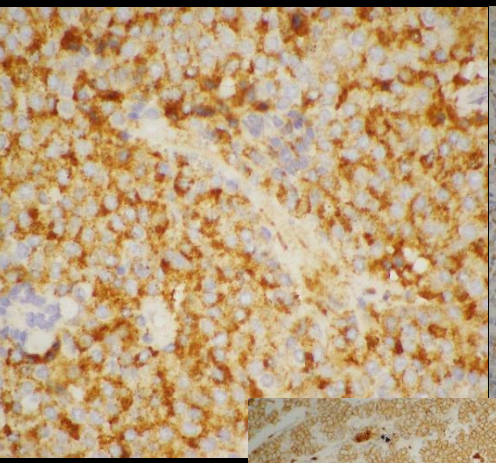


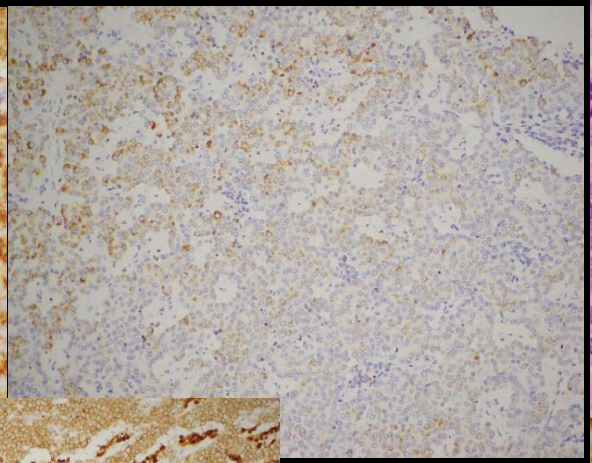


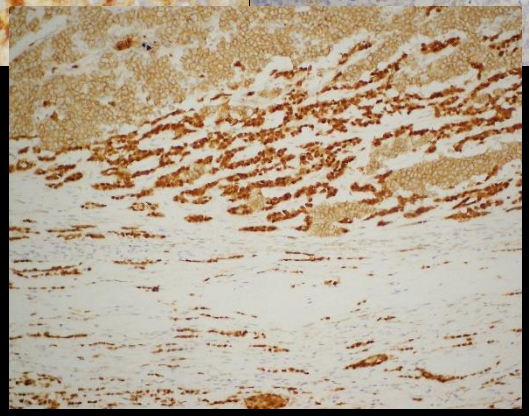
Best markers are BCL10 and Trypsin
Looks like a PNET but negative for chromogranin

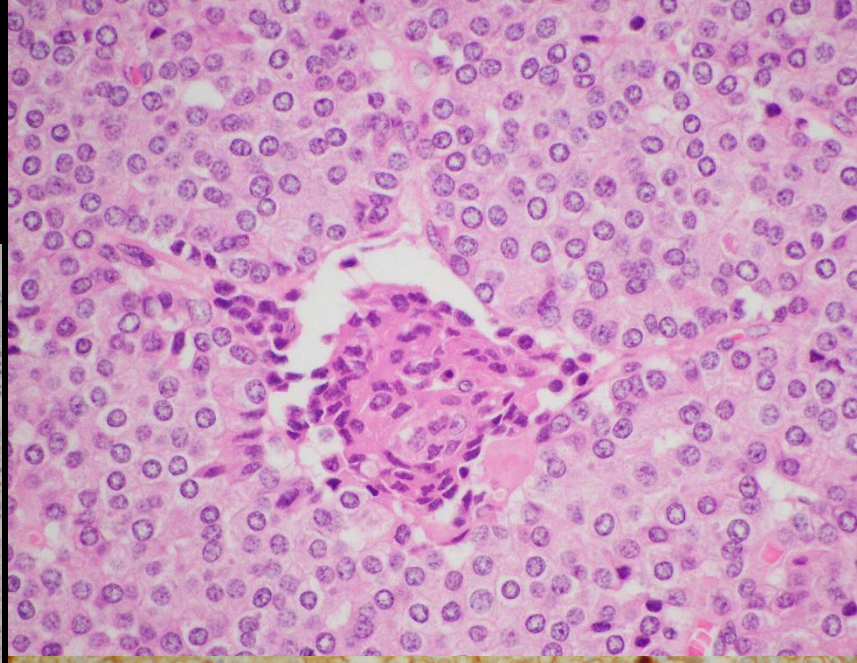
Traps are:
May be mixed (MiNEN)
May have nuclear beta-catenin staining

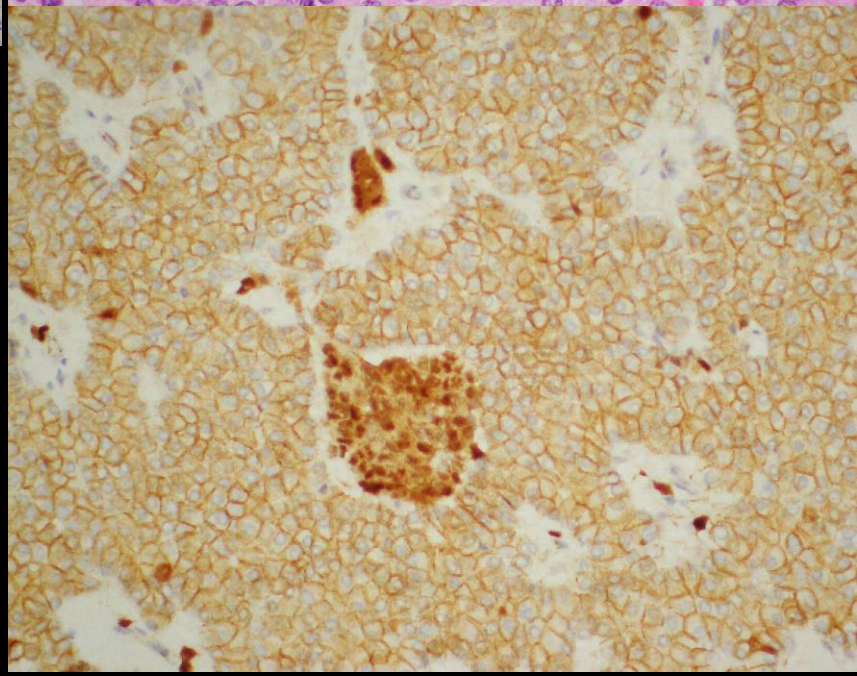
Pancreatoblastoma











Clues are squamous morules (beta-catenin pos)

Traps are:
Not all morules obvious
Trilineage expression (nets,acinar)