Pancreas Fine Needle Aspiration (FNA)

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- No relevant financial relationships with ineligible companies to disclose

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Outlines

- Top 3 pancreas FNA challenges:

1. Normal elements vs neoplasms
2. Mucinous cyst vs contaminants
3. Adenocarcinoma vs other

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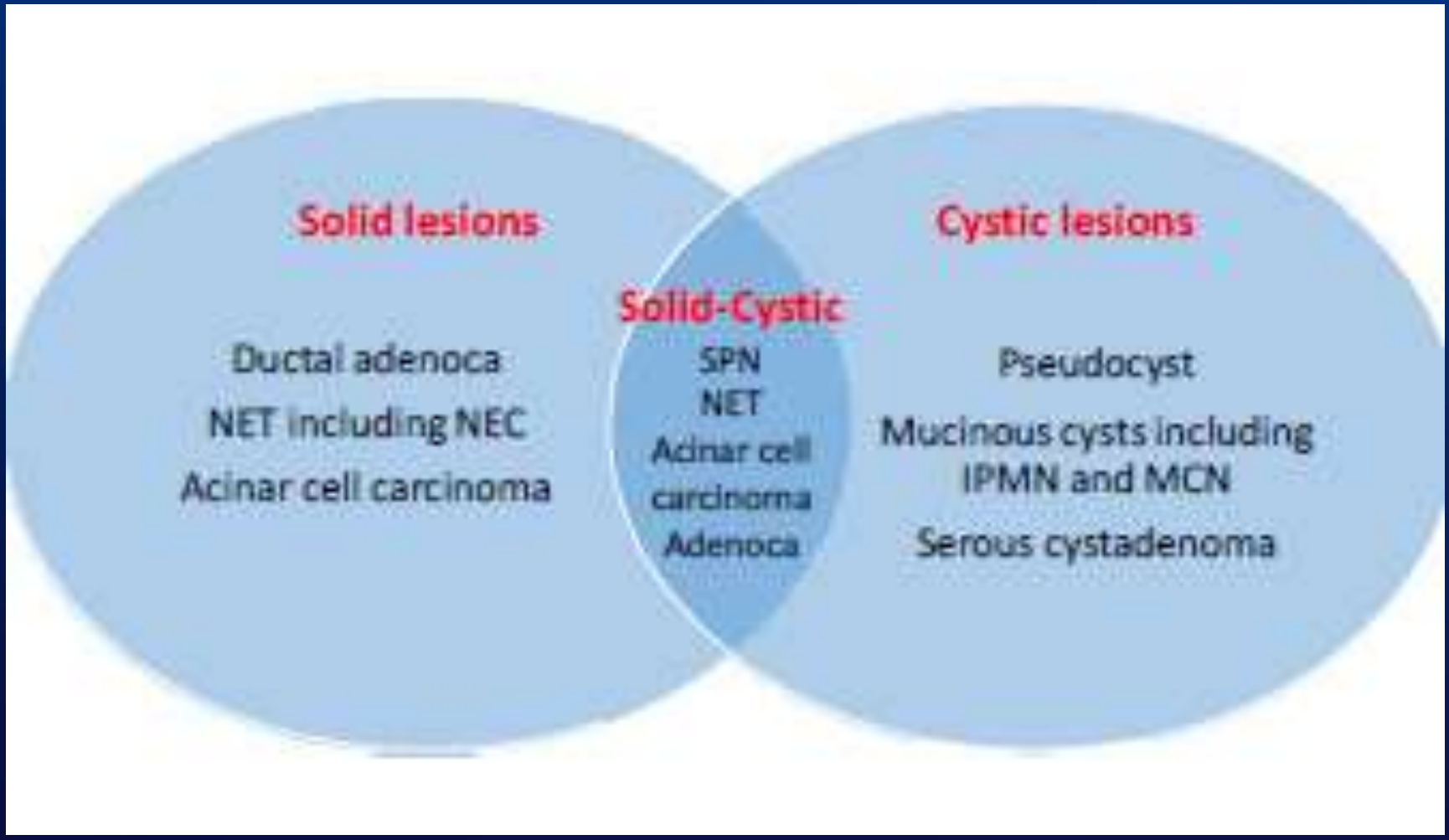
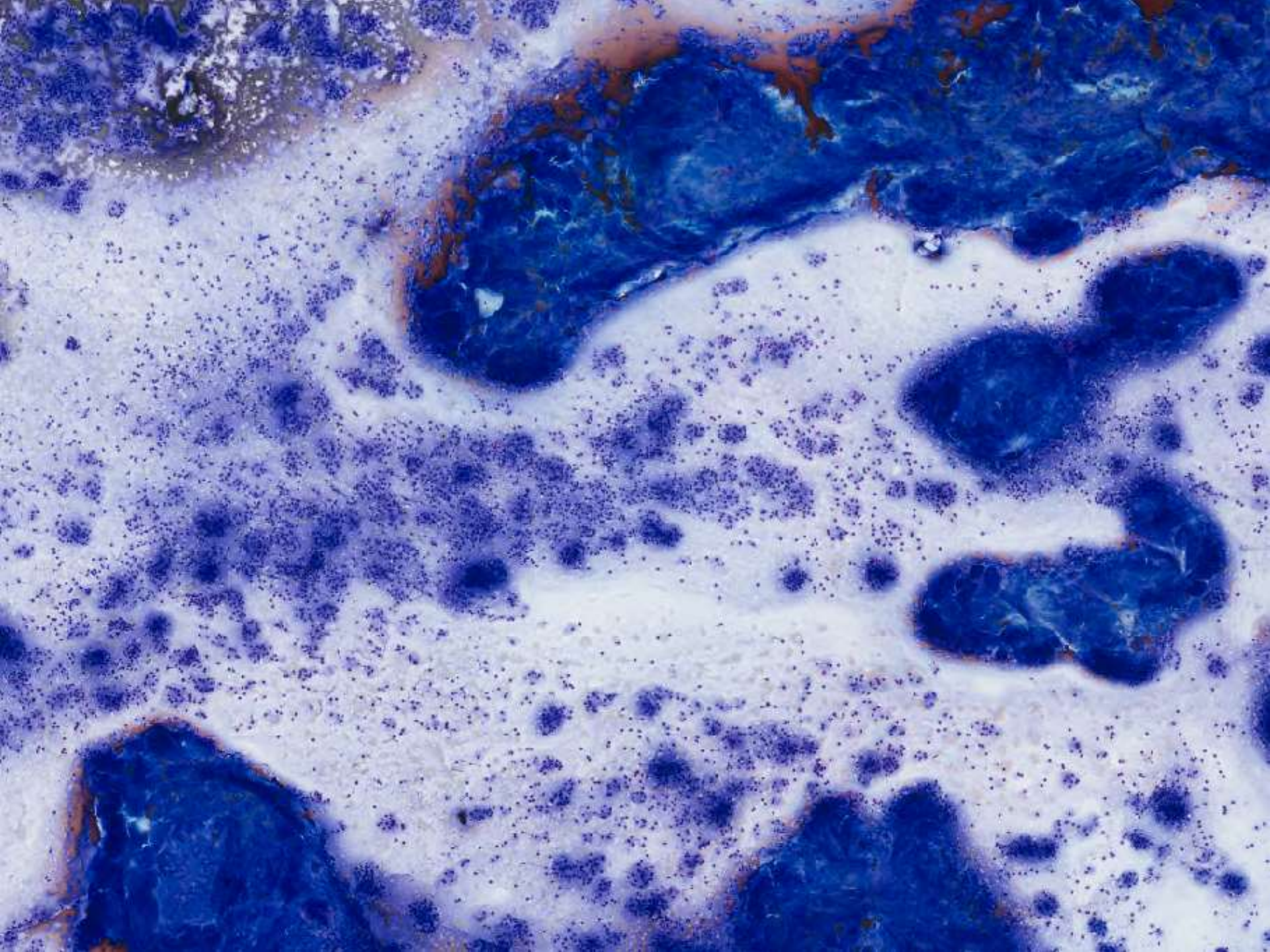
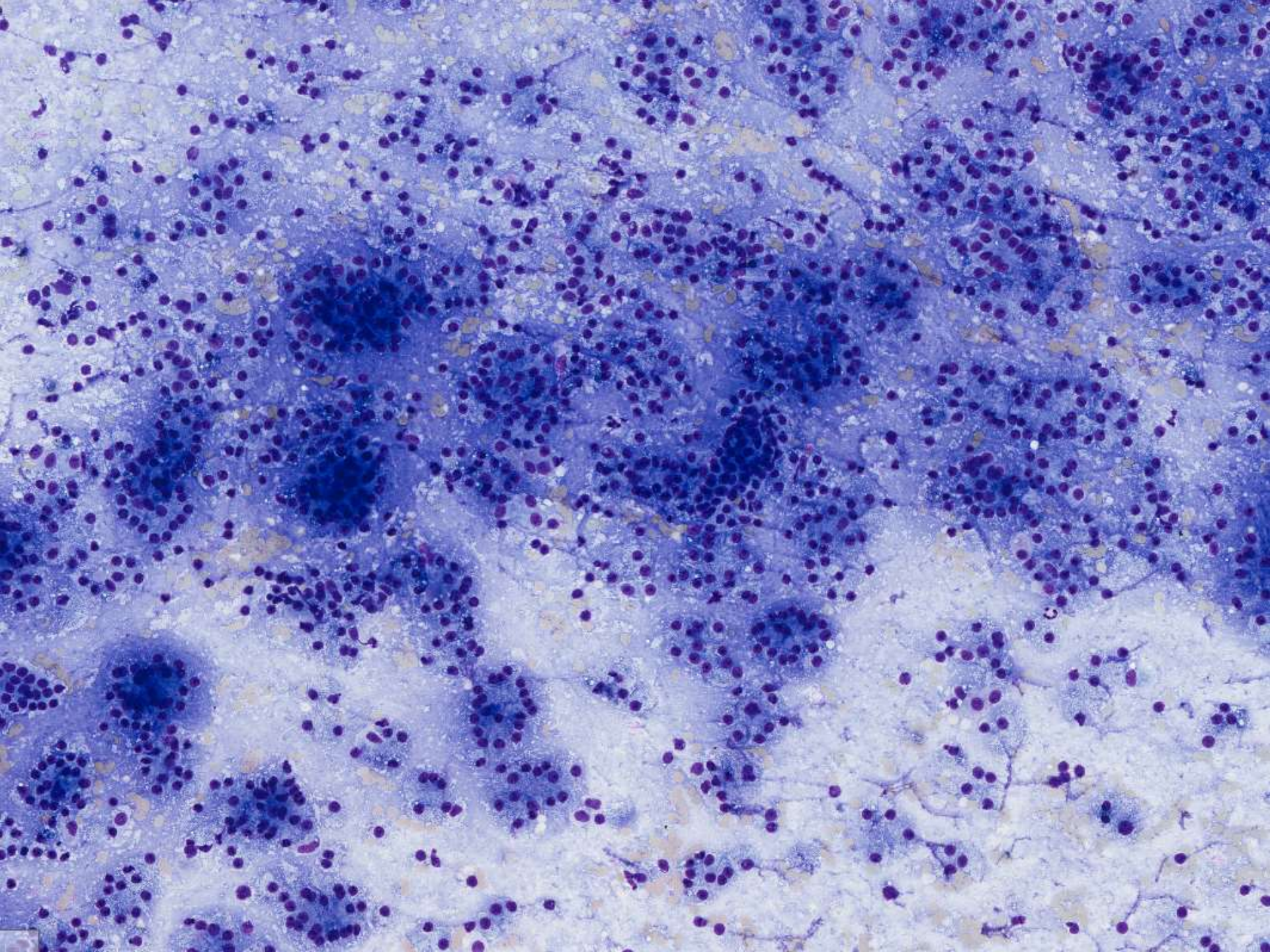
Case 1

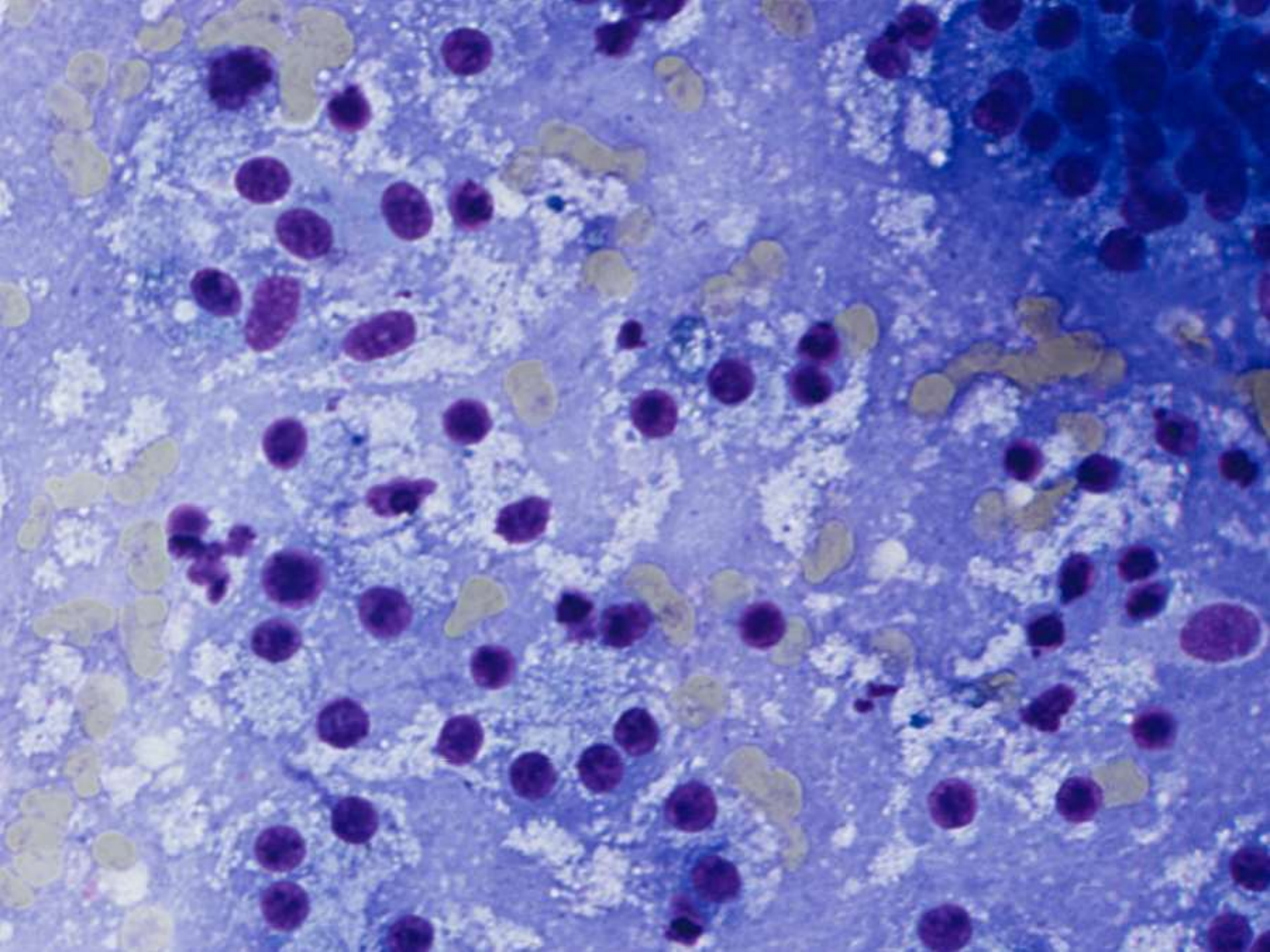
27 year old woman with a 0.7 cm well circumscribed solid-cystic pancreatic body neoplasm

Imaging









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ROSE

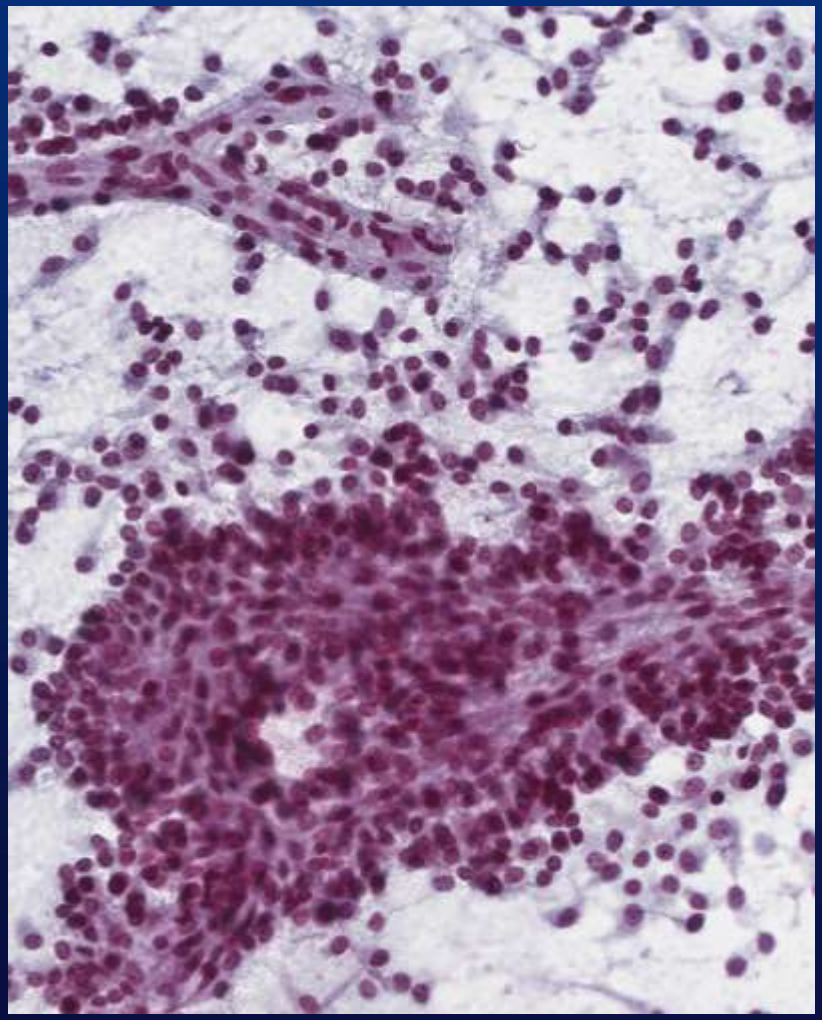
Suspicious for neoplasm, possibly solid pseudopapillary neoplasm (SPN) or pancreatic neuroendocrine tumor (PanNET)

Standardized Terminology and Nomenclature for Pancreato- Biliary Cytology

- I. Non- Diagnostic
- II. Negative for malignancy
- III. Atypical
- IV. Neoplastic:
  - Benign (serous cystadenoma)
  - Other:
    - Mucinous cysts (low- and high- grade dysplasia)
    - Well- differentiated neuroendocrine tumors
    - Solid- pseudopapillary neoplasm
- V. Suspicious for malignancy
- VI. Positive for malignancy

Diagn Cytopathol 2014, April 42 (4):338-50

Solid Pseudopapillary Neoplasm (SPN)



- Highly cellular, dyscohesive cells
- Pseudopapillary structures
- Loosely cohesive clusters, surrounding hyalinized to myxoid stroma with fibrovascular stroma
- Irregular nuclear contours, grooves
- Extracellular hyaline globules

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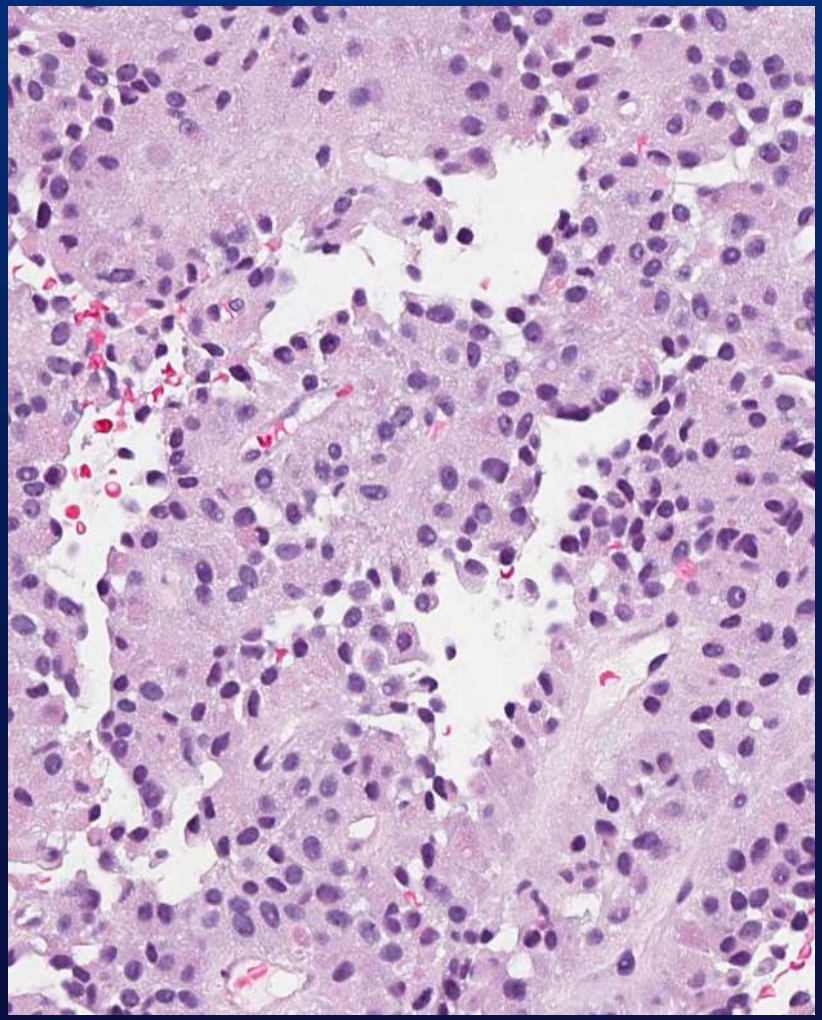
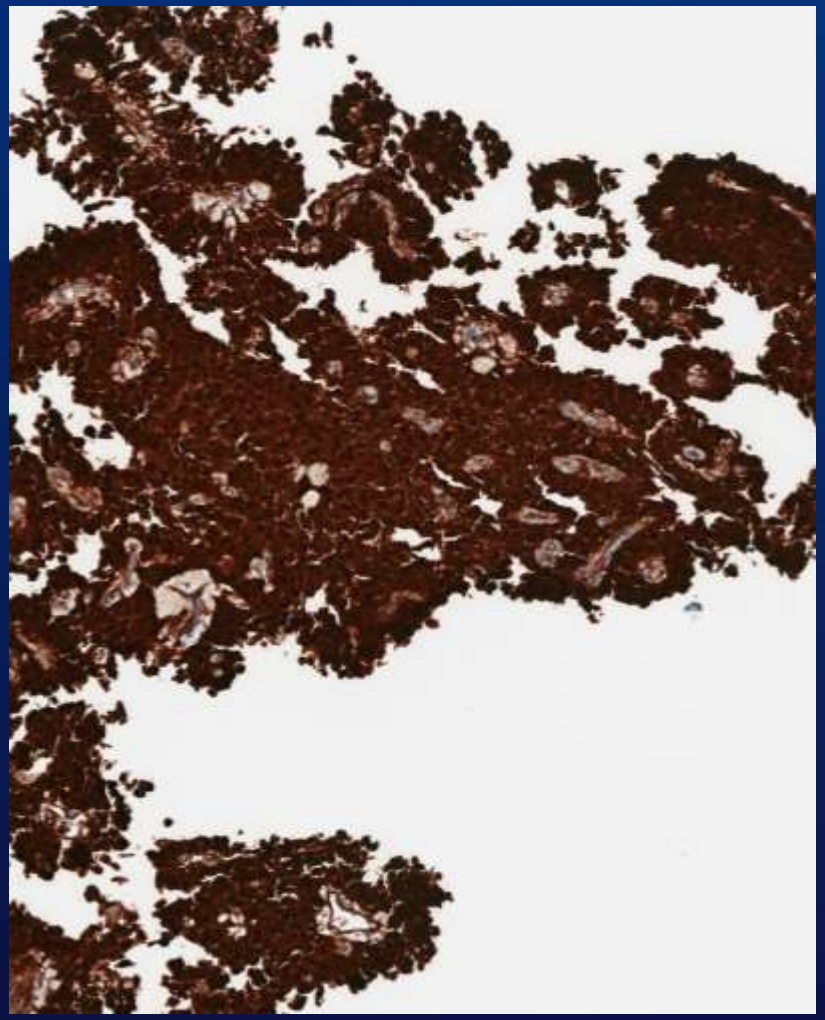
SPN (CB) +Beta- Catenin





Images by Dr. Longwen Chen

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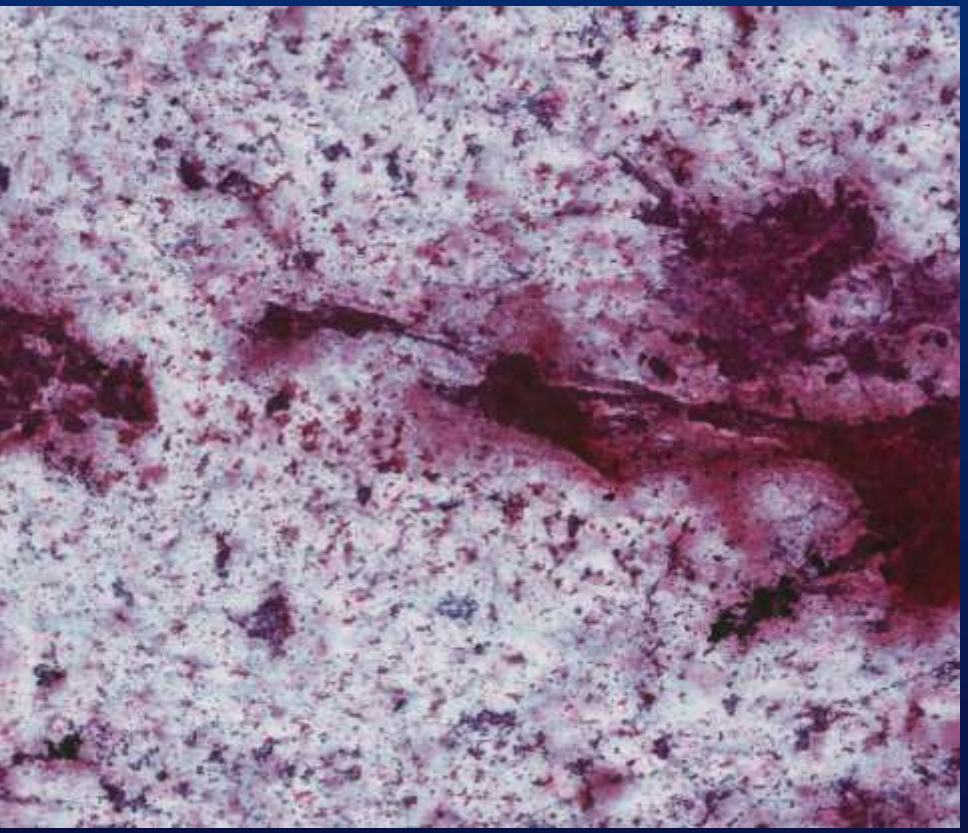
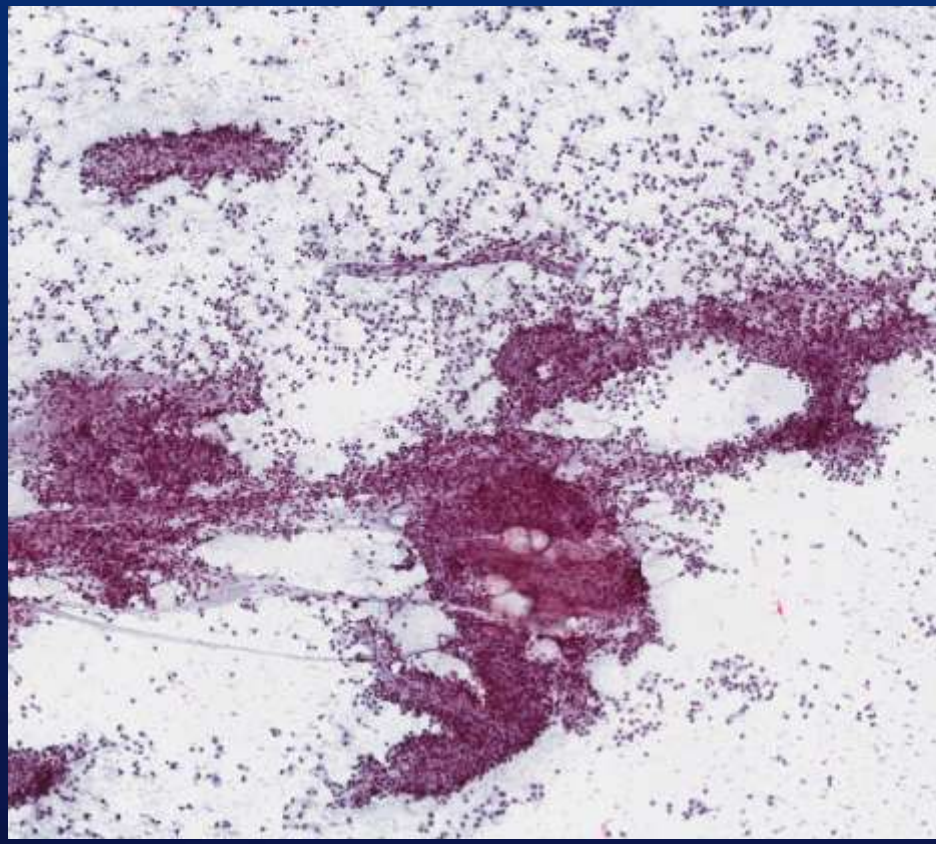
Case 1 Vs SPN





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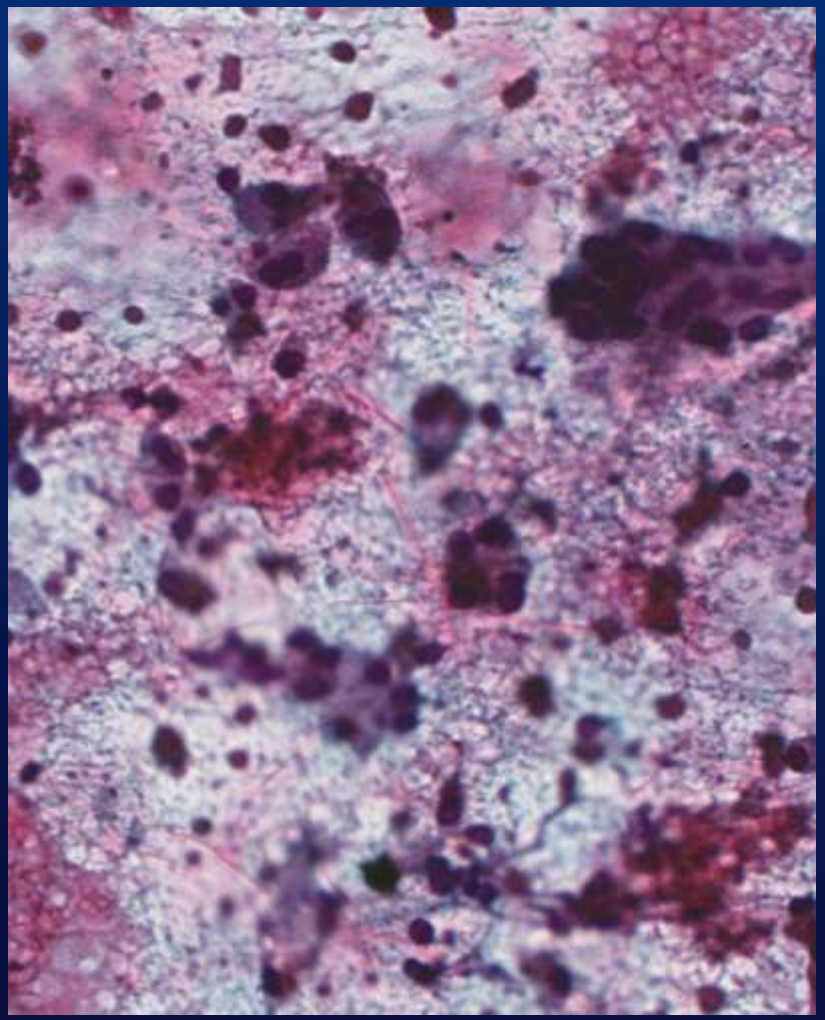

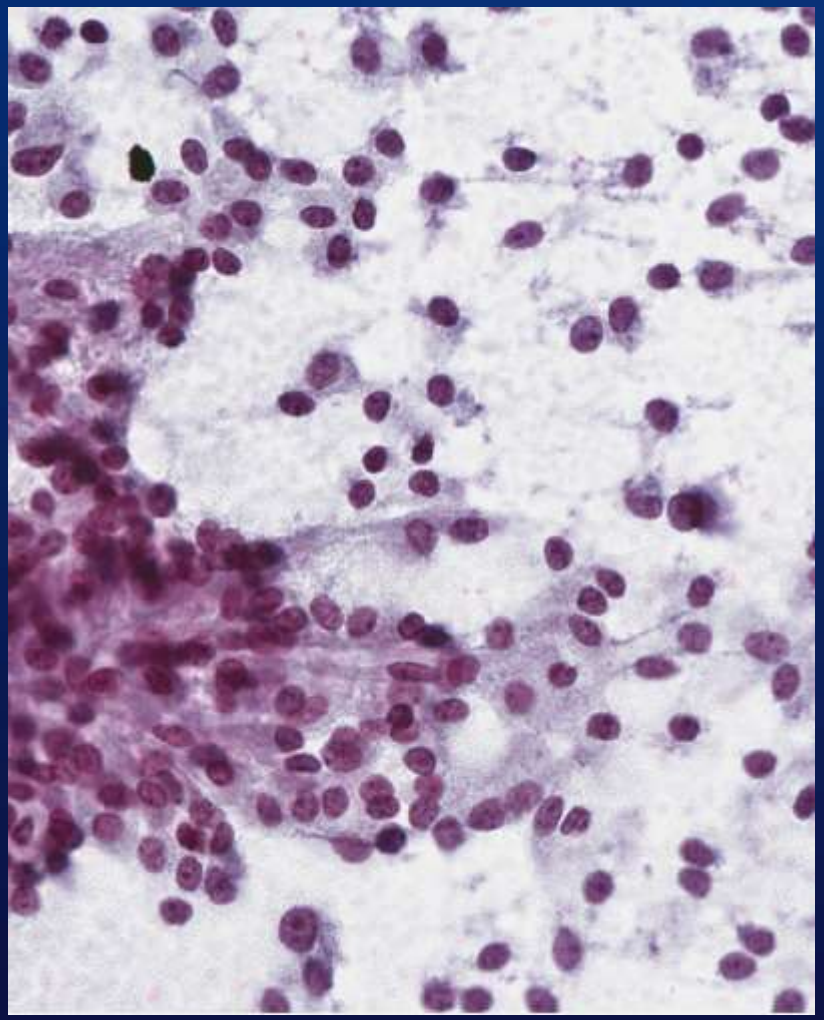

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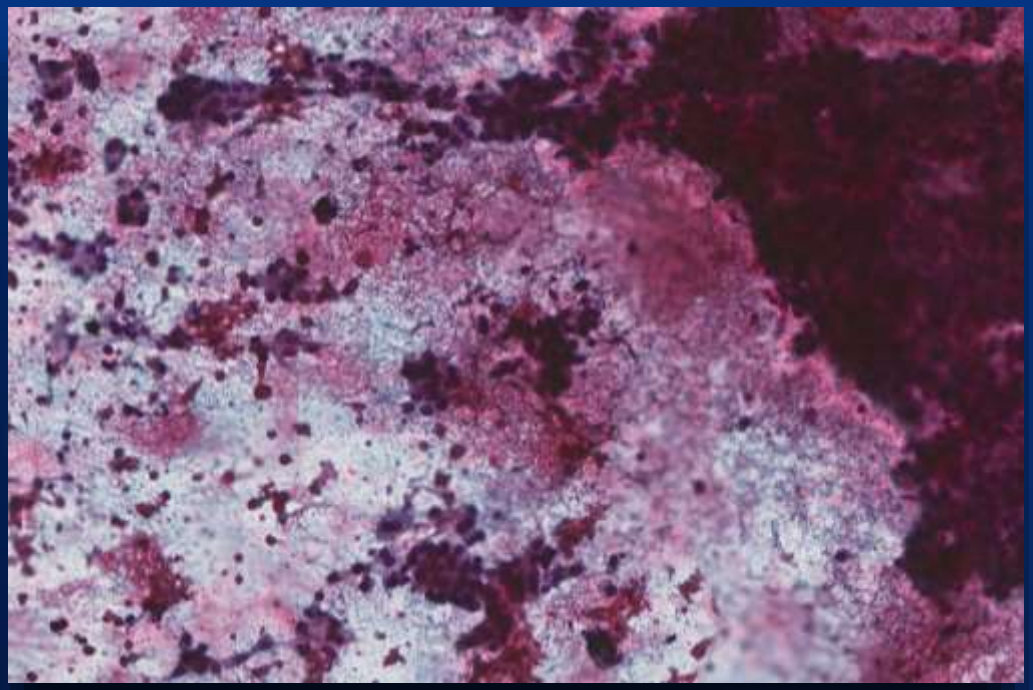
??? Neoplastic vs Non- Neoplastic

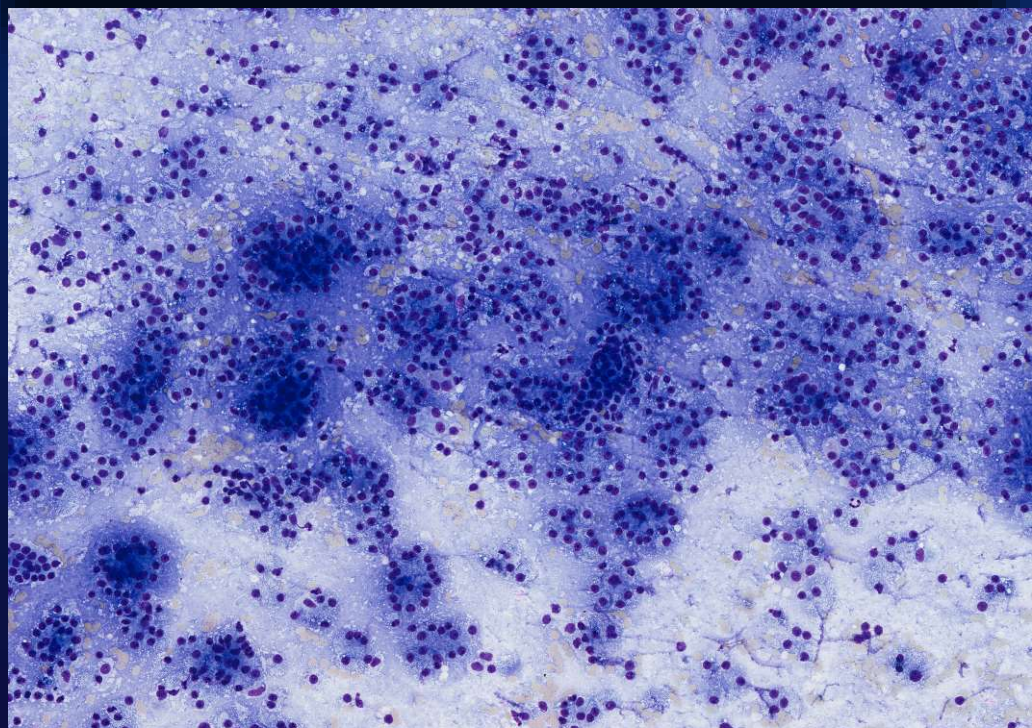
Case 1 Final Diagnosis:
- Non- diagnostic

B9 pancreatic cells only, likely not representative of the lesion seen on imaging.

Case 1: Normal Pancreas Misdiagnosed as Neoplastic

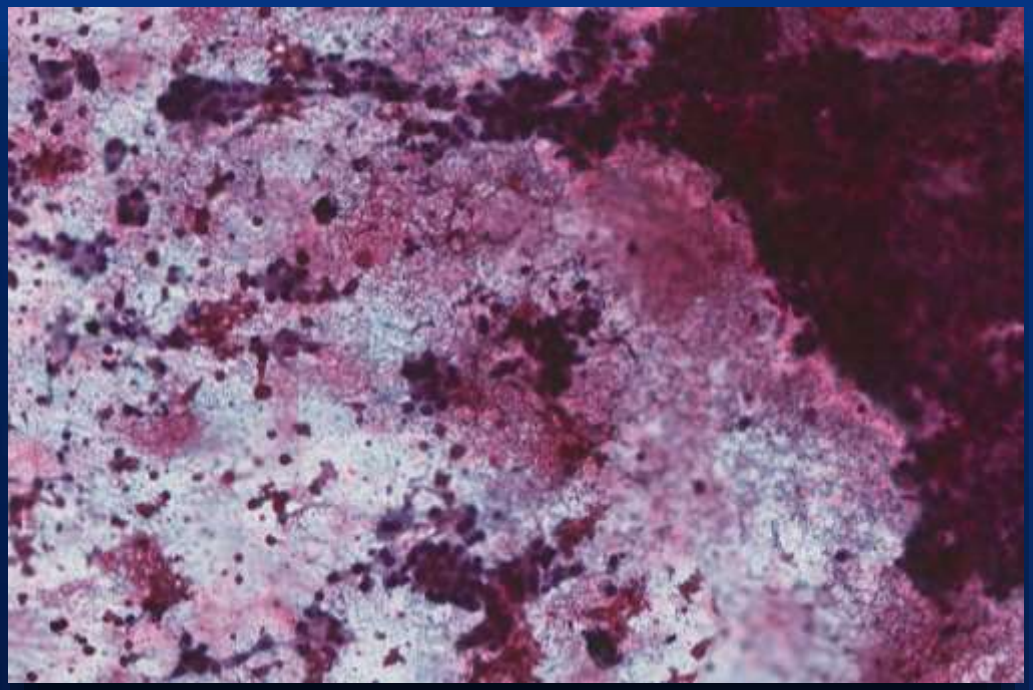
- Predominance of acinar cells:
  - Cohesive, small grape-like, rosette- like clusters adhesed to fibrovascular stroma, scattered single cells and naked nuclei
  - Abundant granular cytoplasm (DQ: small vacuoles)
  - Basally located, round nuclei, central to eccentric, uniform chromatin, single prominent nucleoli

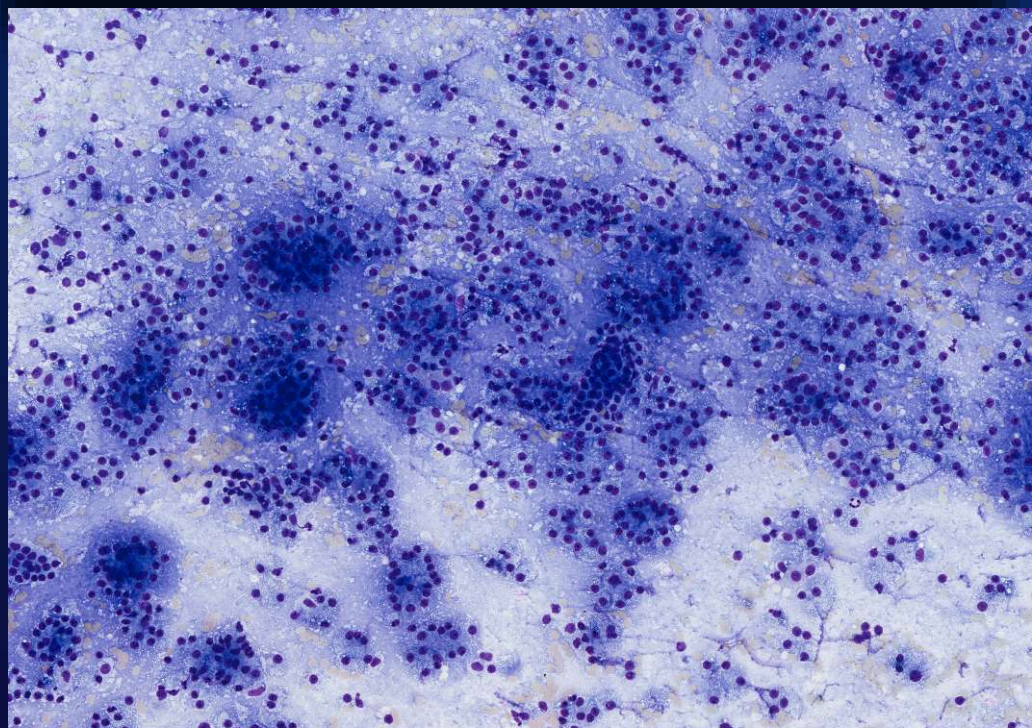




Case 1: Normal Pancreas Misdiagnosed as Neoplastic

- **Architecture: Key to differentiate B9 acinar cells (small uniform grape- like, adhesed to fibrovascular stroma) from neoplasm**





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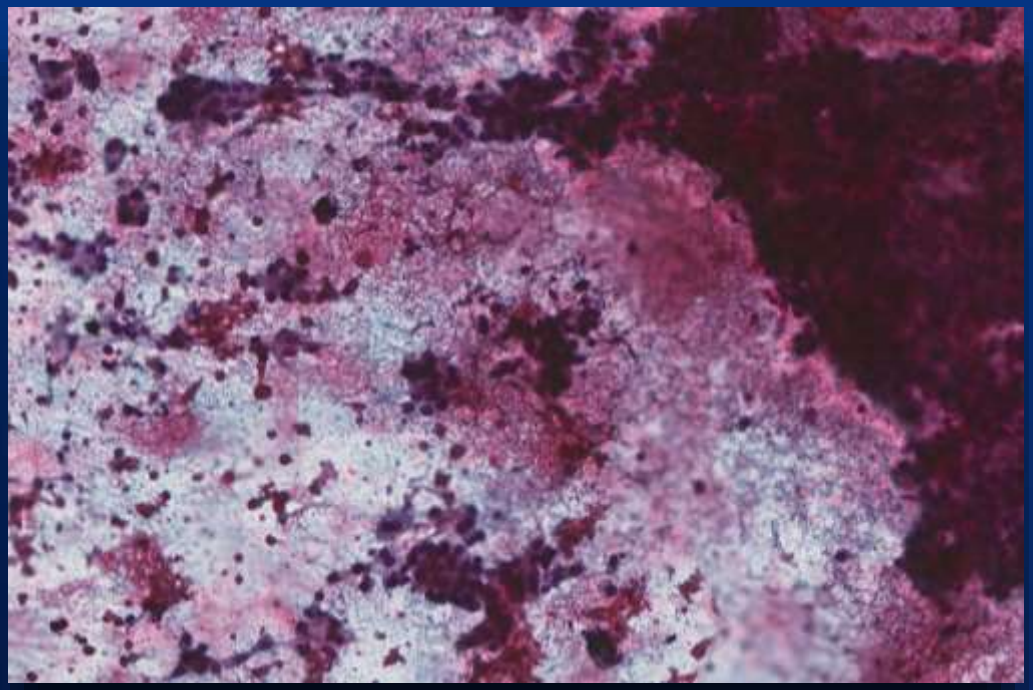
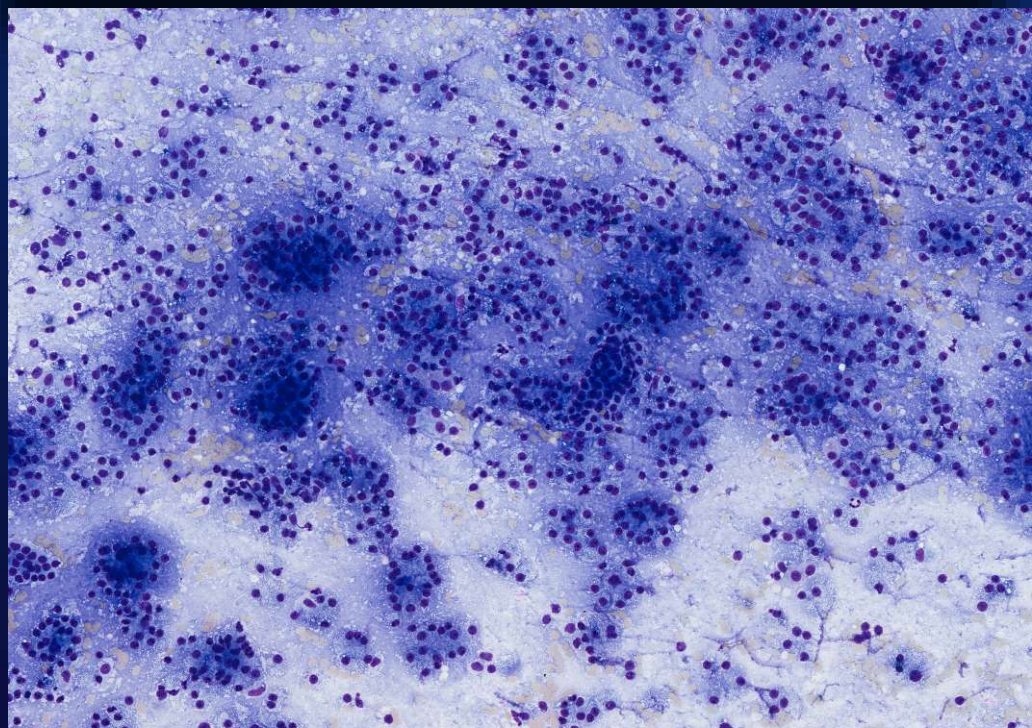
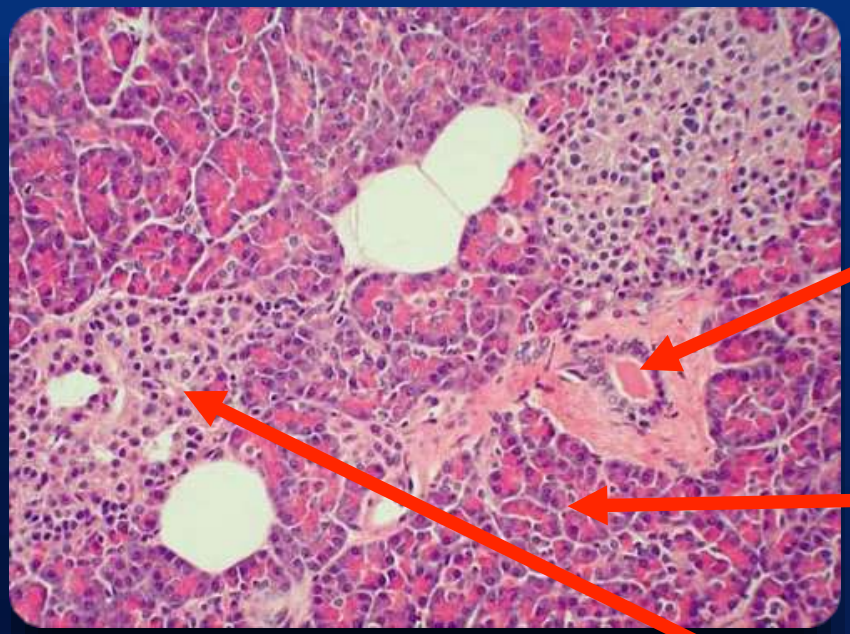
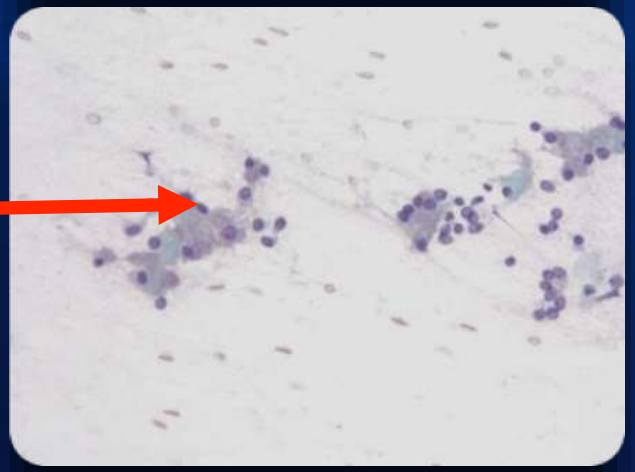




Normal Pancreas



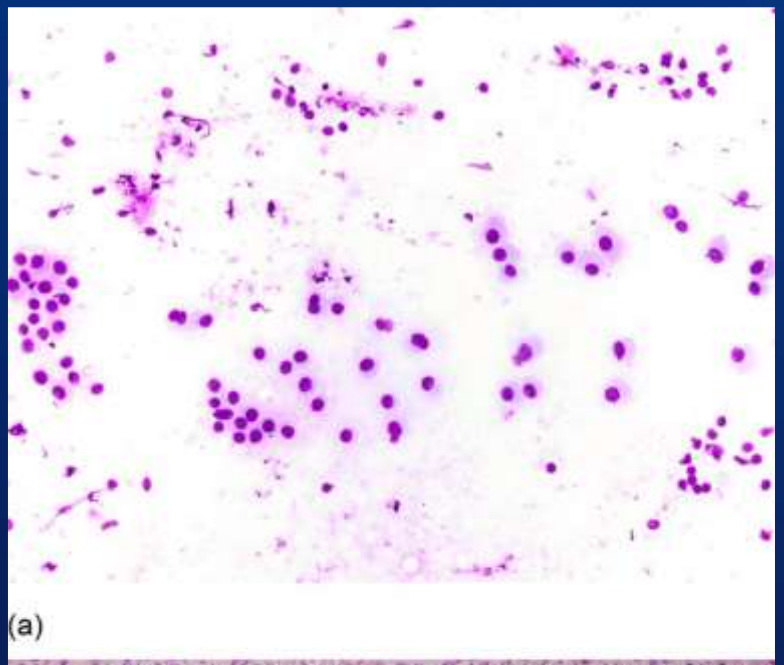


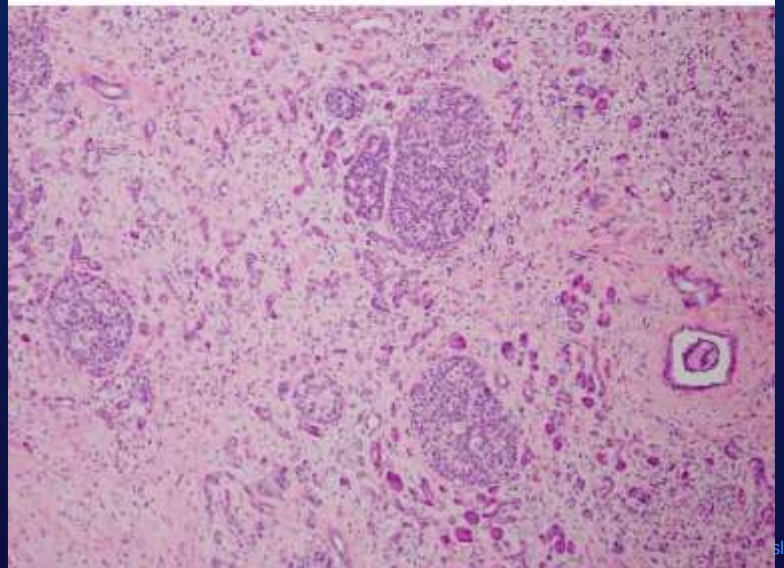
- Ductal cells
- Acinar cells
- Islet cells

Slide by Dr. Matthew Zarka

Islet Cells in Chronic Pancreatitis (CP) Misdiagnosed as PanNET on FNA

- Isolated and loosely cohesive cells with eccentrically located bland appearing nuclei
- Background of lymphocytes
- Resection:
  - CP with Predominance of islet cells





Begeron JP et al. Endoscopic Ultrasound- Guided Pancreatic Fine- Needle Aspiration: Potential Pitfalls in One Institution's Experience of 1212 Procedures. Cancer Cytopathology 2015; 98-107.

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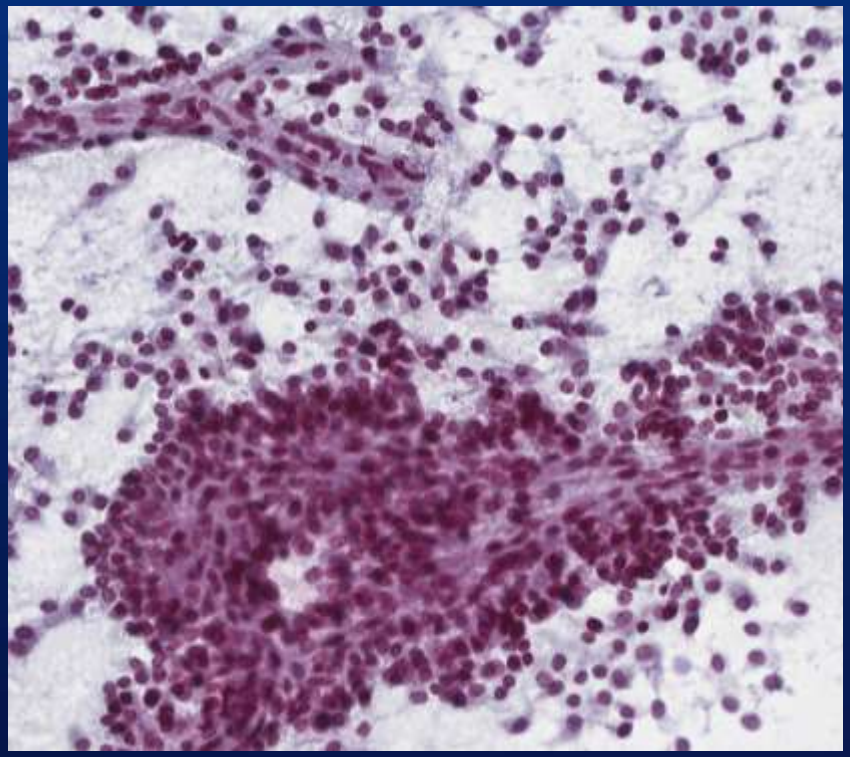
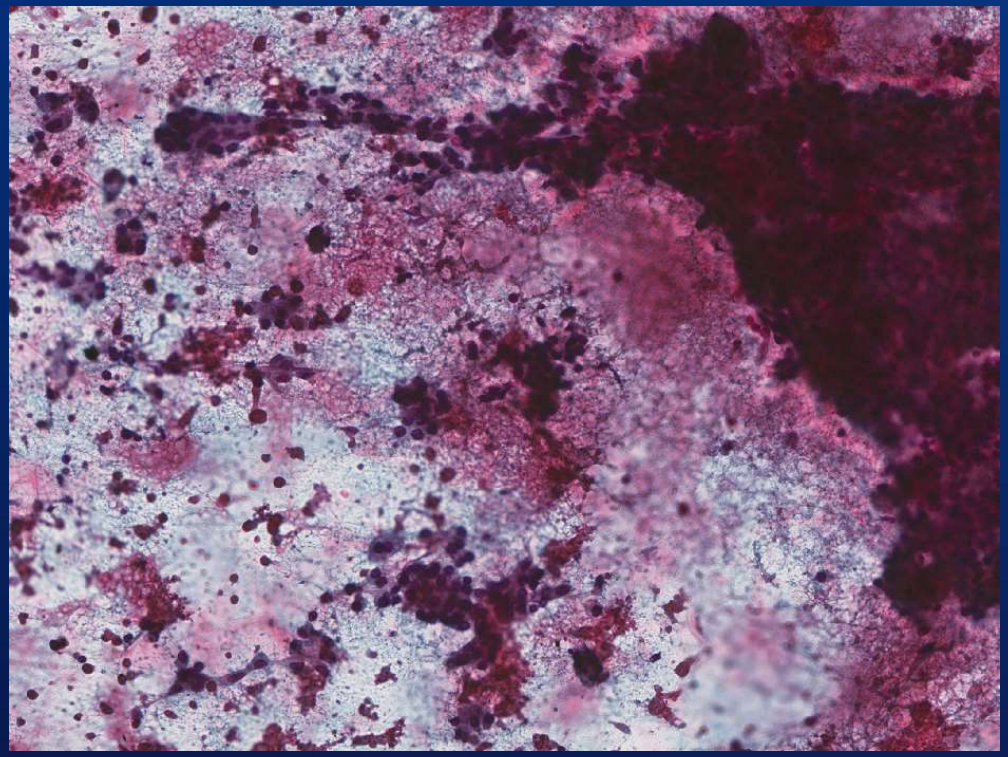
B9 Pancreas FNA

SPN vs B9 Pancreas

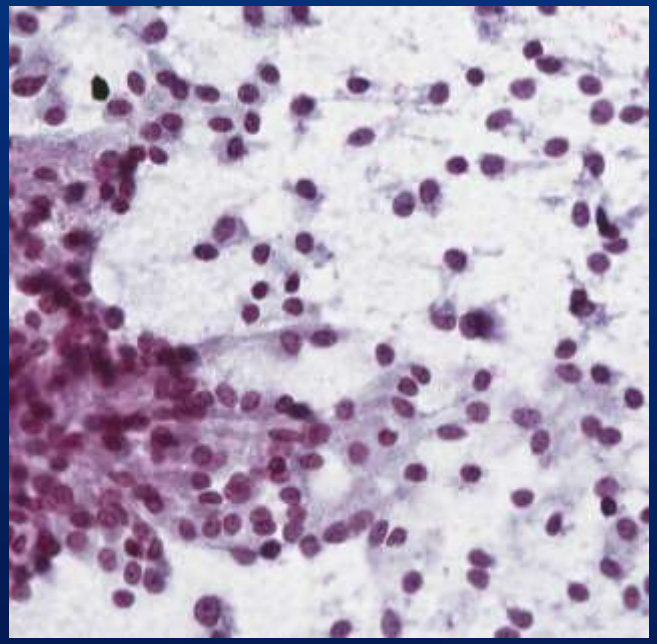




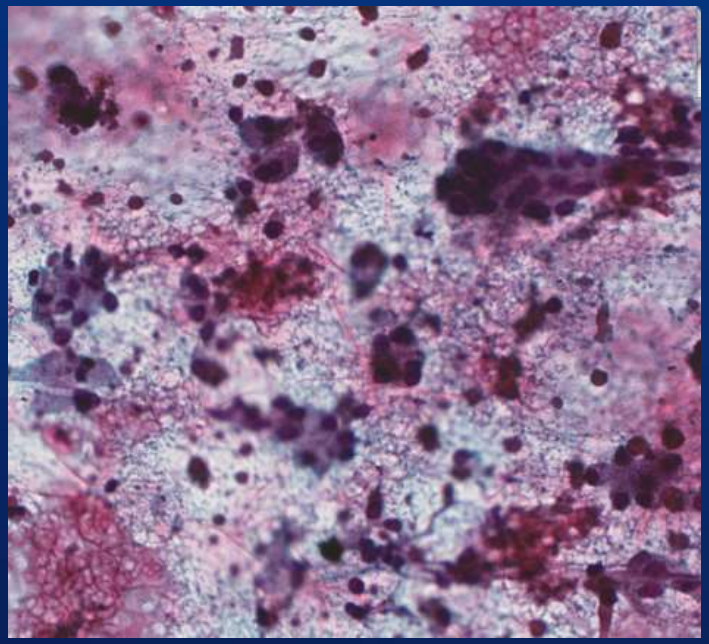
- Loosely cohesive clusters
- Cells surround hyalinized to myxoid stroma with fibrovascular stroma

- Majority of groups more cohesive and uniform clusters
- “Grape-like” architecture
- Uniform cells adhesed to fibrovascular core

SPN vs B9 Pancreas

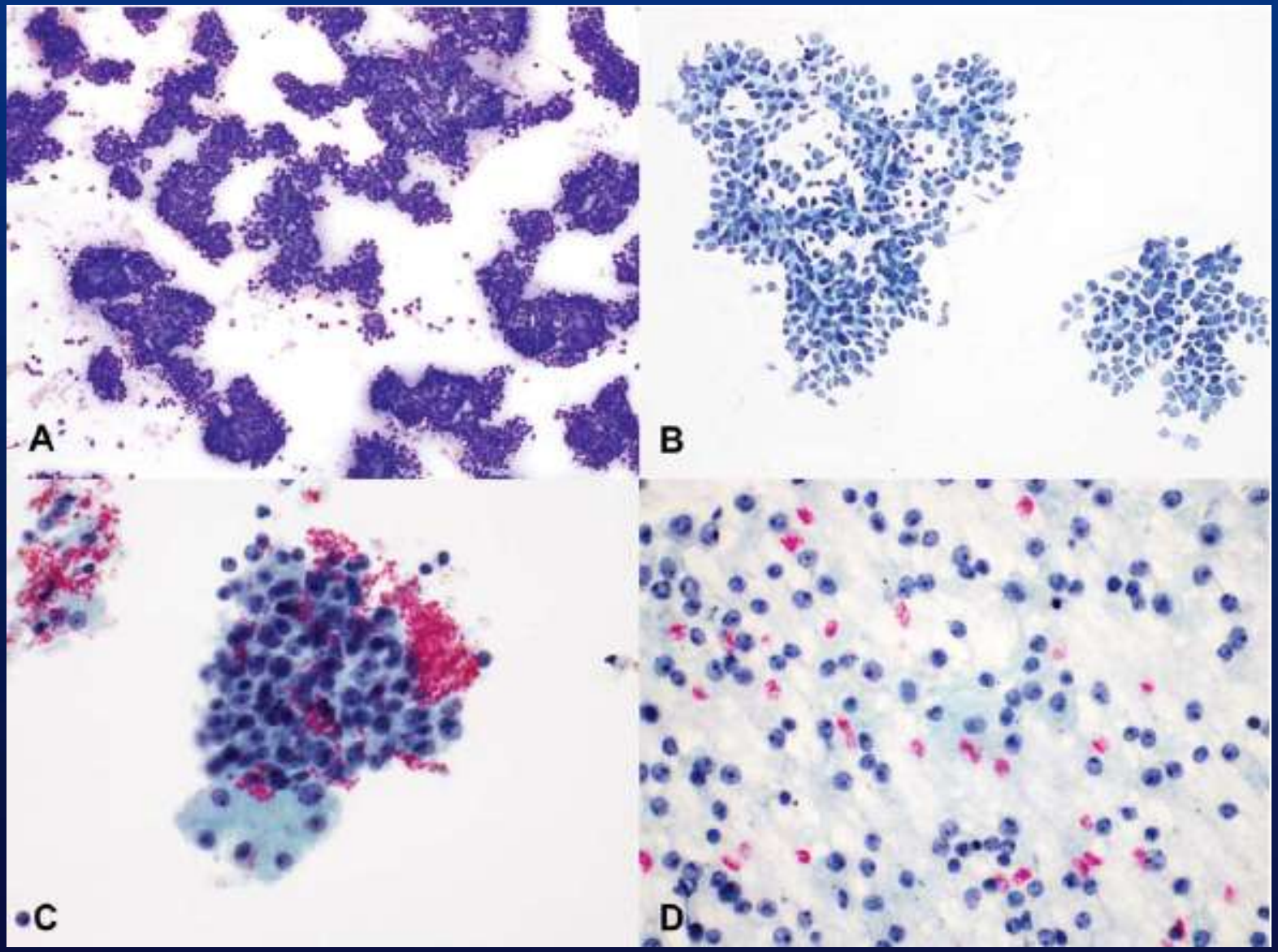


- Mild nuclear enlargement
- Nuclei: irregular contours, bean shaped, grooves
- Cytoplasmic tails
- Extracellular PAS+ hyaline globules



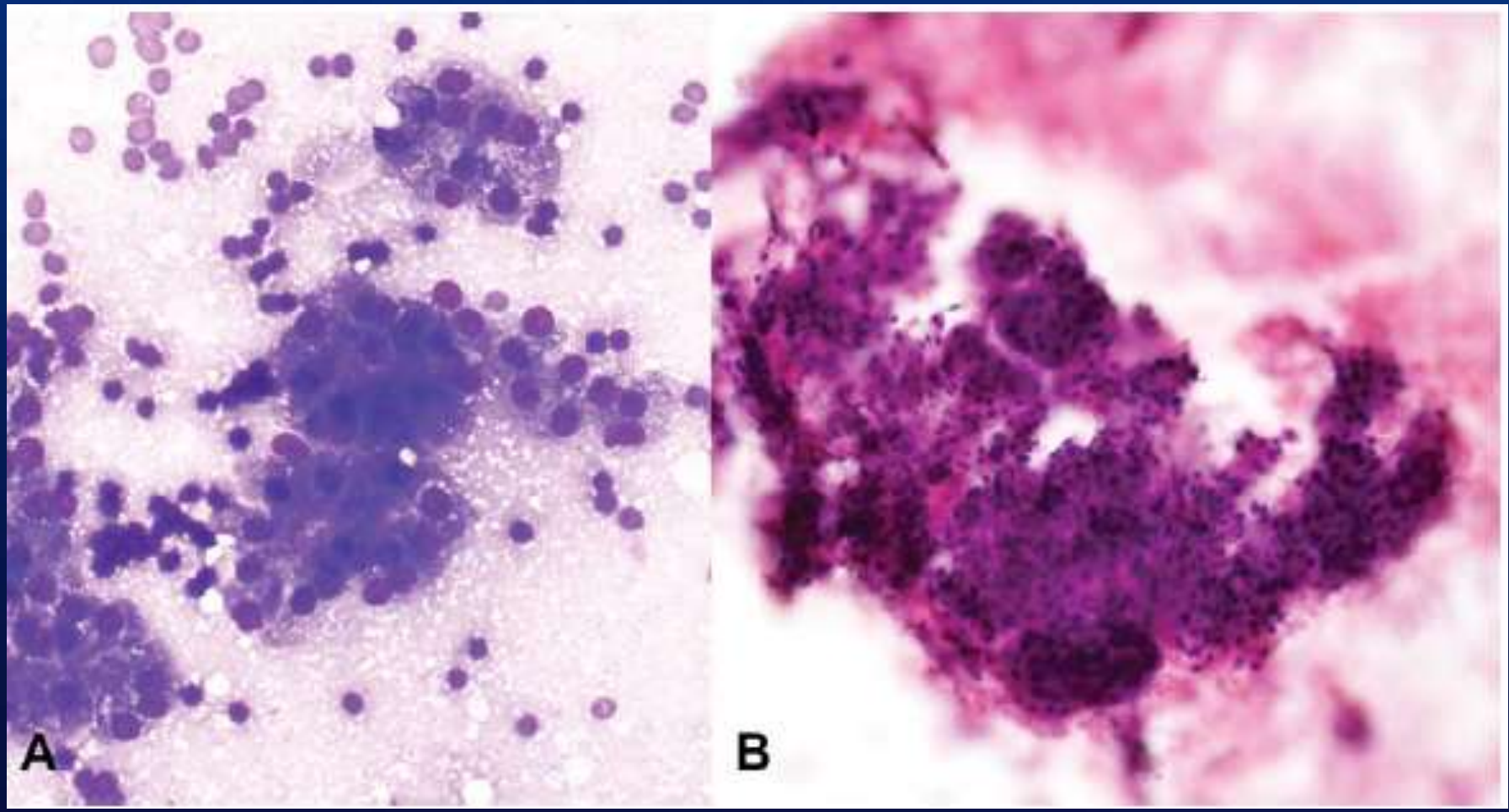
- Nuclear (N) size = RBC
- Basally located N
- Round, smooth membranes

Acinar Cell Carcinoma



Sigel Cancer Cytopathology 2013

B9 Acinar Cells Misdiagnosed as Acinar Cell Carcinoma



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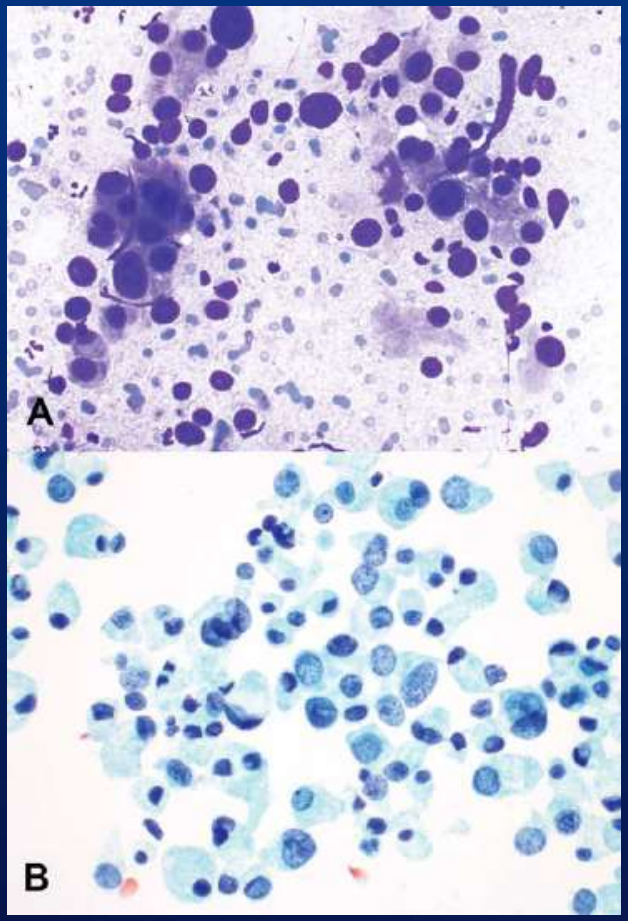
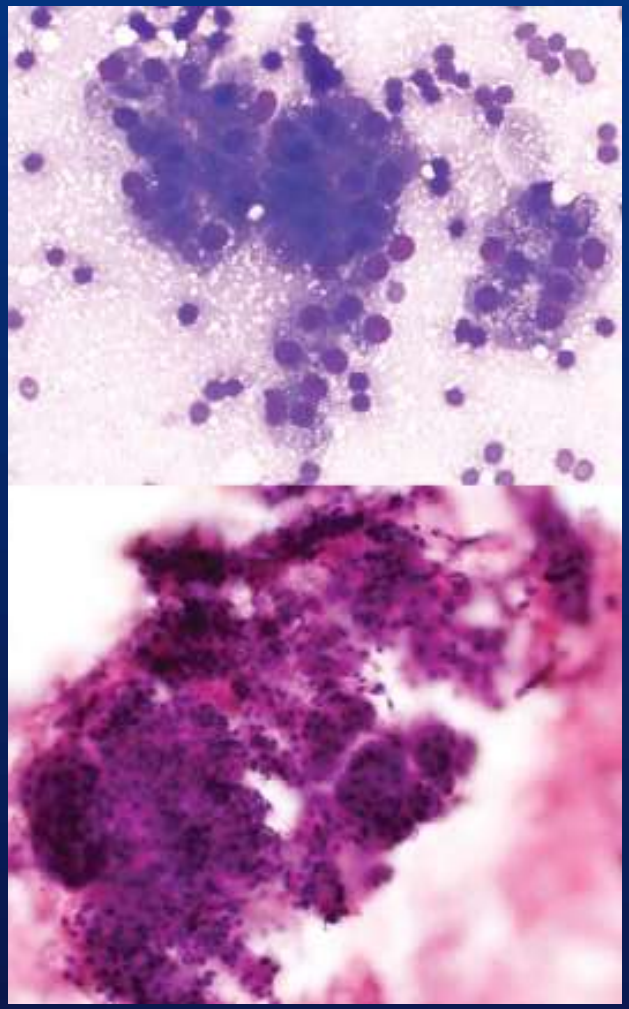
Sigel Cancer Cytopathology 2013

ACC vs B9 Acinar Cells



- Cellular aspirate
- Ovoid cells, round smooth nuclear contours
- **N enlargement, high N/C, coarse chromatin**
- **Prominent nucleoli**
- Large Cytoplasmic granules



- More cohesive
- Uniform cell aggregates
- N = size RBC

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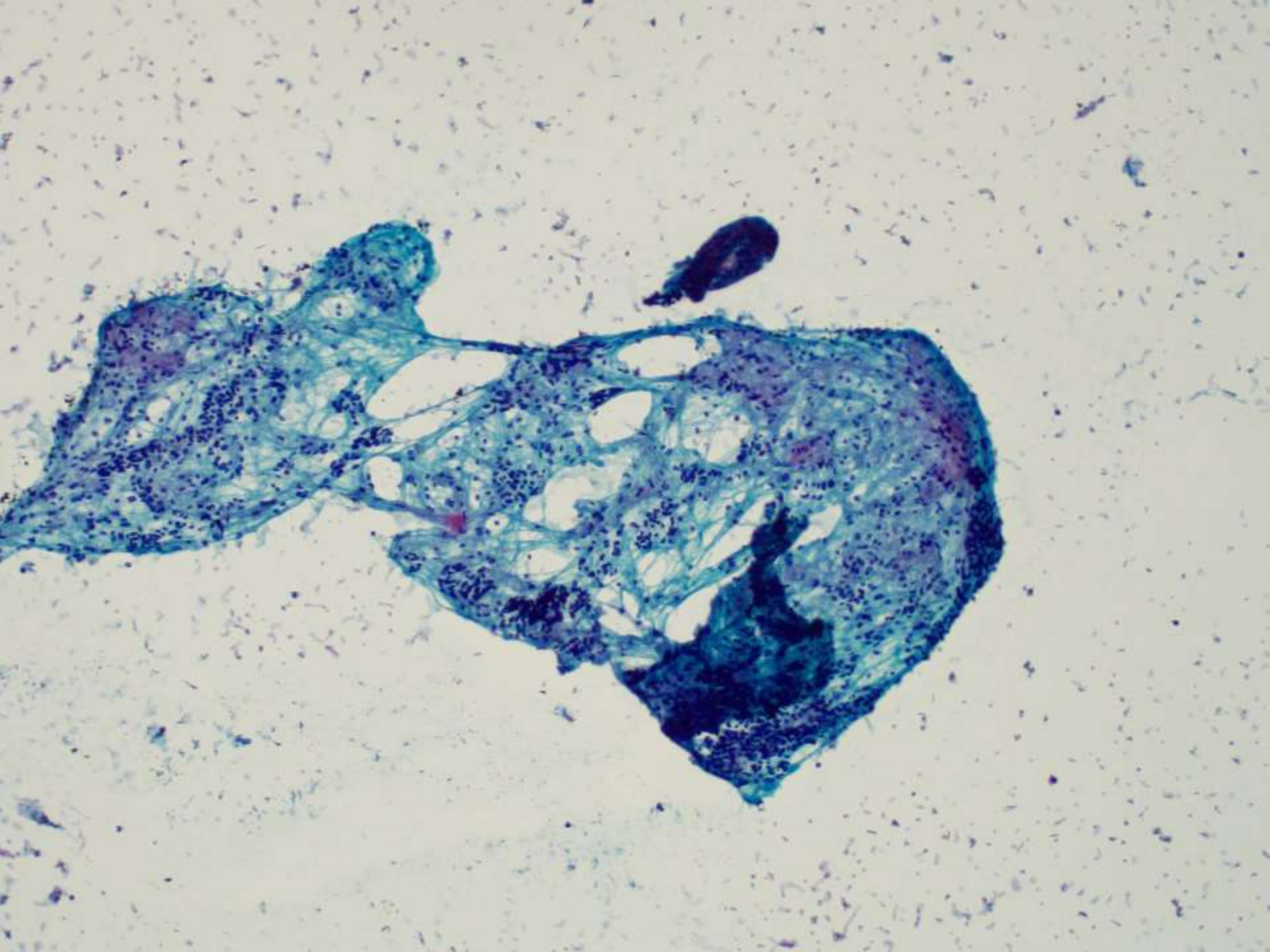
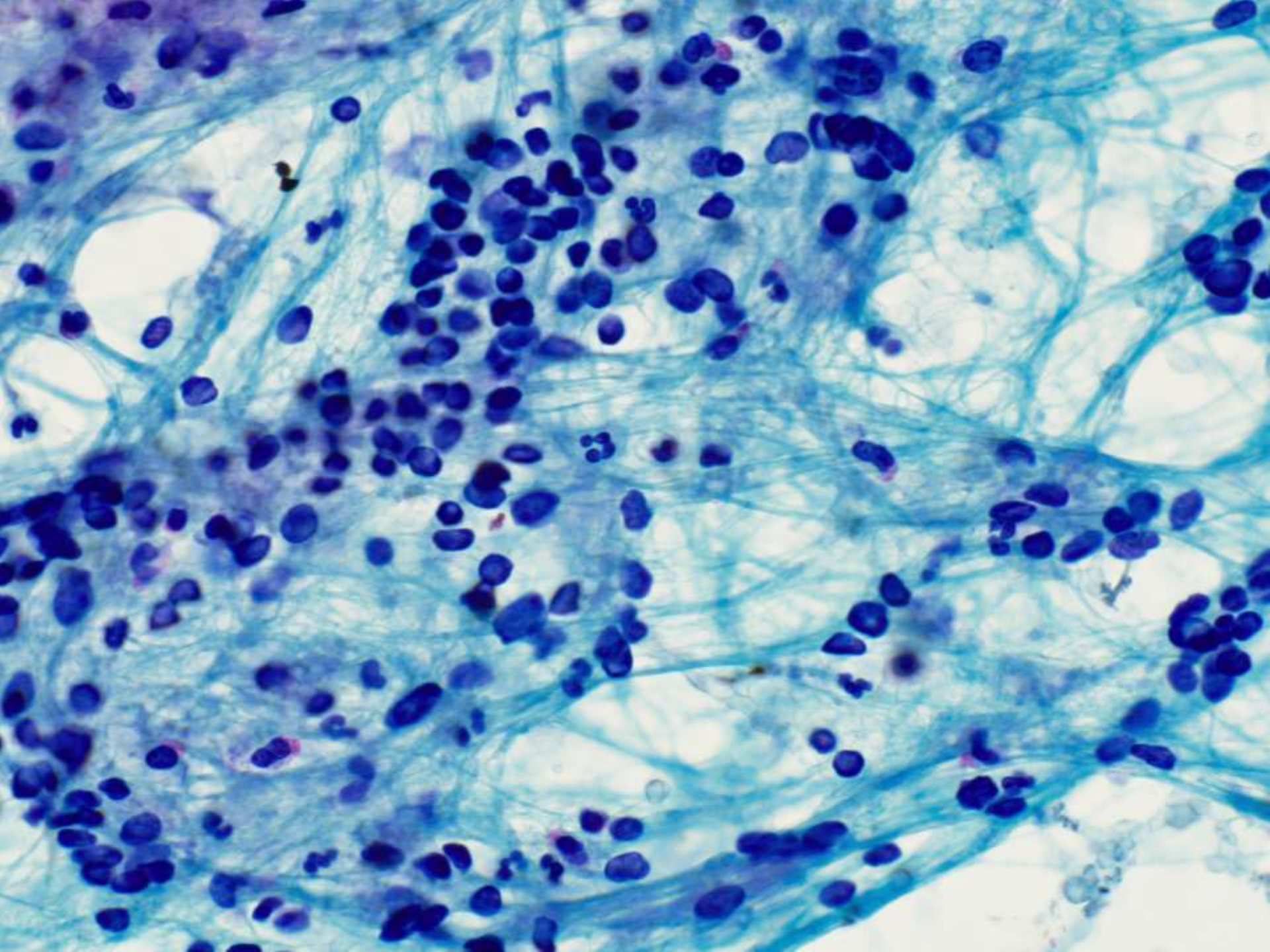
Bonus Case: "Non- diagnostic"

Rare non- neoplastic acinar cells





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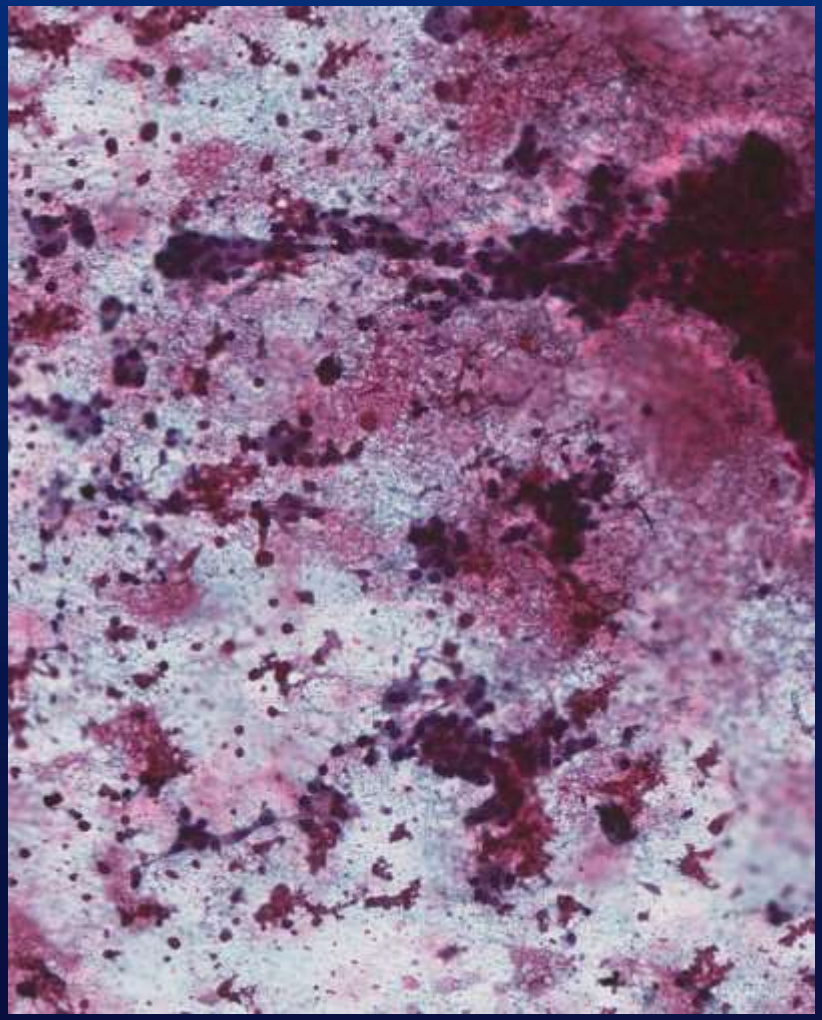
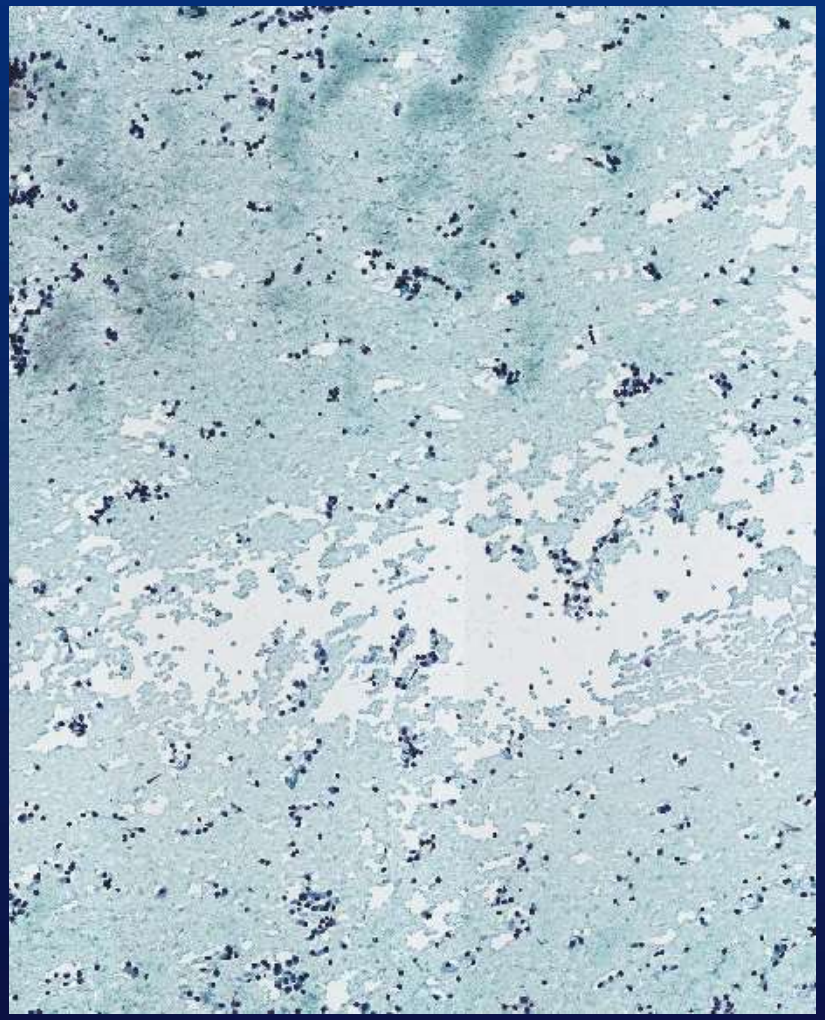
??? Non- diagnostic

B9 Pancreas vs PanNET





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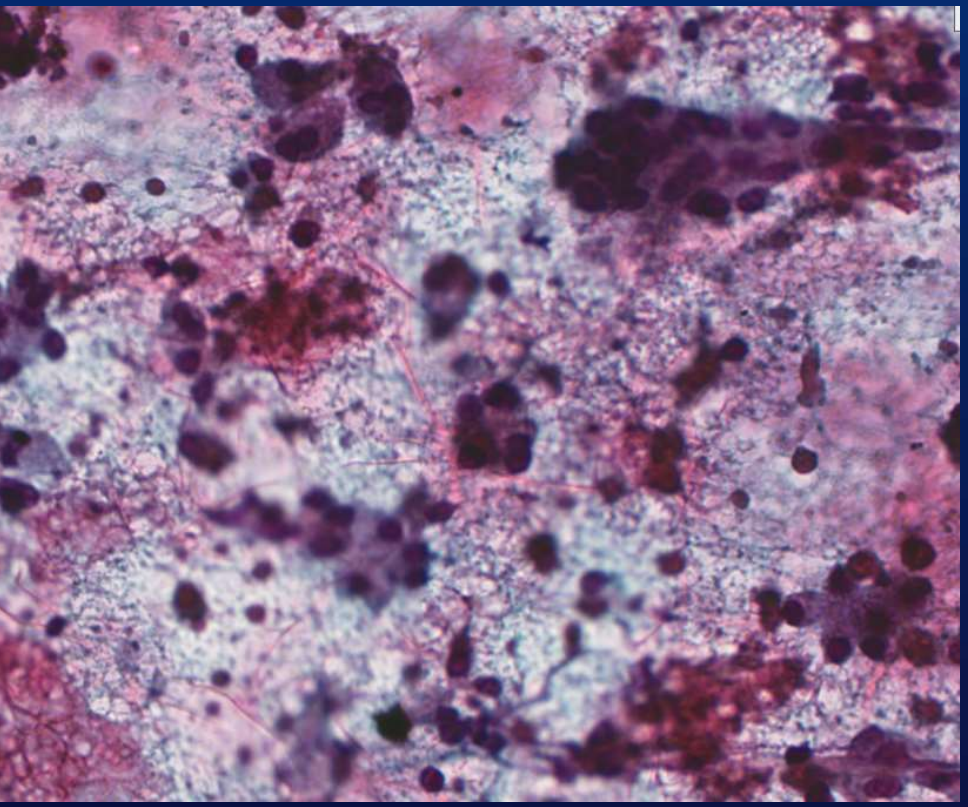
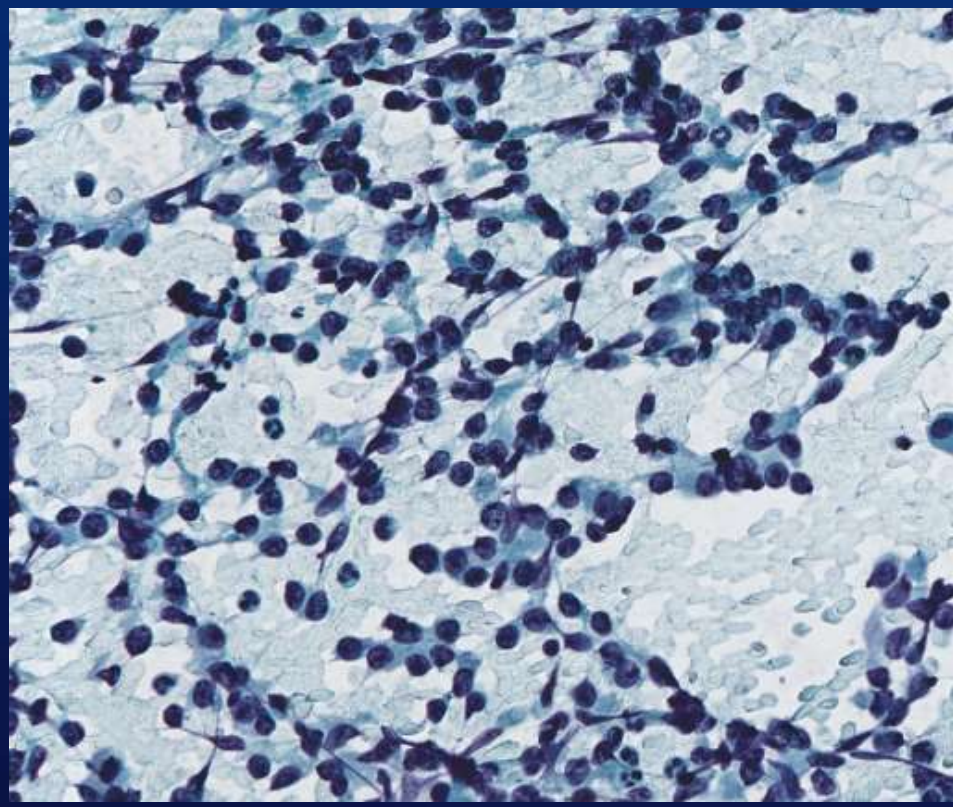
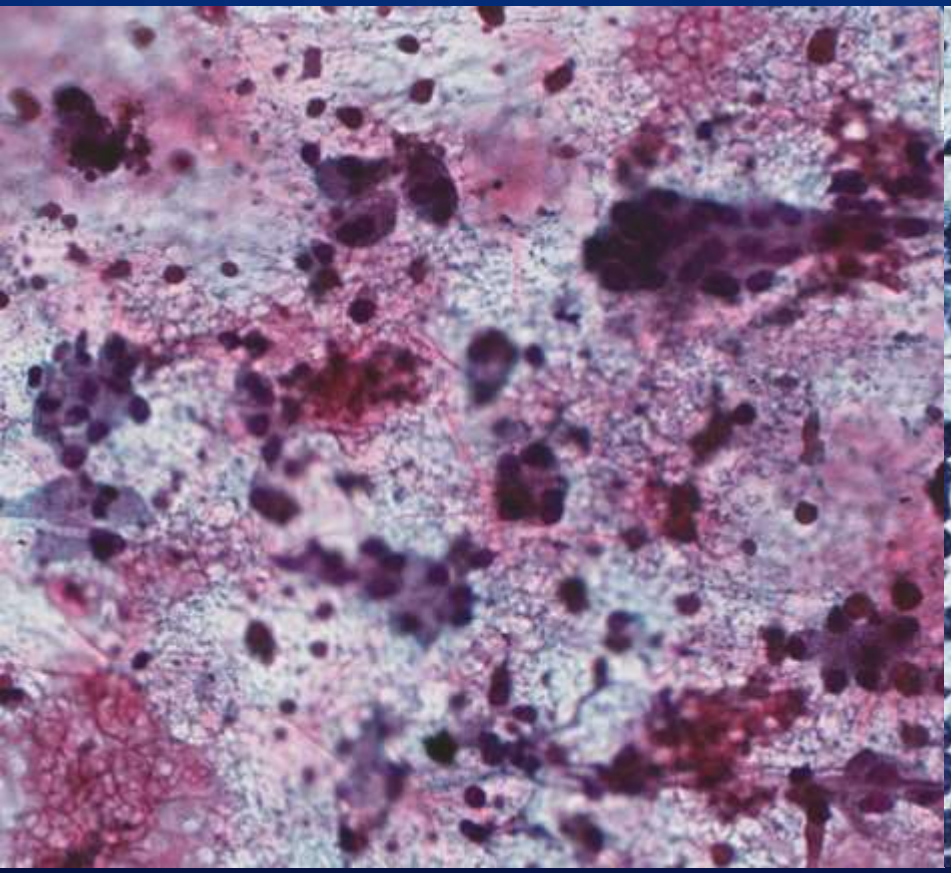
B9 Pancreas vs PanNET



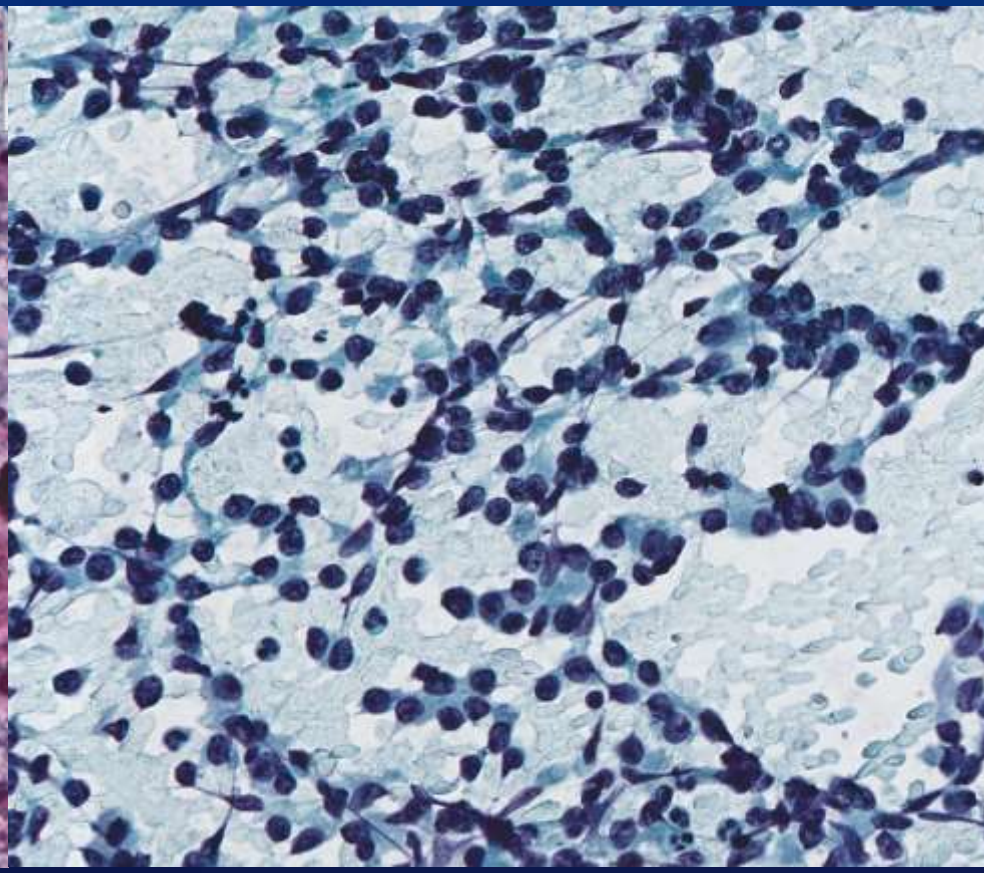


Acinar groups in B9 may look like pseudorosettes in PanNET

Normal vs PanNET



- More cohesive clusters



- Loosely cohesive clusters
- Predominance of single cells

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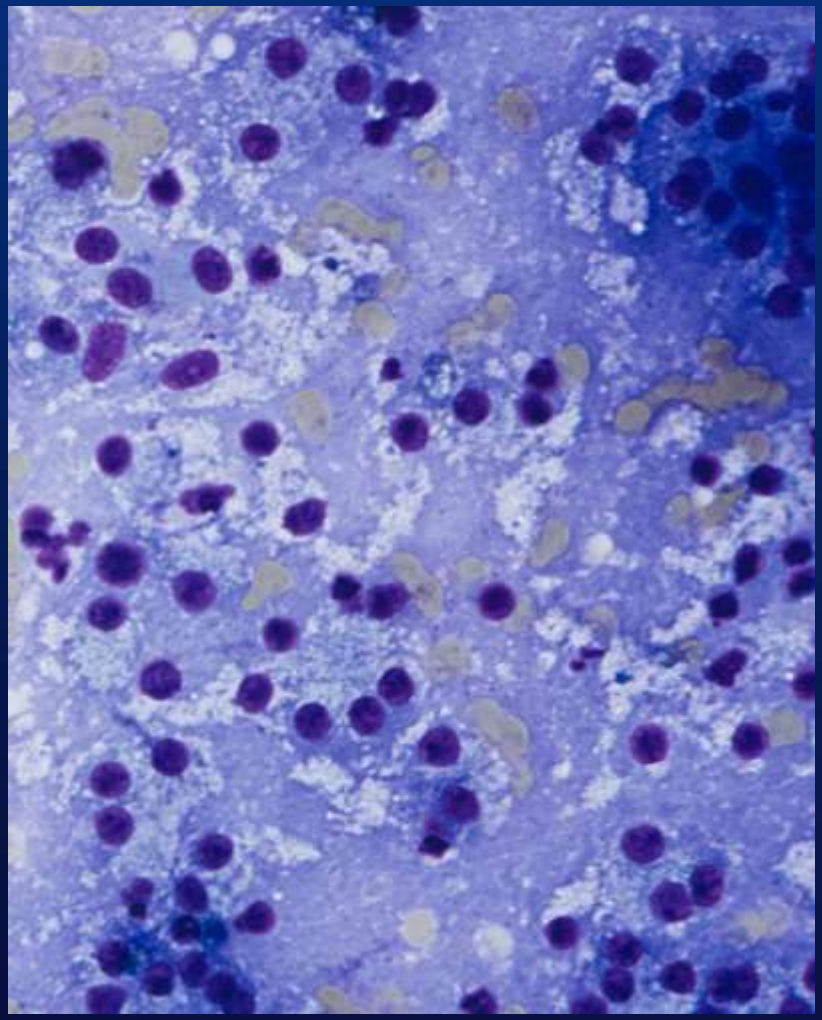
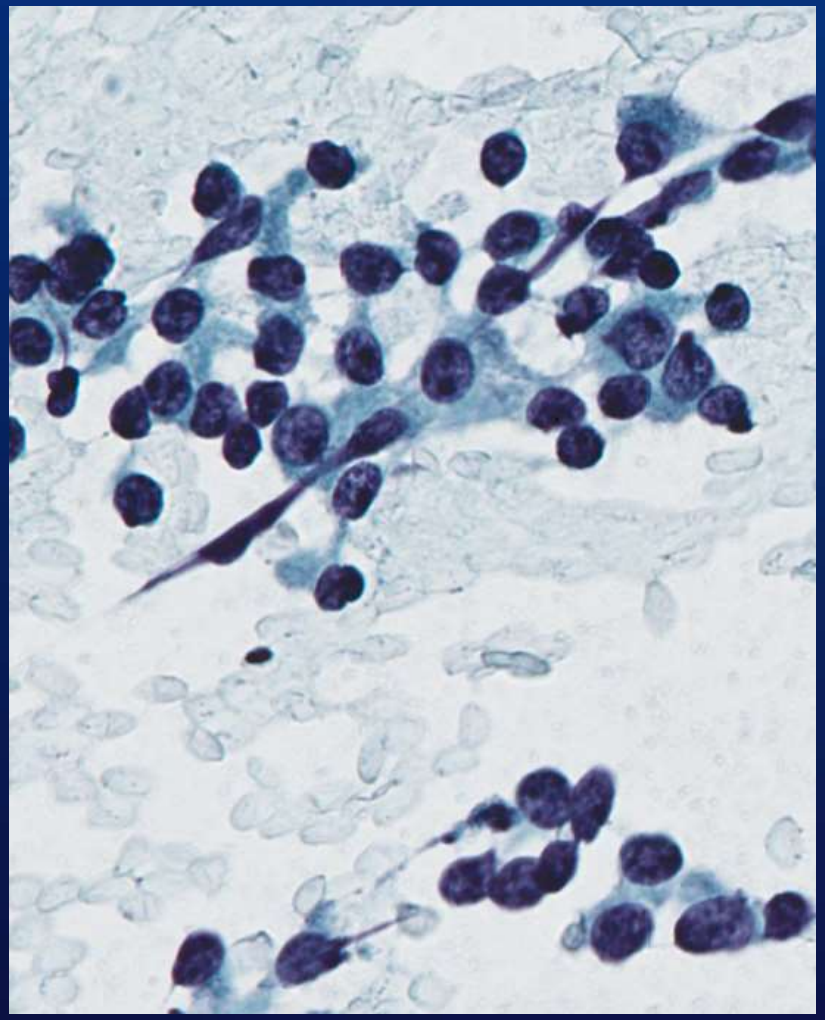
B9 Pancreas vs PanNET



Occasional single cells



Single cells predominate

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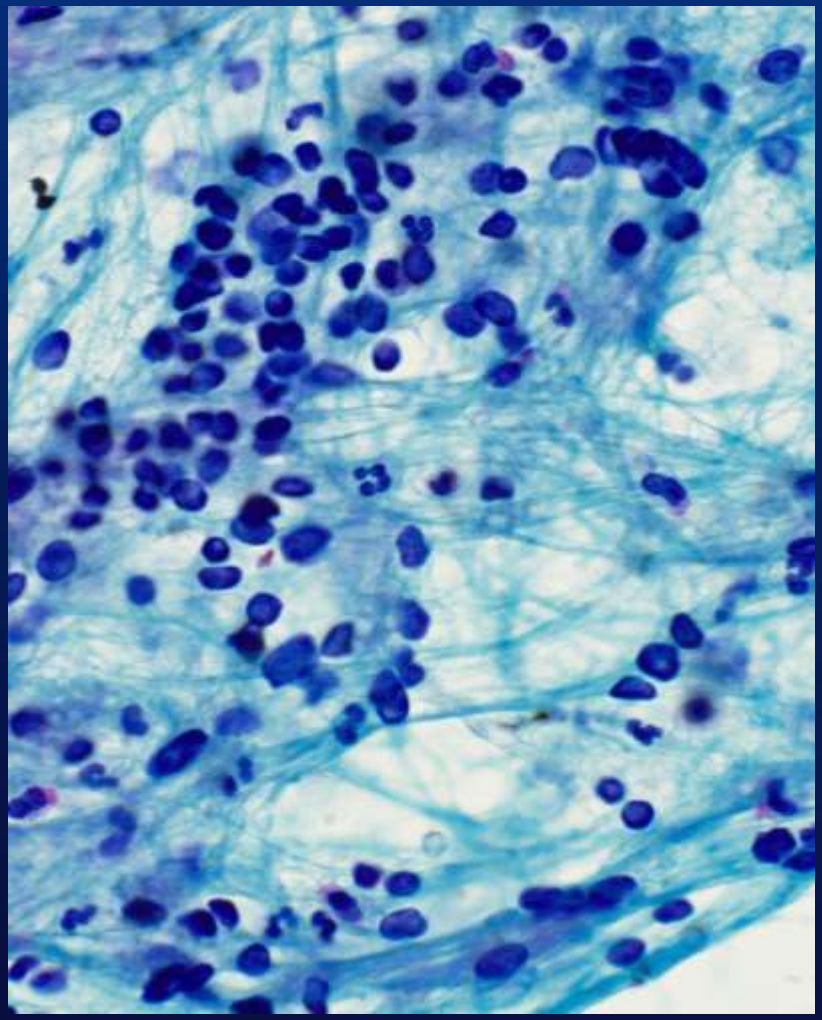
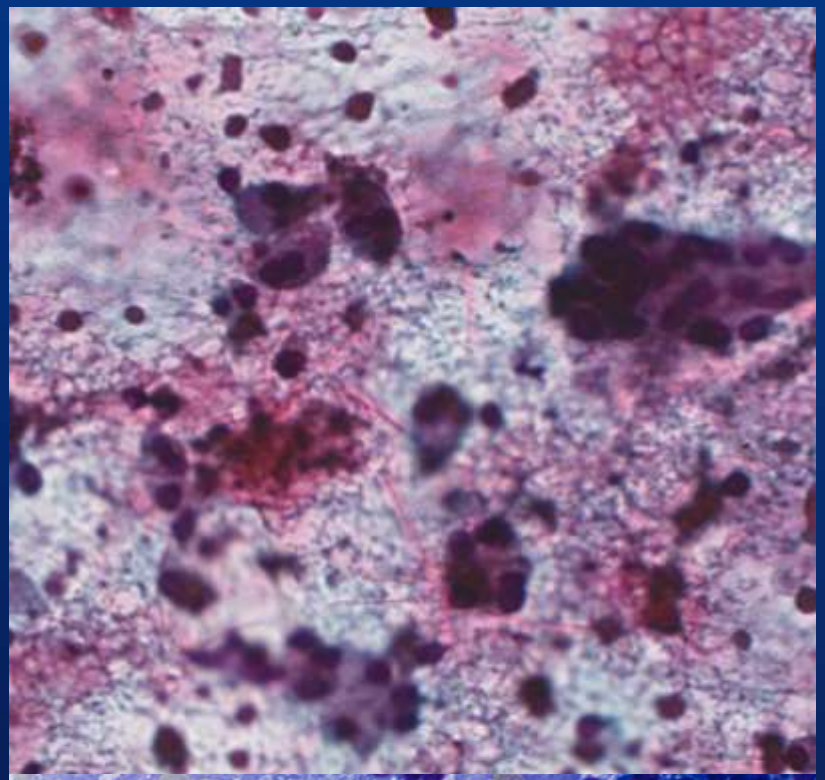
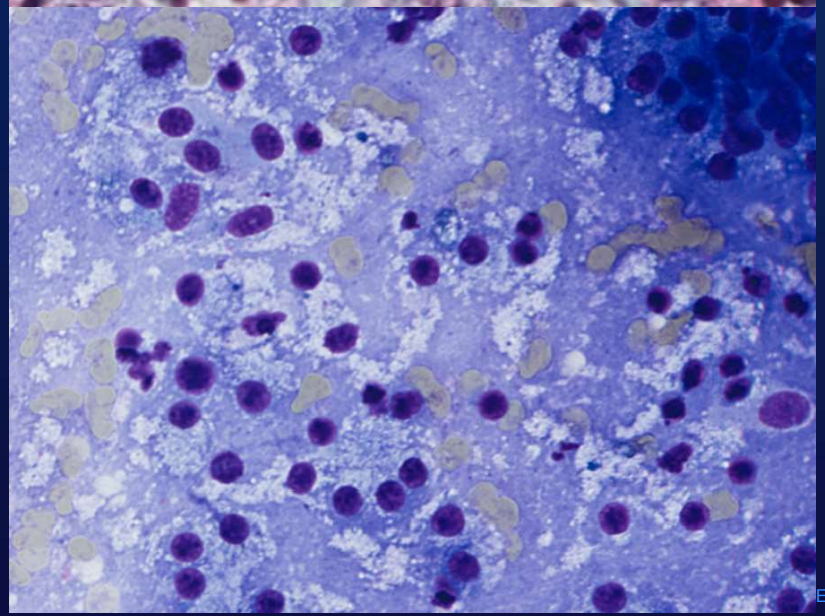
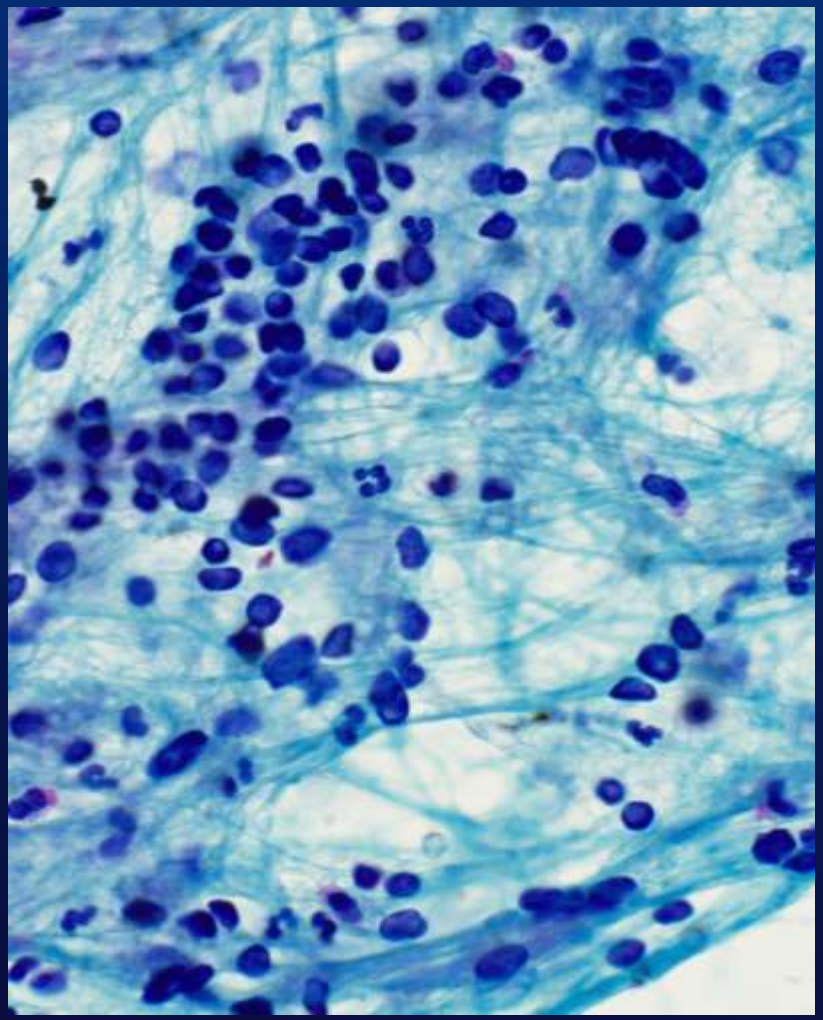
Bonus Case Vs Normal

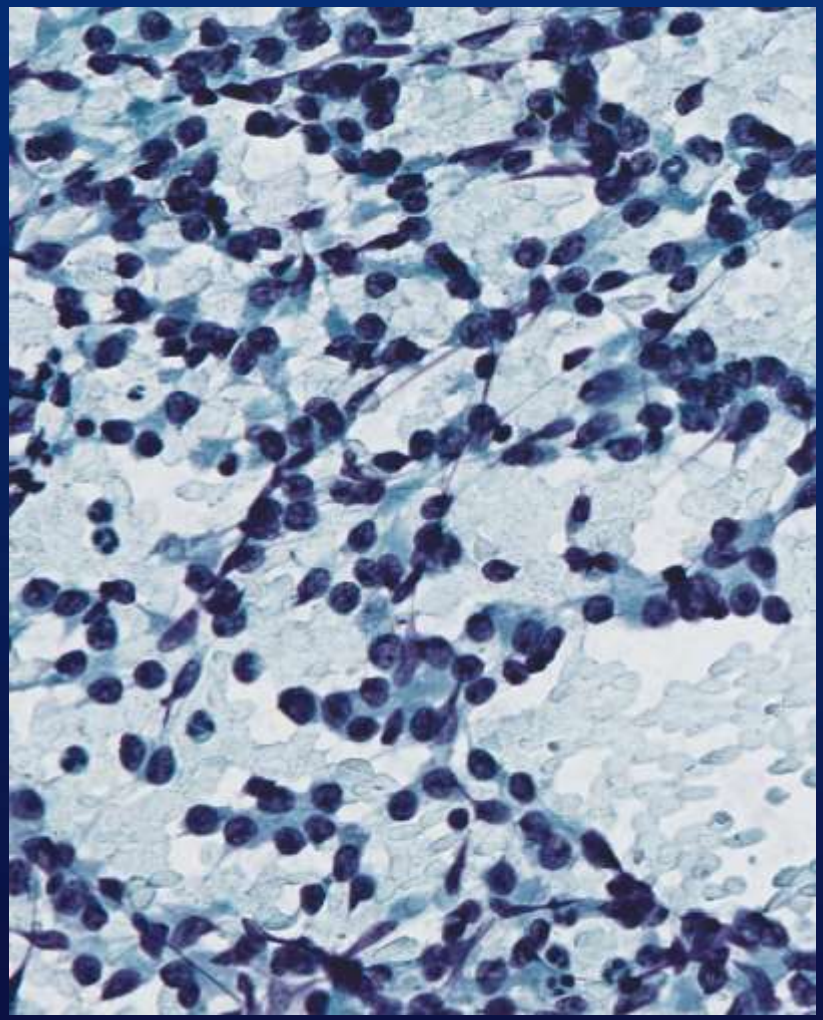






Bonus Case Vs PanNET





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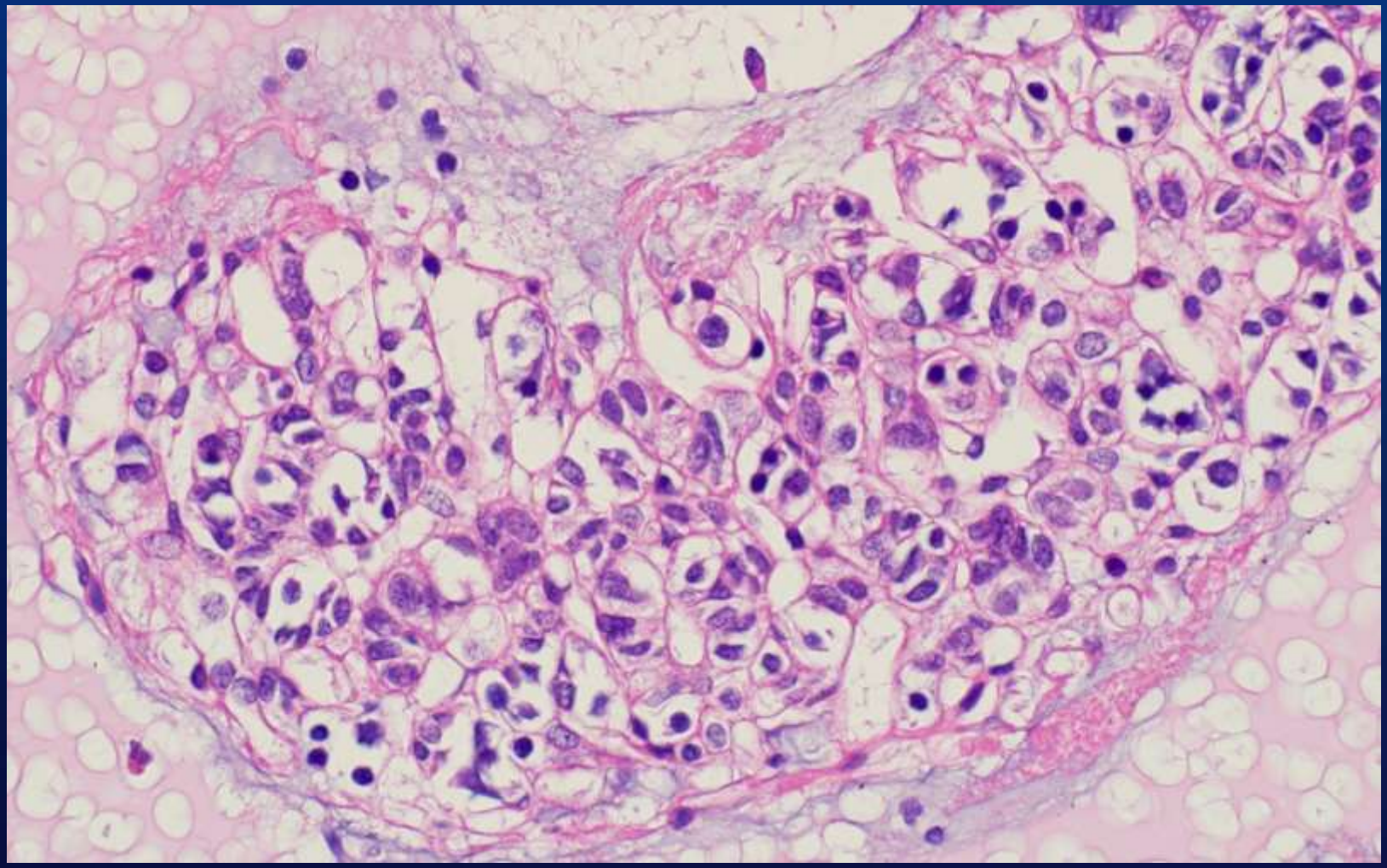
Bonus Case CB



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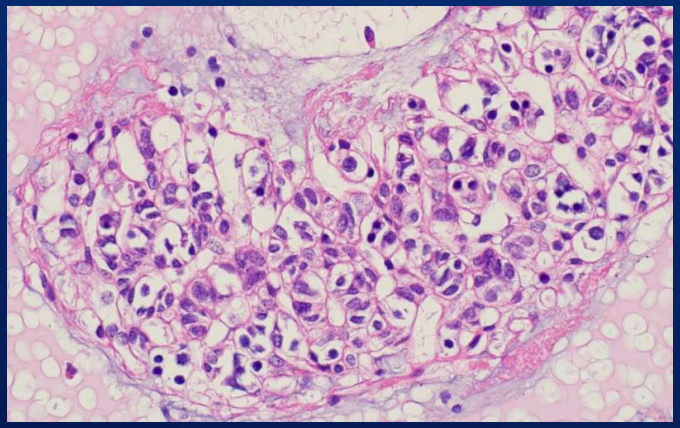
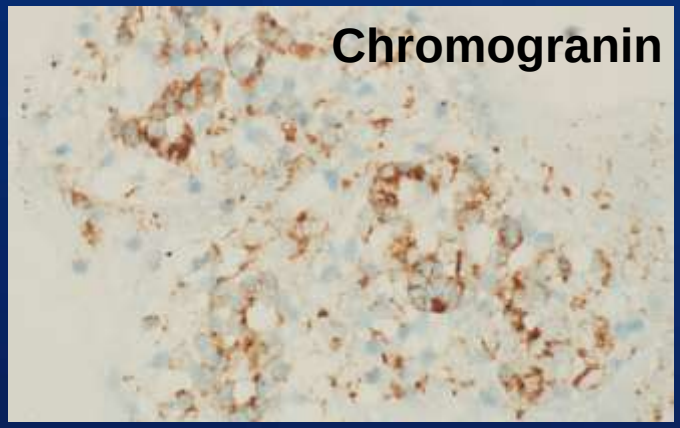
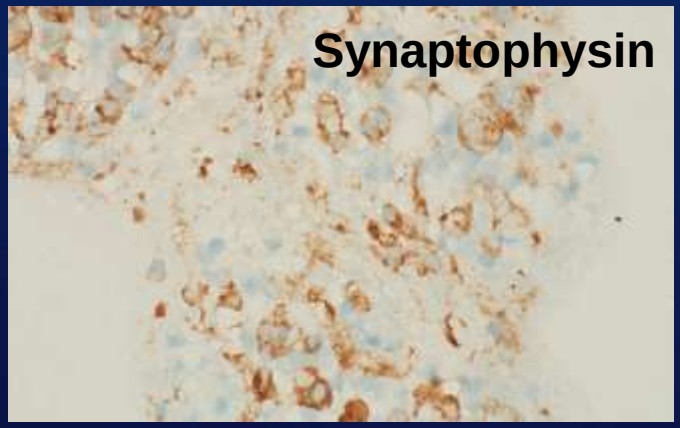
Follow up: PanNET







- CK
- Ki-67
- Necrosis
- Atypia

WHO 2017 Classification of Well-Differentiated Pancreatic Endocrine Tumors

Grade	Ki67 (%)	Mitotic index (per 10 hpf)
1	<3	<2
2	3-20	2-20
3	>20	>20

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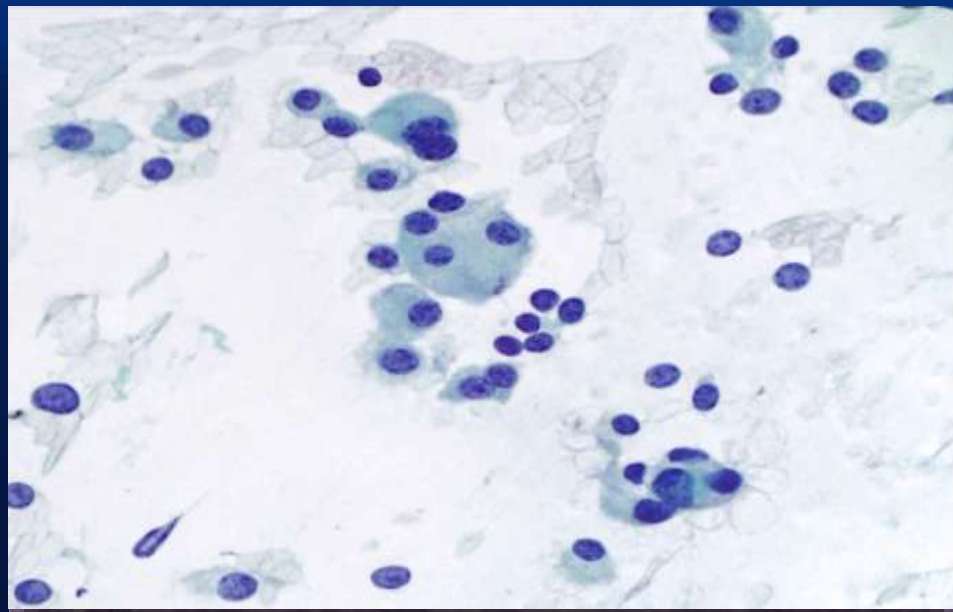
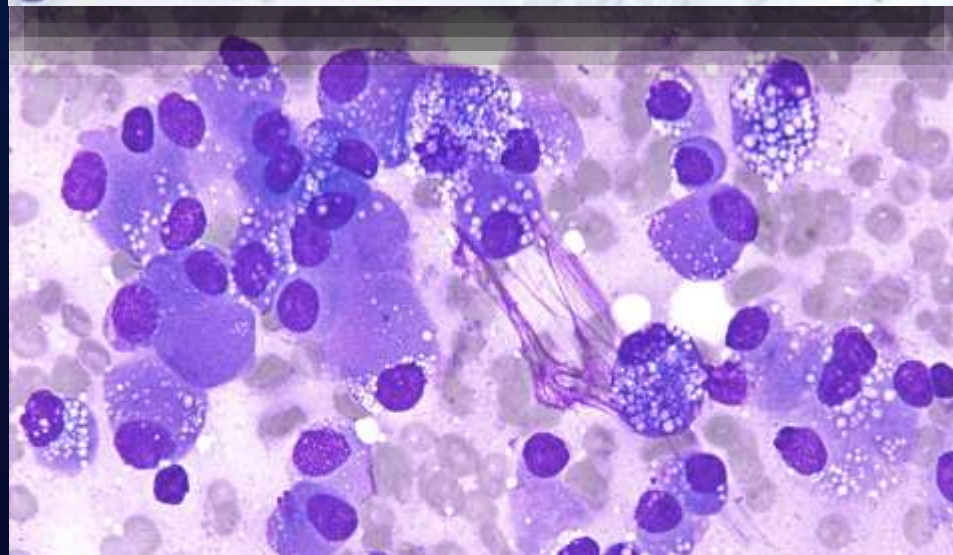
Neuroendocrine Tumors Cytology

- Loosely cohesive clusters with fibro vascular core/stroma, but single cells predominate, bare nuclei in the background, pseudorosettes
- Uniform tumor cells with round to oval nuclei, some cells out of proportion to others
- Plasmacytoid, binucleate cells
- Regular nuclear membranes
- “Salt and pepper” chromatin
- Moderate cytoplasm with fine granules (pink granules DQ)





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Images by Dr. Matthew Zarka

Case 2

69 year old male
EUS: 30 x 20 mm septated cystic lesion in pancreatic head communicating with pancreatic duct, consistent with IPMN
No worrisome findings on imaging

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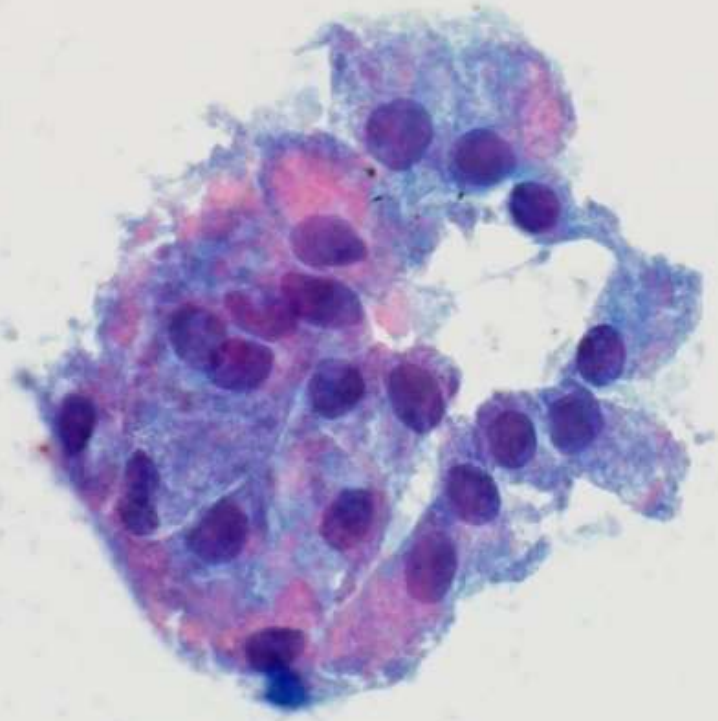
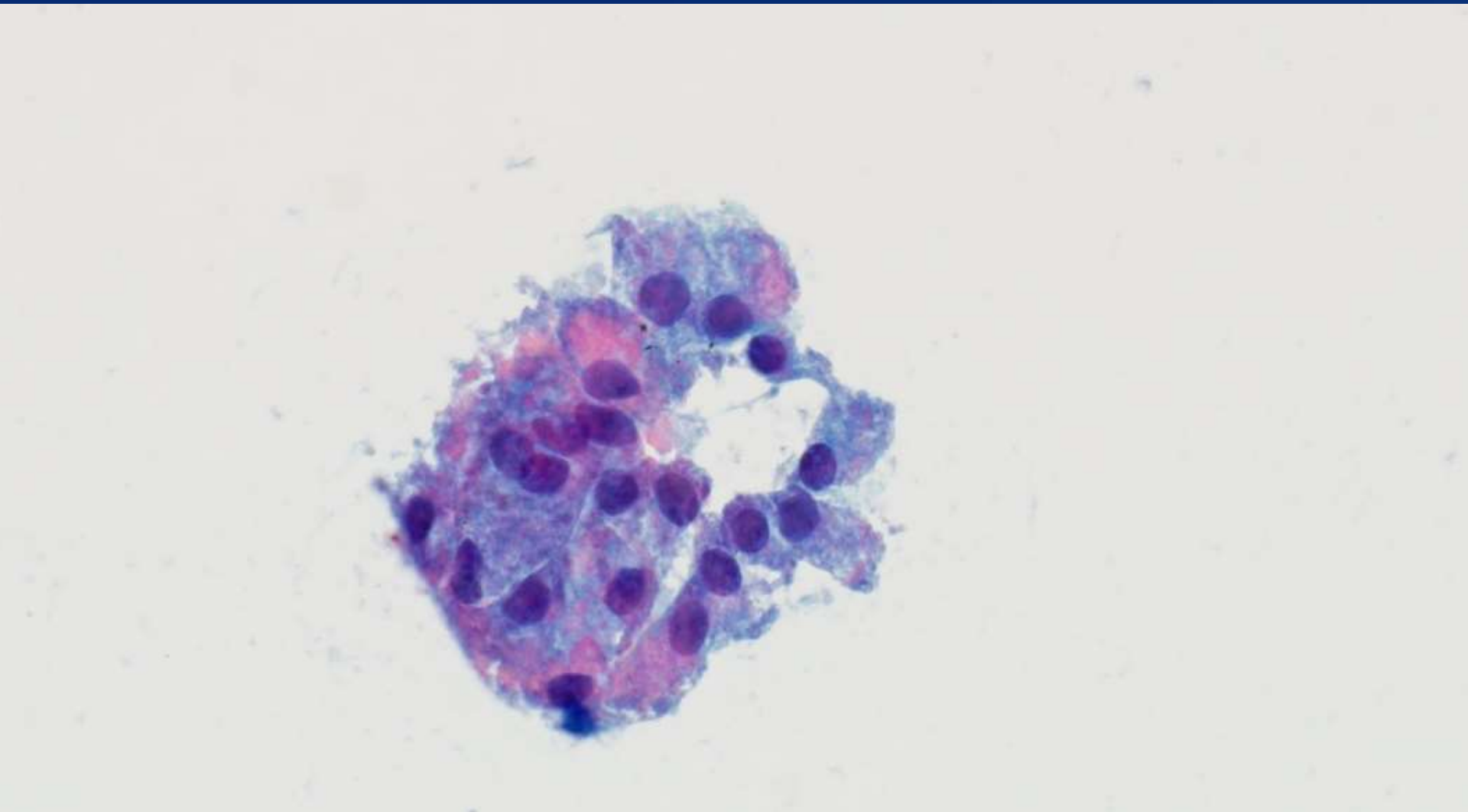
Case 2

69 year old male
EUS: 30 x 20 mm septated cystic lesion in pancreatic head communicating with pancreatic duct, cw IPMN
No worrisome findings on imaging
ROSE: solid lesions only

Image by Dr. Matthew Zarka



Any visible mucin is pathologic; overtly mucinous ductal cells from pancreas represent either MCN/ IPMN or adenocarcinoma



Standardized Terminology and Nomenclature for Pancreato- Biliary Cytology

- I. Non- Diagnostic
- II. Negative for malignancy
- III. Atypical
- IV. Neoplastic:
  - Benign (serous cystadenoma)
  - Other:
    - Mucinous cysts (low- and high- grade dysplasia)
    - Well- differentiated neuroendocrine tumors
    - Solid- pseudopapillary neoplasm
- V. Suspicious for malignancy
- VI. Positive for malignancy

Diagn Cytopathol 2014, April 42 (4):338-50

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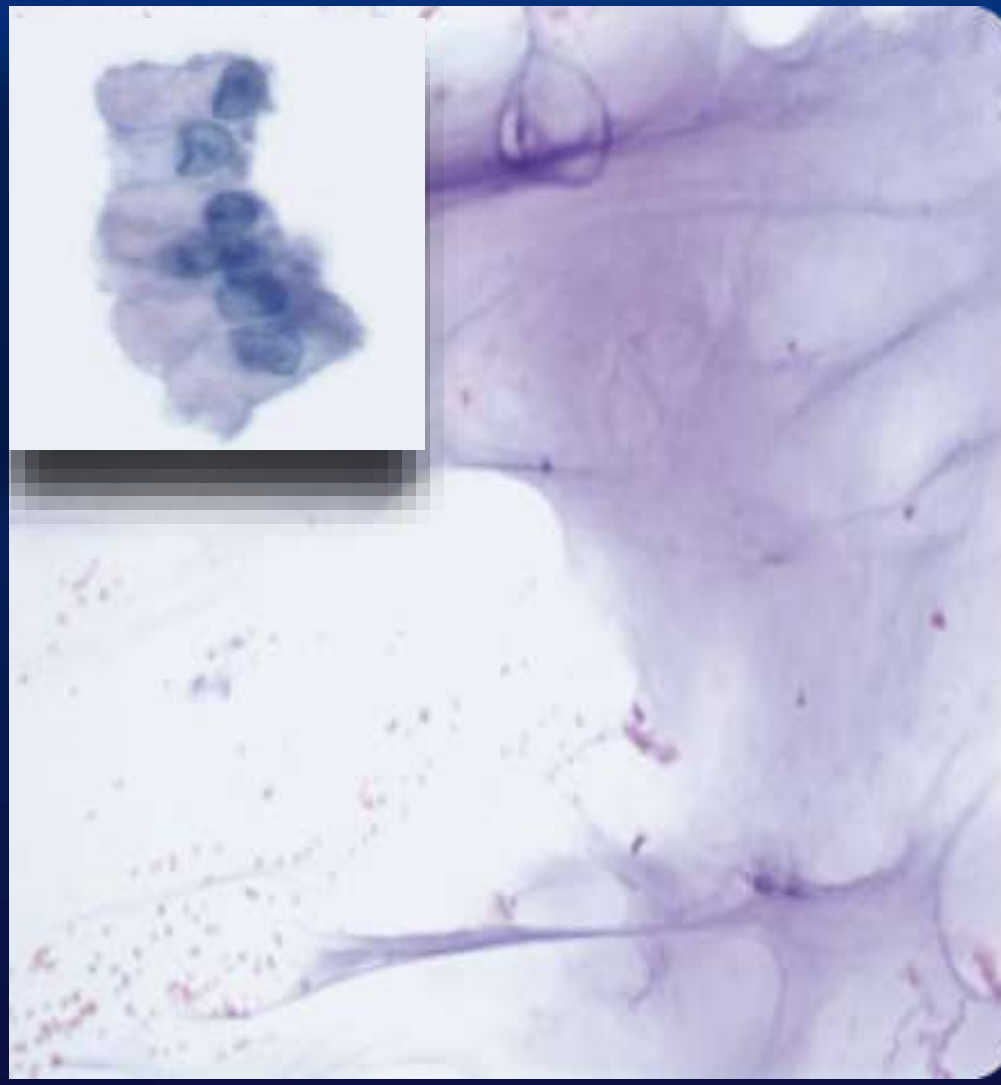
Neoplastic cells present

Mucinous epithelium present in a background of abundant mucin, consistent with IPMN

No high-grade dysplasia or malignancy

Mucinous Cystic Neoplasms

- Thick mucous
- Low cellularity
- Columnar cytoplasm with mucin and basally located nuclei
- Some nuclear stratification, single mucous cells
- Atypia depends on degree of differentiation



Images by Dr. Matthew Zarka

Pitman et al. Cancer Cytopathol. 2010:1181-13

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Mucinous Background

- **Benign**
  - Gastric epithelium
  - Duodenal epithelium
- **Neoplastic**
  - Mucinous cystic neoplasm (MCN)
  - Intraductal papillary mucinous neoplasm (IPMN)
- **Malignant**
  - Mucinous non-cystic adenocarcinoma
  - Signet ring carcinoma

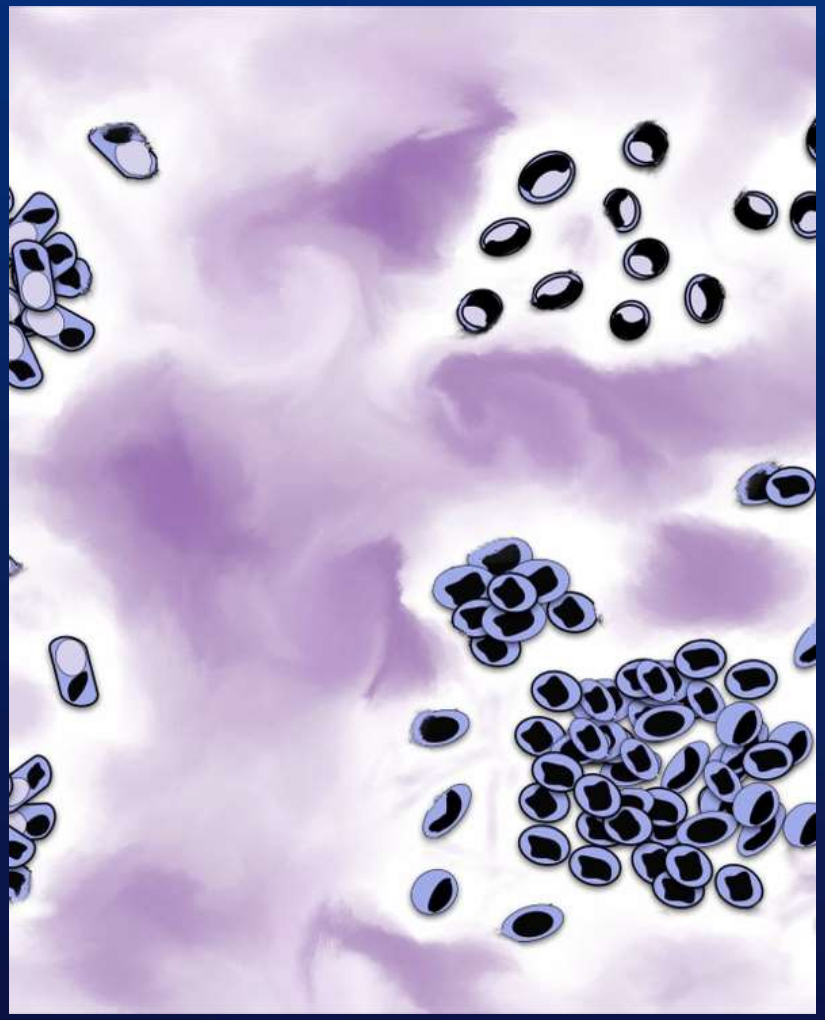

Image by Dr. Matthew Zarka

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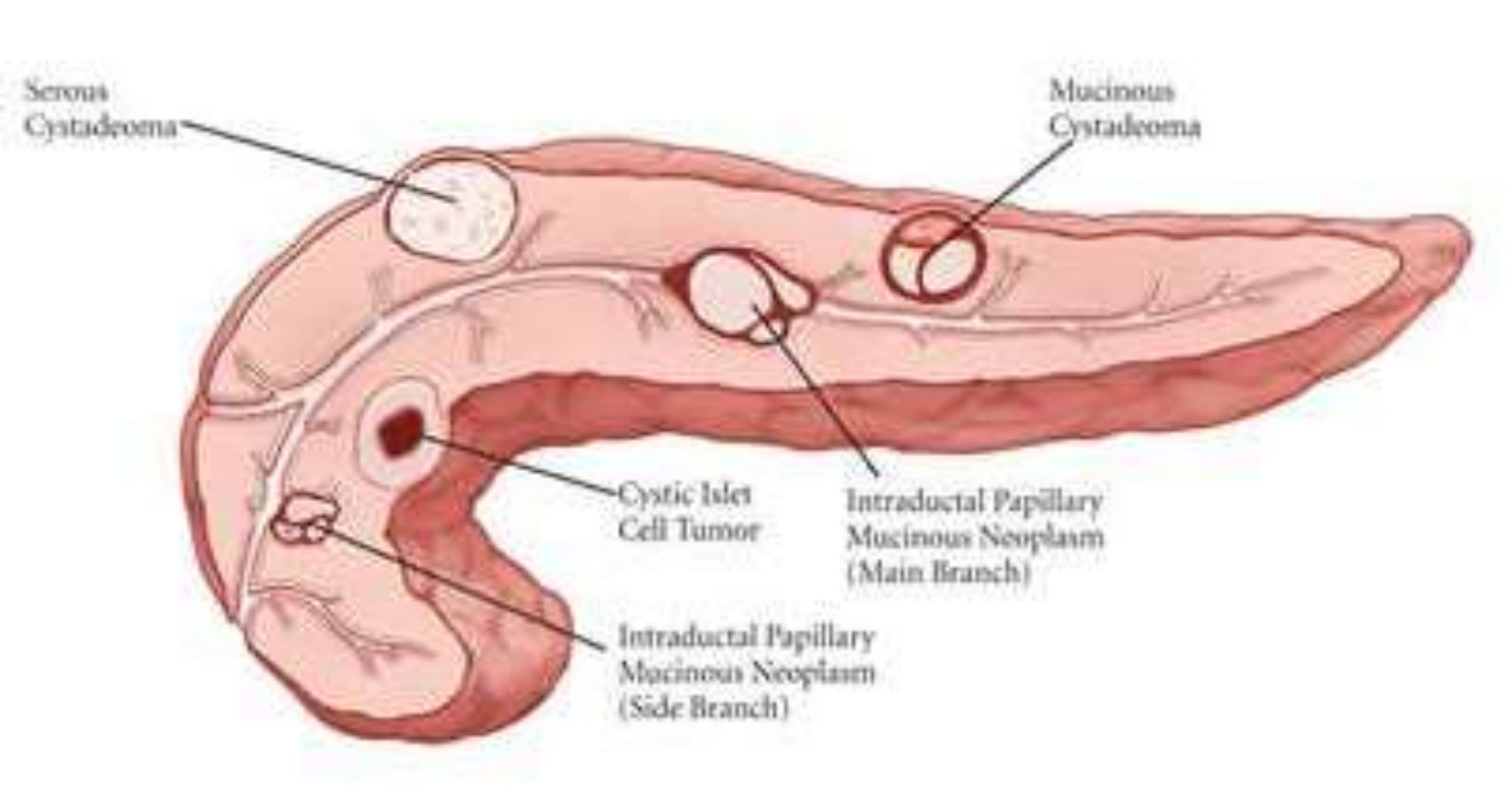
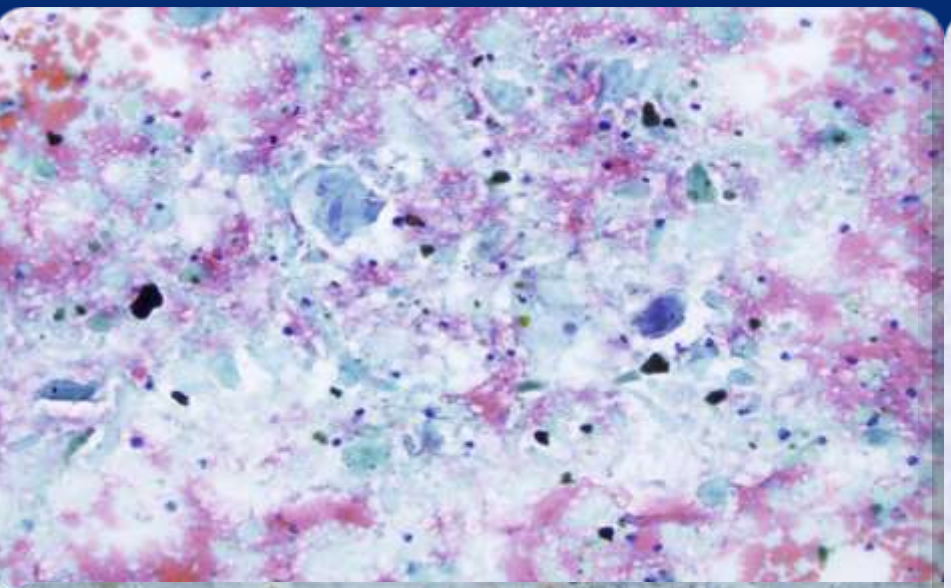
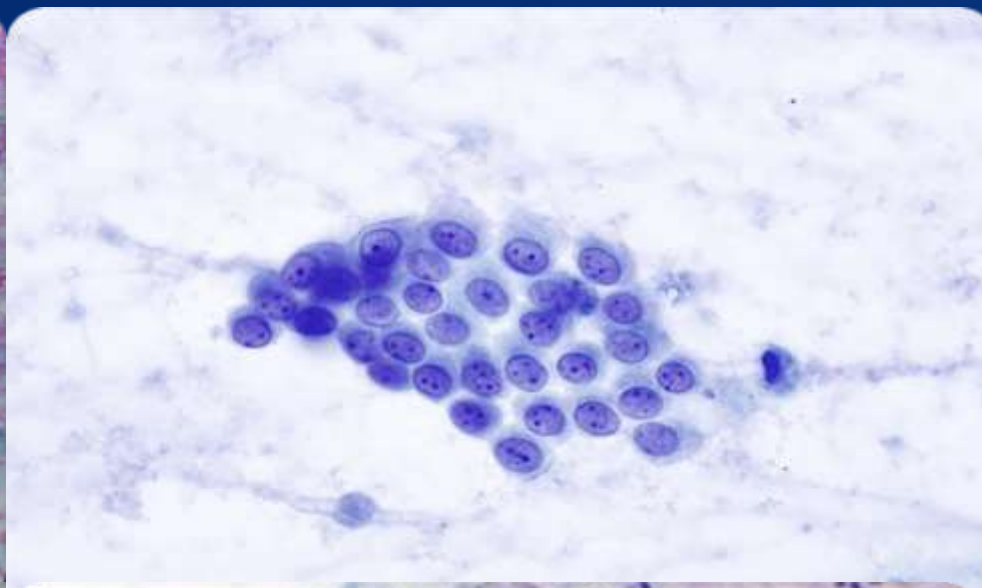
Common Pancreatic Cystic Lesions

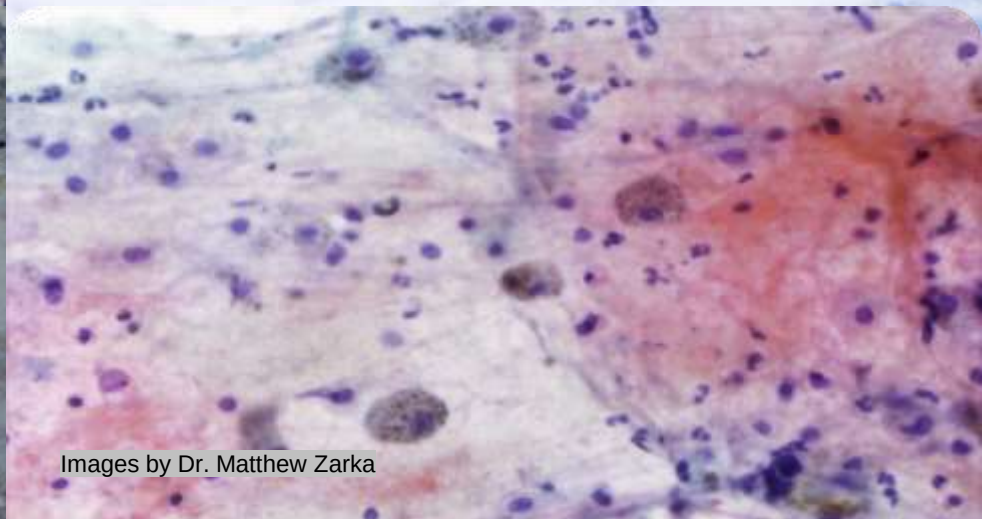


Slide by Dr. Matthew Zarka

Pseudocyst vs Serous Cyst







Images by Dr. Matthew Zarka

Fluid Chemistry and Molecular Analysis in Cystic Lesions

- Very helpful in cystic lesions with:
  - Atypical diagnosis
  - Normal appearing or non- diagnostic
- CEA> 192 ng/ml: highly suggestive of MCN

	CEA	Amylase
IPMN	High	Variable
MCN	High	Variable
Serous cystadenoma	Low, <5 ng/ml	Low
Pseudocyst	Low	High

Molecular Analysis in Cystic Lesions

- **Helpful if CEA level low**
- **Does not distinguish B9 from malignant**
- KRAS mutations: IPMN (61%) and MCN (21%)
- GNAS mutations almost exclusive in IPMN (also in SCA, but **not in MCN**)
- VALUE: helps distinguishing IPMN from MCN (MCN always resected)
- KRAS and GNAS:
  - If + together: suggest IPMN
  - No prognostic indication
  - Seen in low and high grade dysplasia

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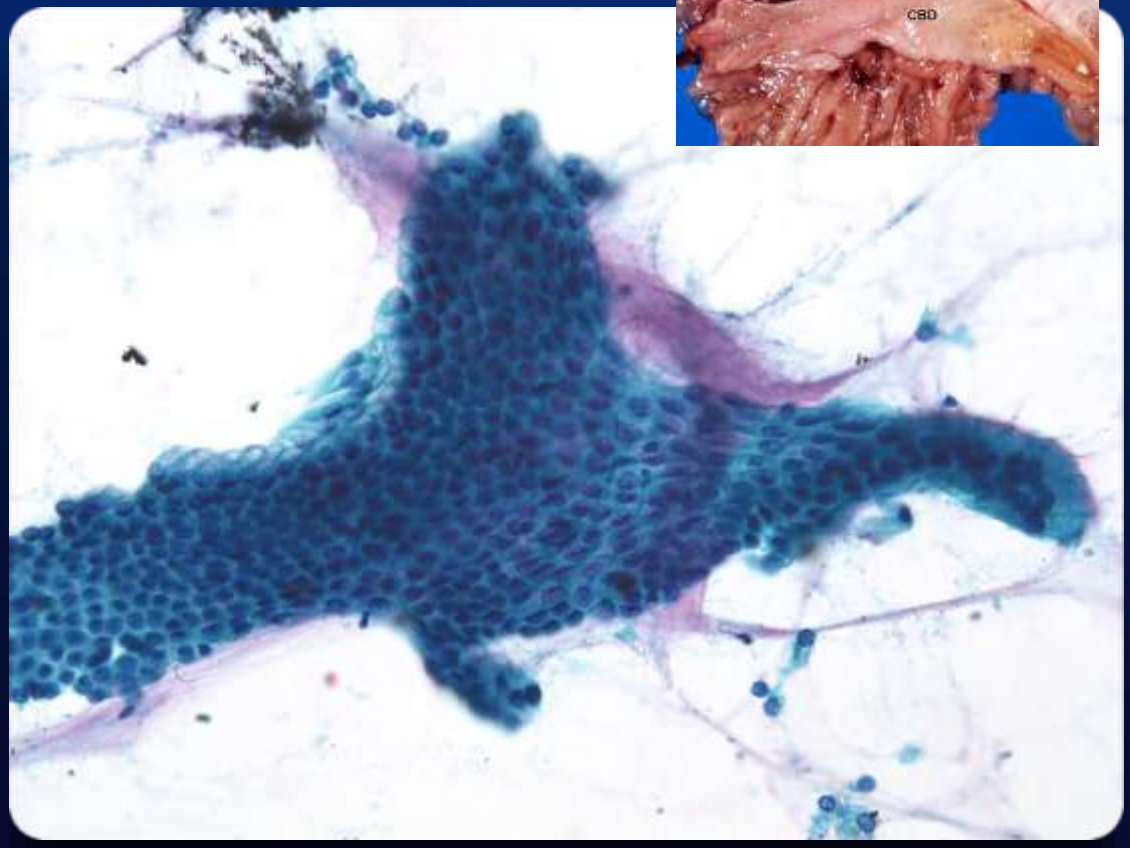
PSC Category IV, other: Mucinous cystic neoplasm, favor IPMN

- "The category of "Neoplastic: Other" should be used when the cyst has been classified as a neoplasm, which may be based solely on ancillary tests." —Pitman M B, Layfield L. The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology. Springer 2015

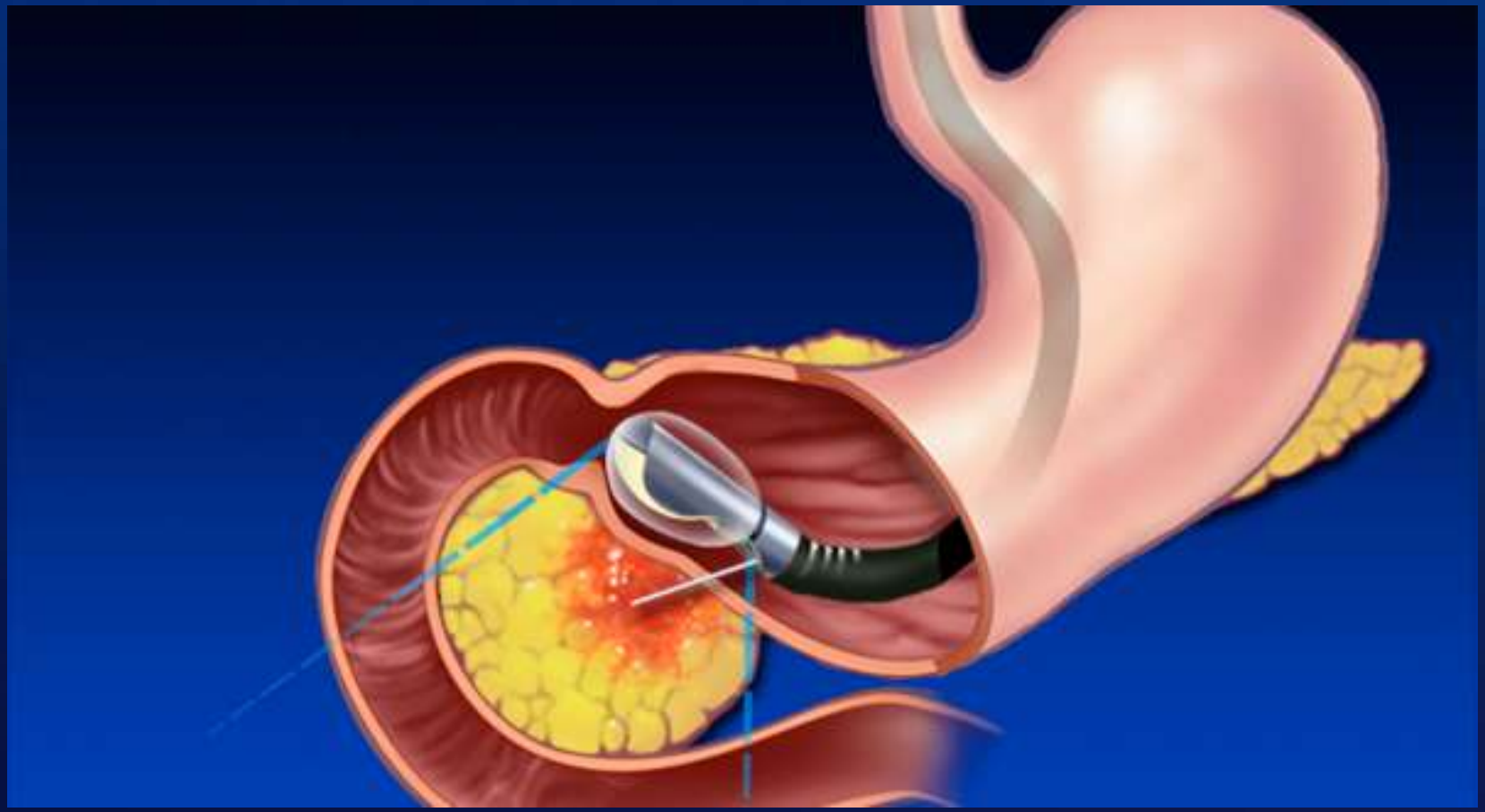
IPMN – "Quadruple" Test

- **Clinical-EUS/ Gross**:
  - Thick mucin
- **Radiographic**:
  - Dilated duct system, cyst communicate with pancreatic duct
- **Cytology:**
  - Mucinous epithelium
- **Ancillary tests:**
  - Fluid chemistry (CEA, amylase), molecular



Images and partial content by
Dr. Matthew Zarka

Contaminants in EUS-Fine Needle Aspiration



Transgastric: body and tail of pancreas

Transduodenal: head of pancreas

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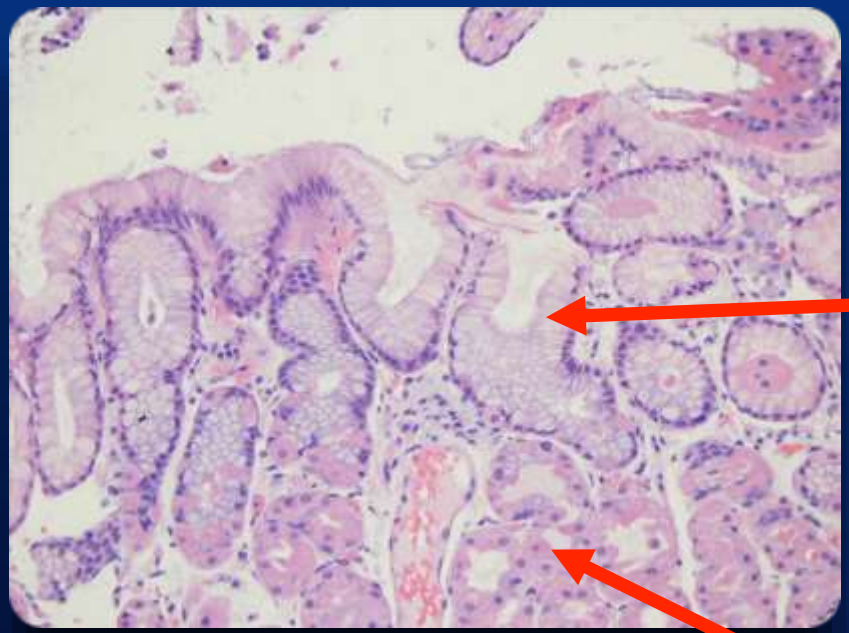
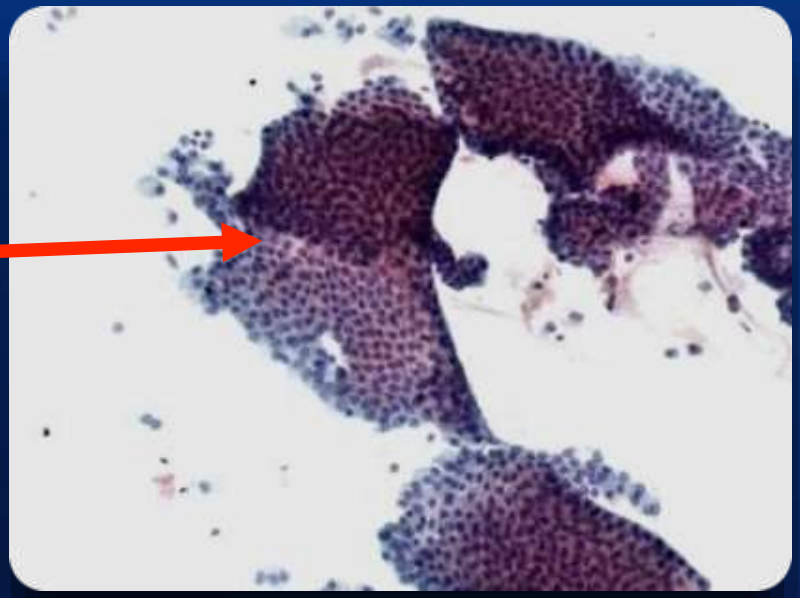
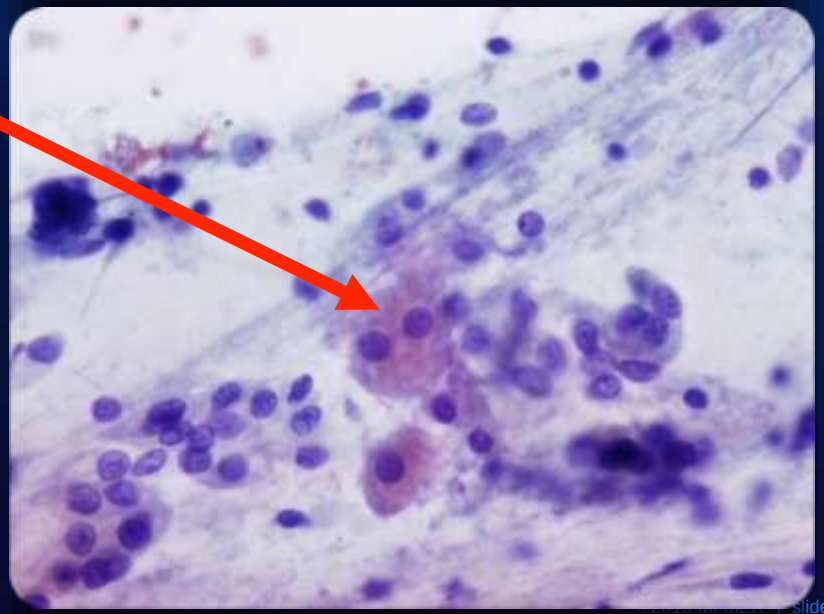
Stomach







- Thin, watery mucin
- Small /intermediate/large clusters
- Apical mucin cups
- Grooved naked nuclei within mucin
- Cell types:
- Mucinous, parietal, chief cells

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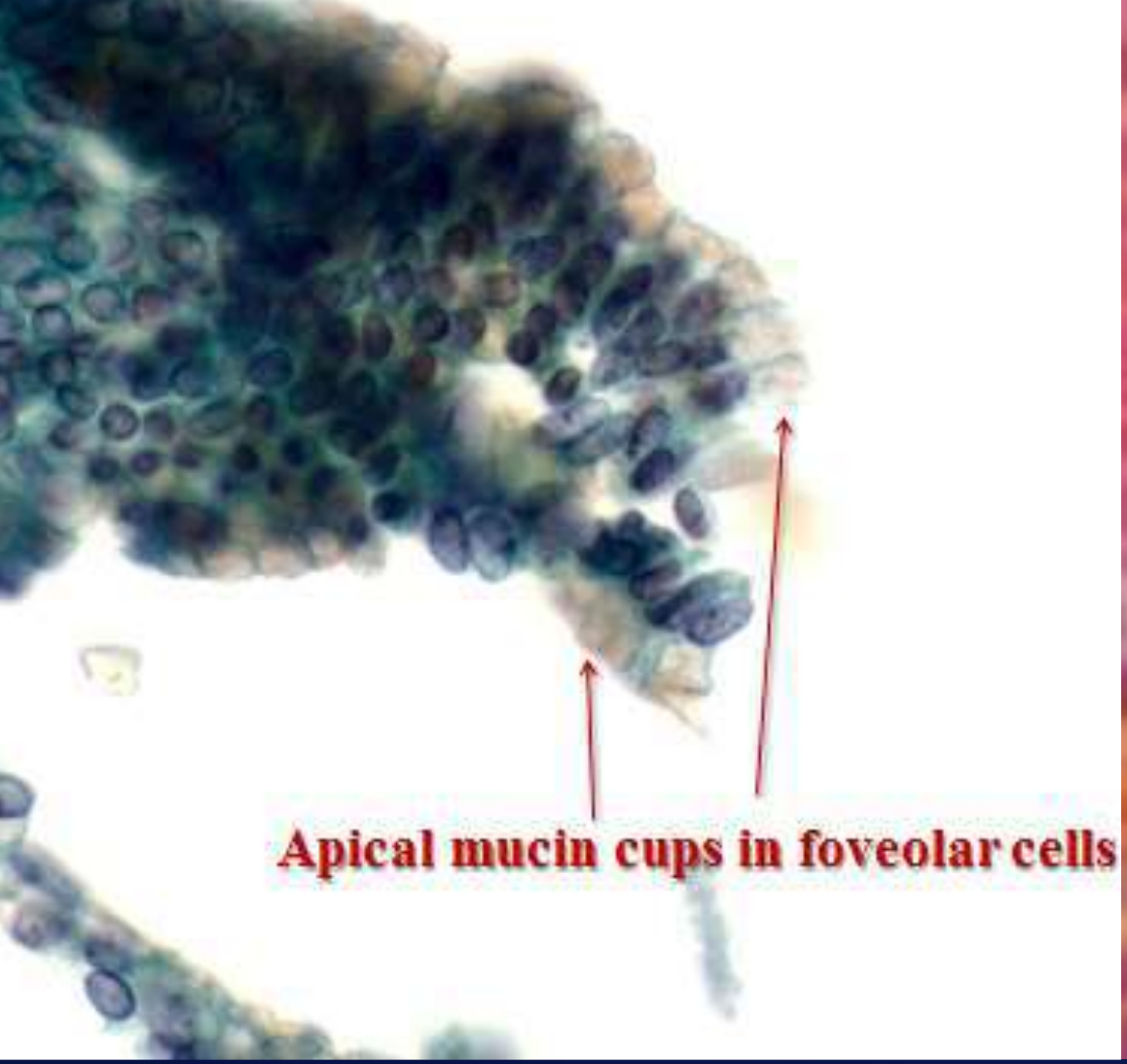

Images: left side Dr. Miguel- Perez (left) ASC Meeting 2021 (right)

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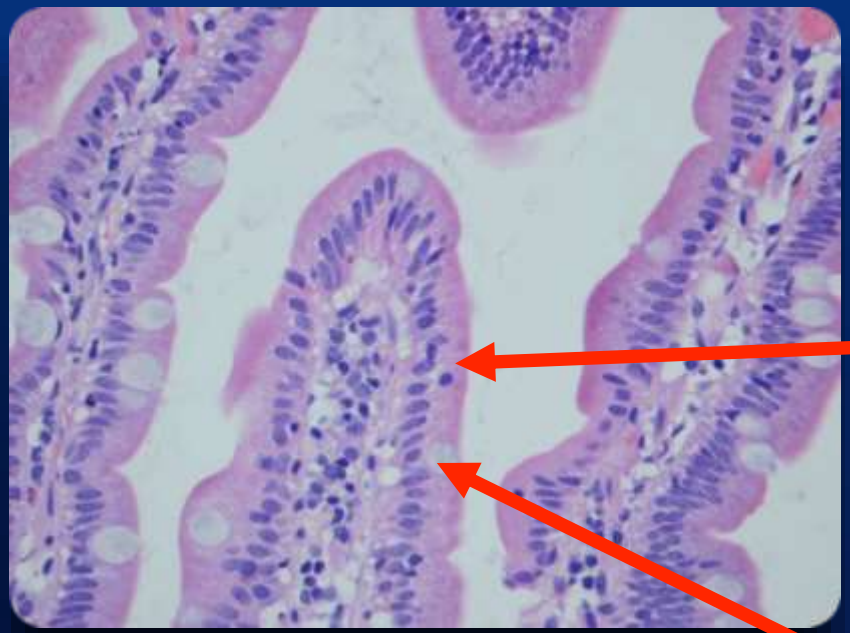
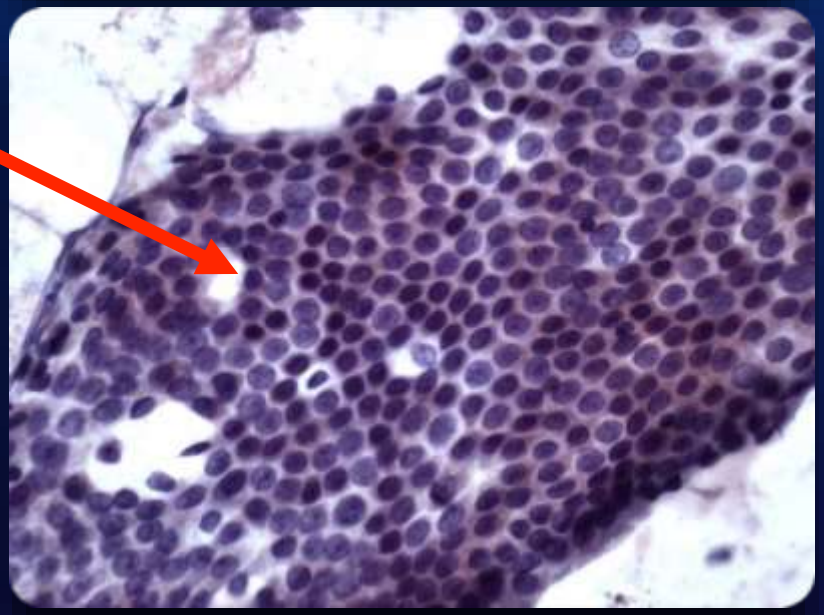
Duodenum

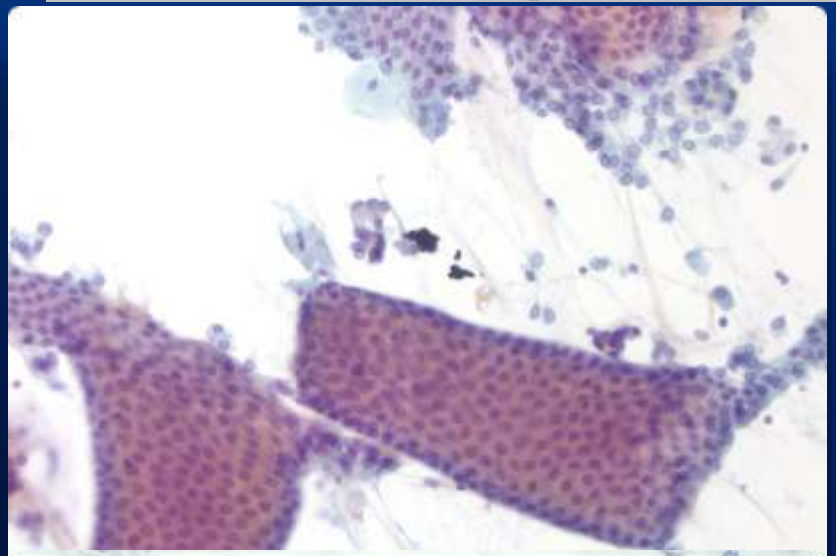


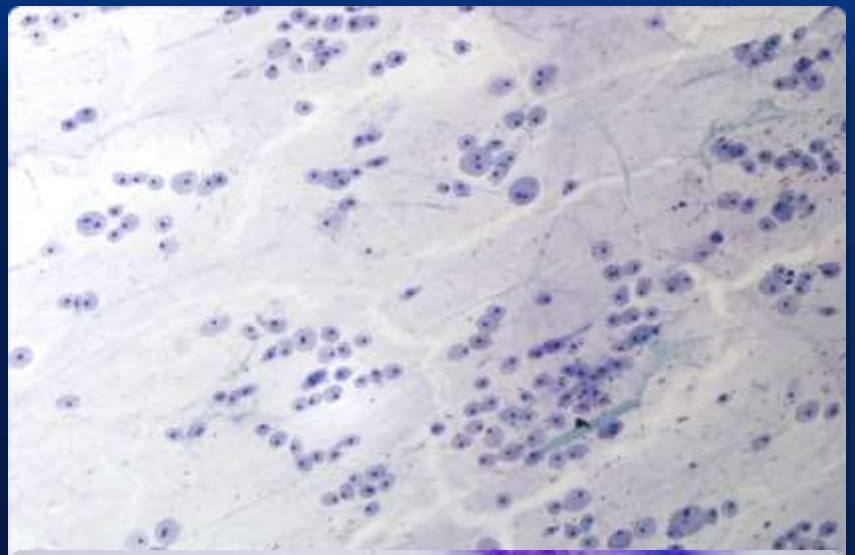


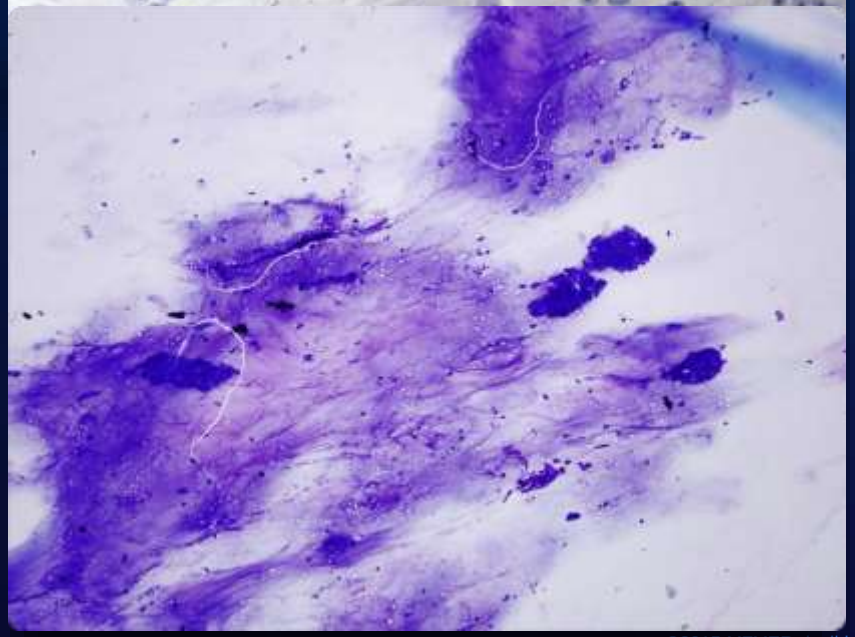
- Generally thin mucus
- Large tissue fragments
- Goblet cells (“fried eggs”), lymphocytes (“sesame seeds”)
- Brush borders

Images by Dr. Matthew Zarka

Which images correspond to GI contaminants and which to pancreatic mucinous cyst???







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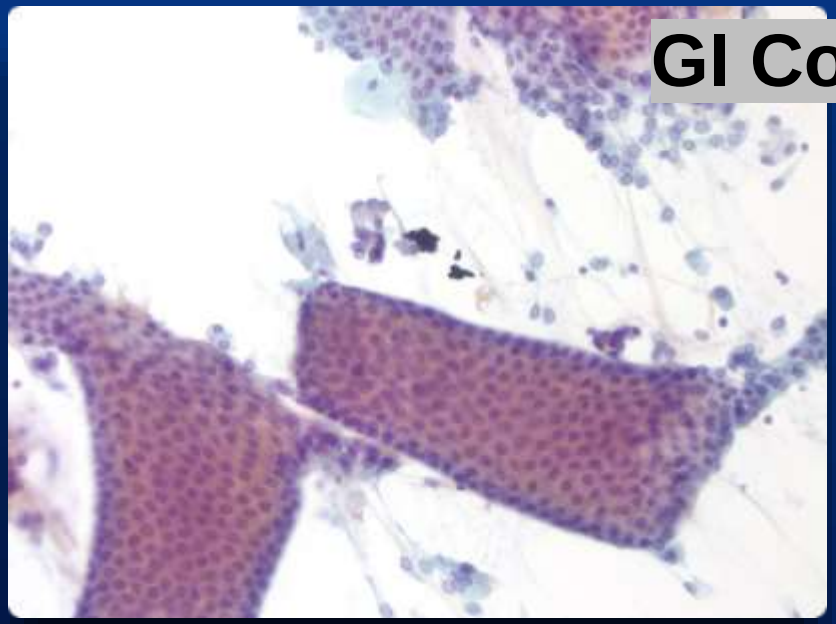
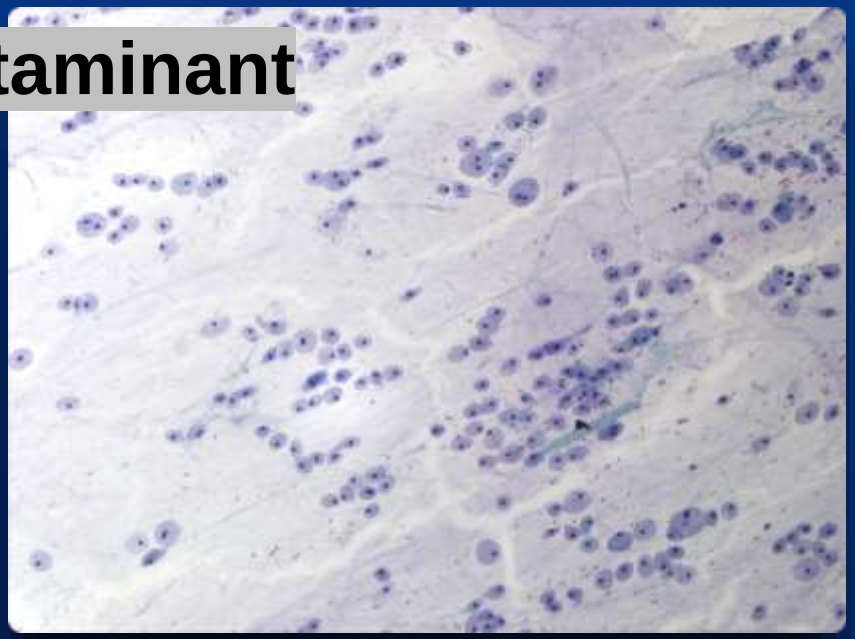
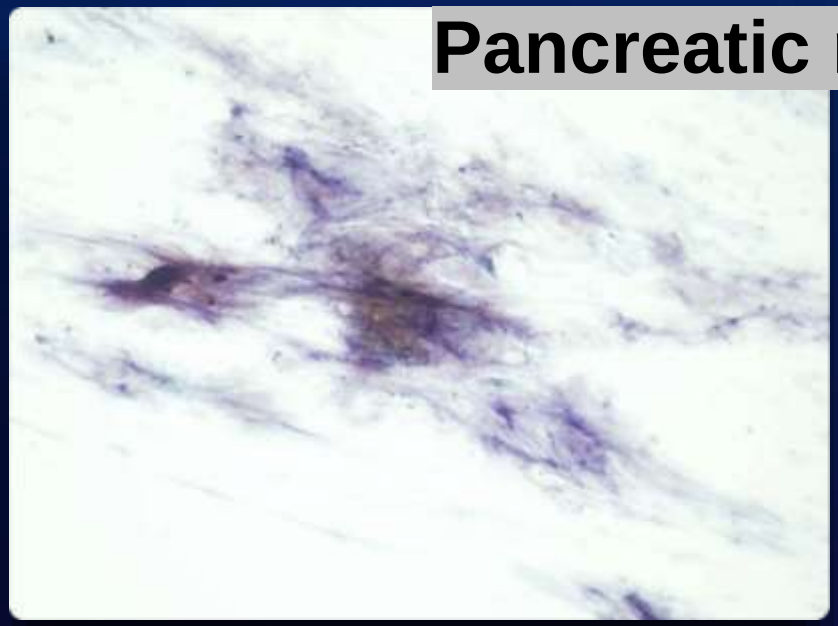
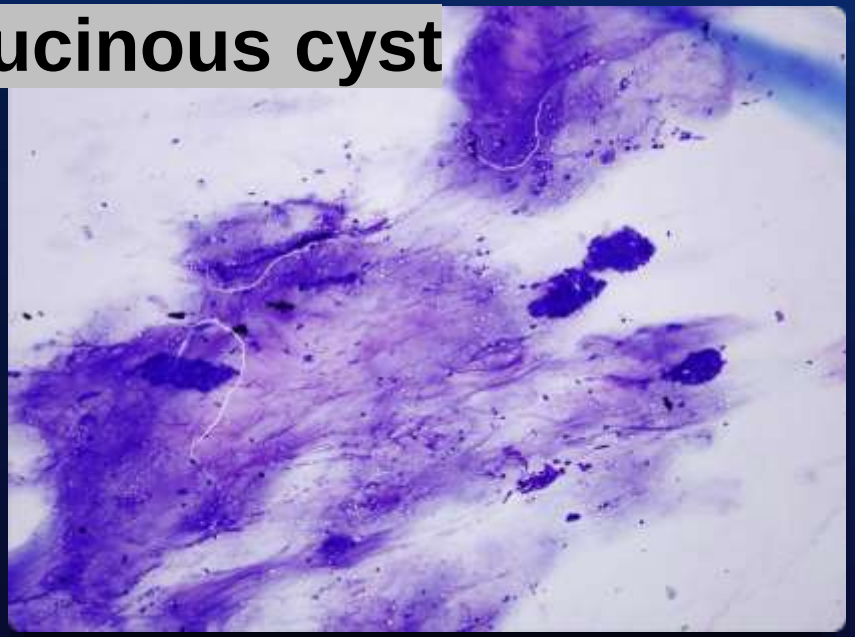
GI Contaminant





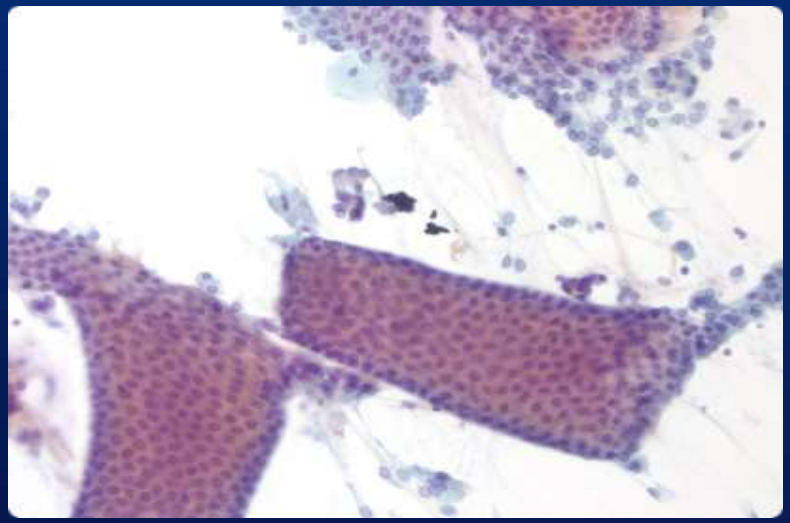
Pancreatic mucinous cyst

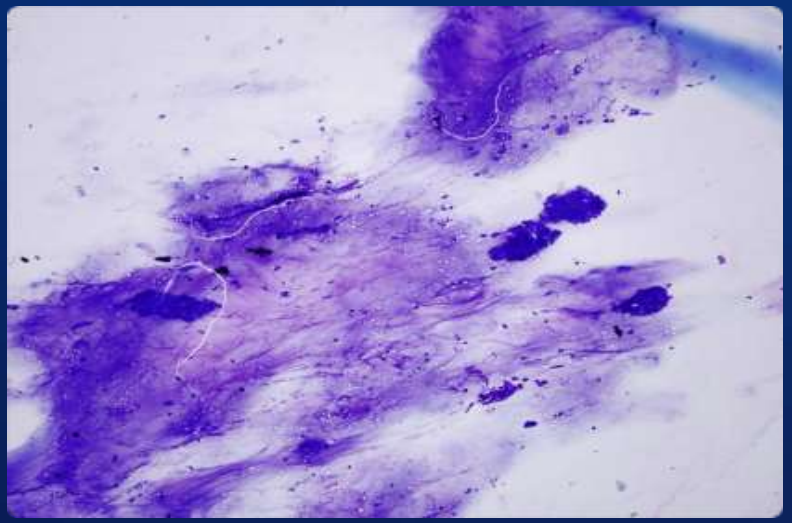




Images by Dr. Matthew Zarka

GI Contaminant vs Mucinous Neoplasm



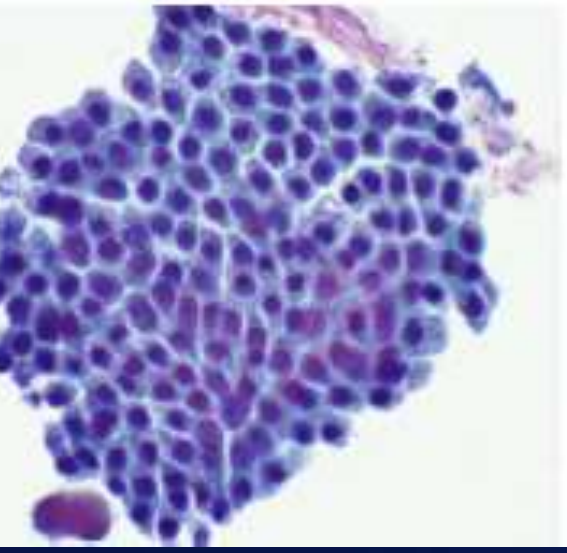


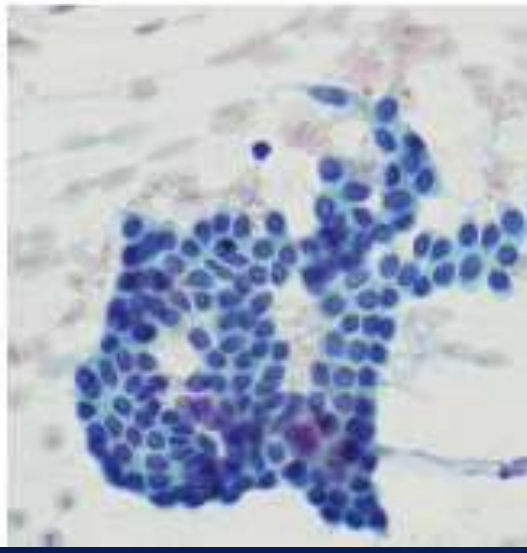
- No “colloid- like” mucin
- Identifiable gut epithelium in background

- +Thick “colloid- like” mucin (mucinous neoplasms may lack mucin in +- 50% of cases)
- +INC (1/3 of IPMN)

Images by Dr. Matthew Zarka

Which of the following is IPMN?





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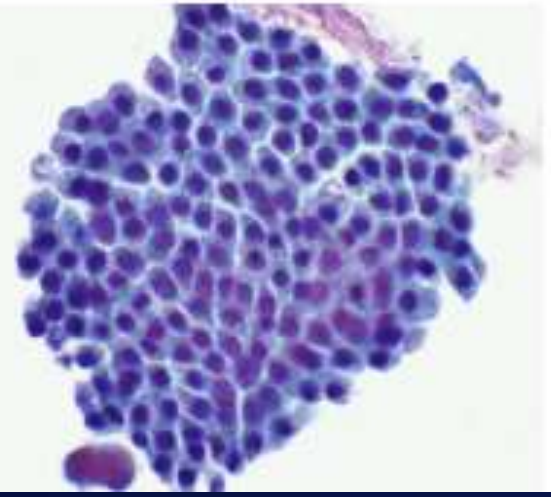
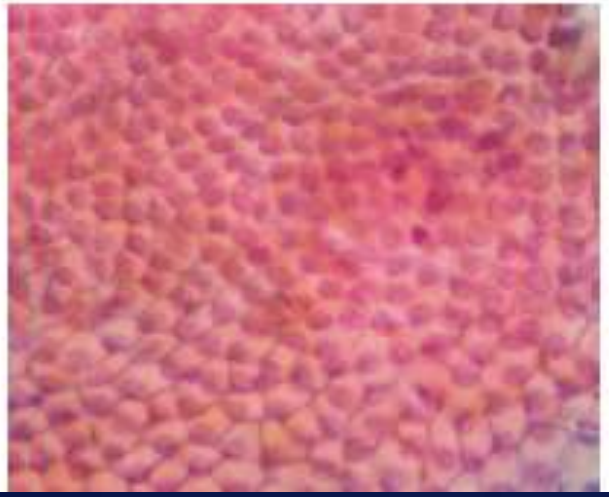
Which of the following is IPMN?

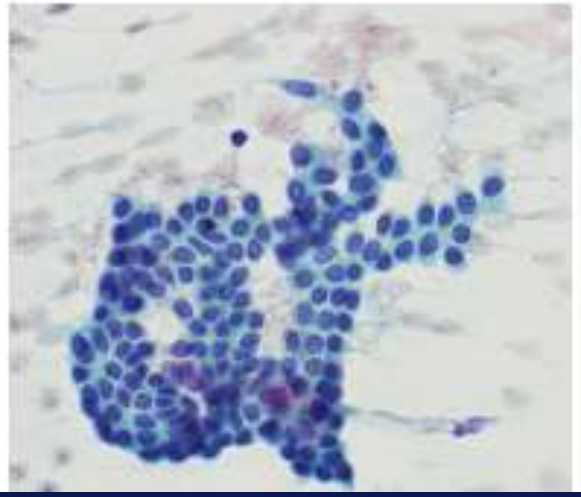
IPMN, LOW GRADE



GASTRIC FOVEOLAR CELLS



BENIGN PANCREATIC DUCTAL CELLS



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What if not sure???

When unsure if lesion or contaminant and no supportive evidence for mucinous cyst:

- *"Negative for malignancy: Non- specific cyst fluid negative for high- grade epithelial atypia"*

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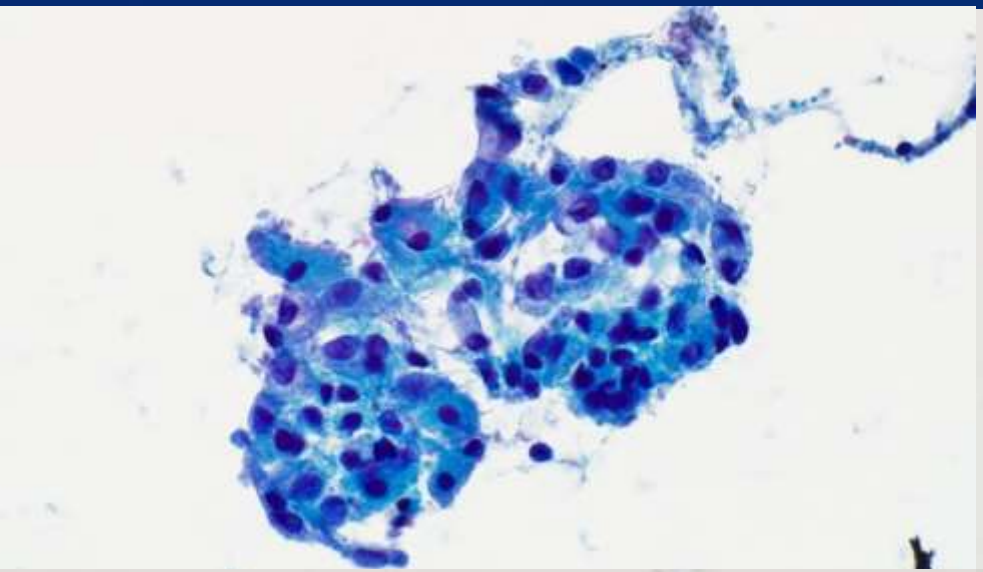
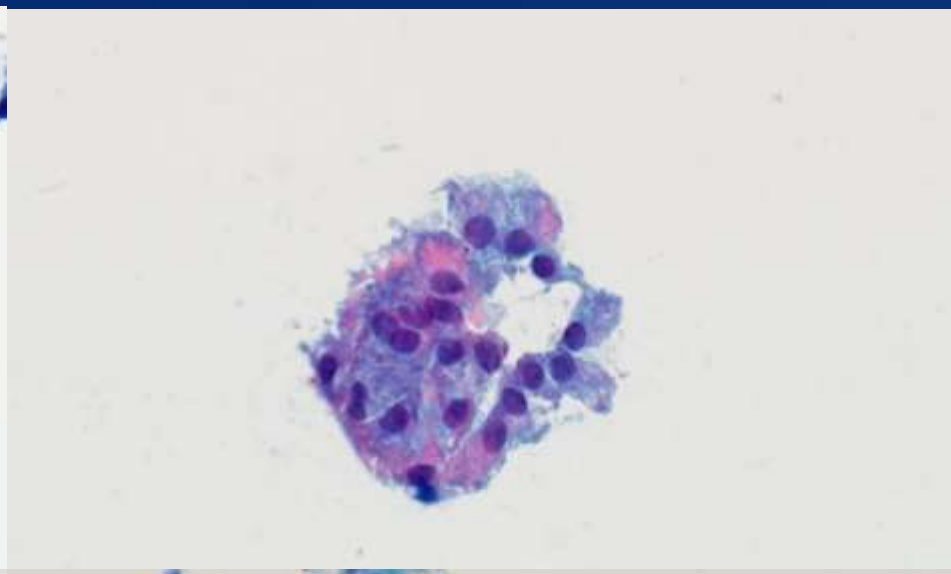
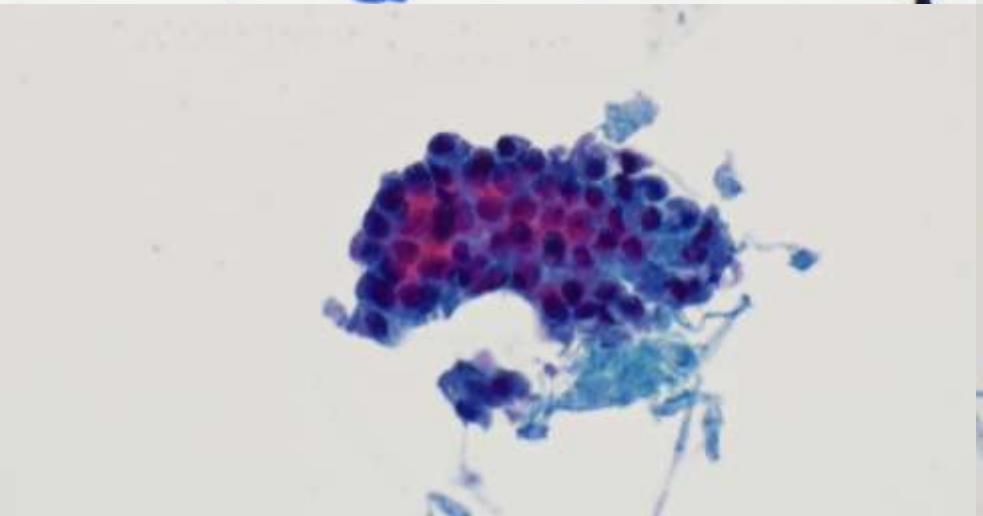
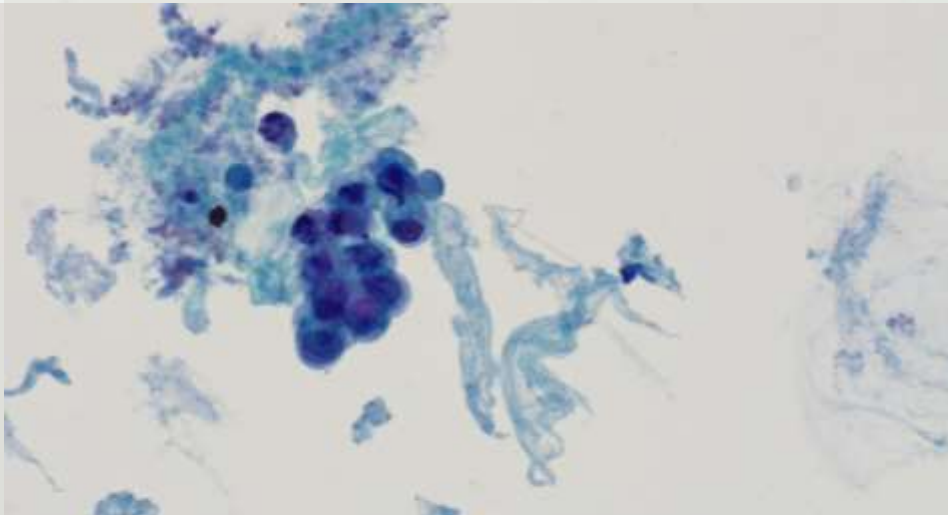
Which of the following is IPMN?

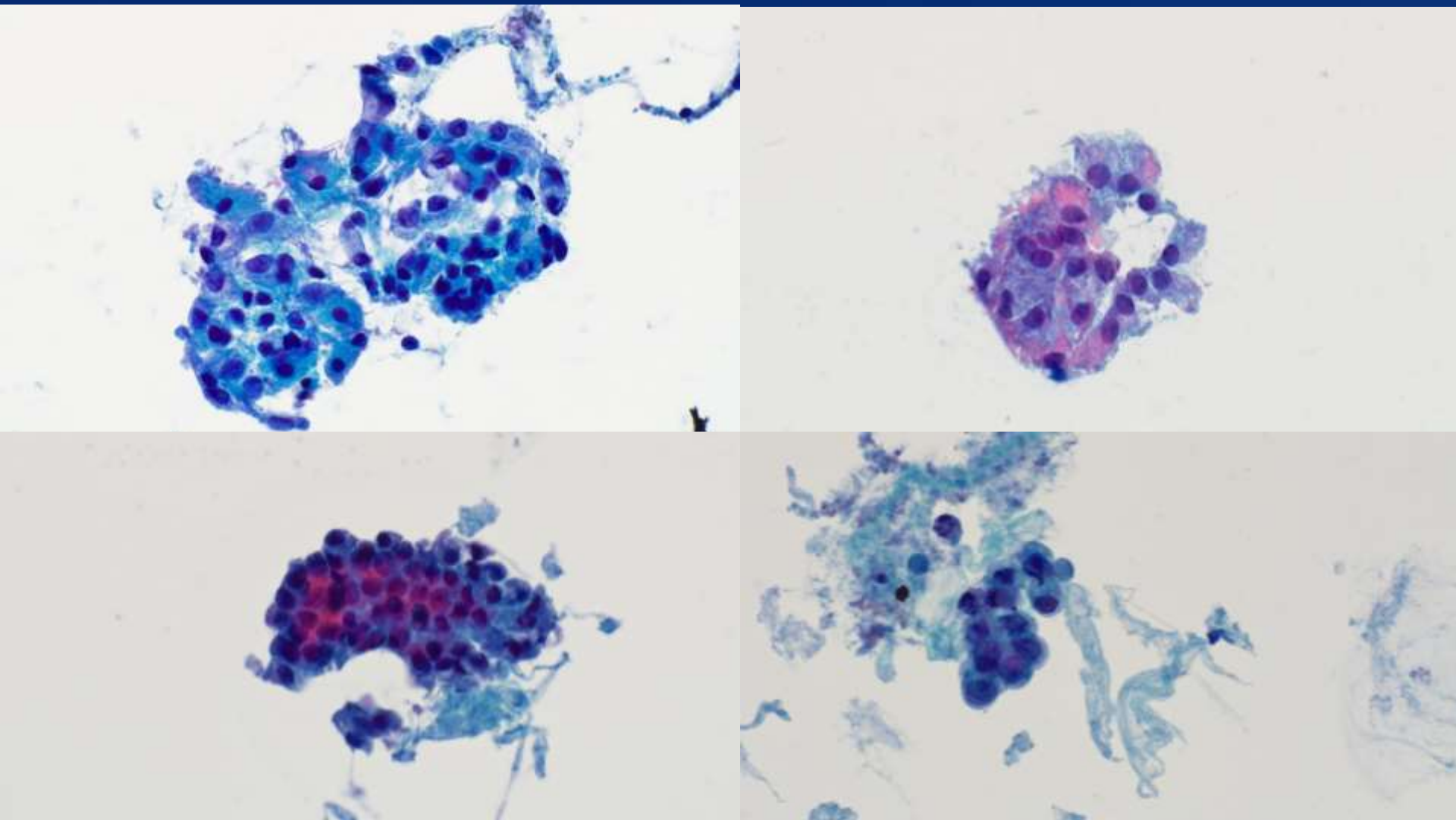




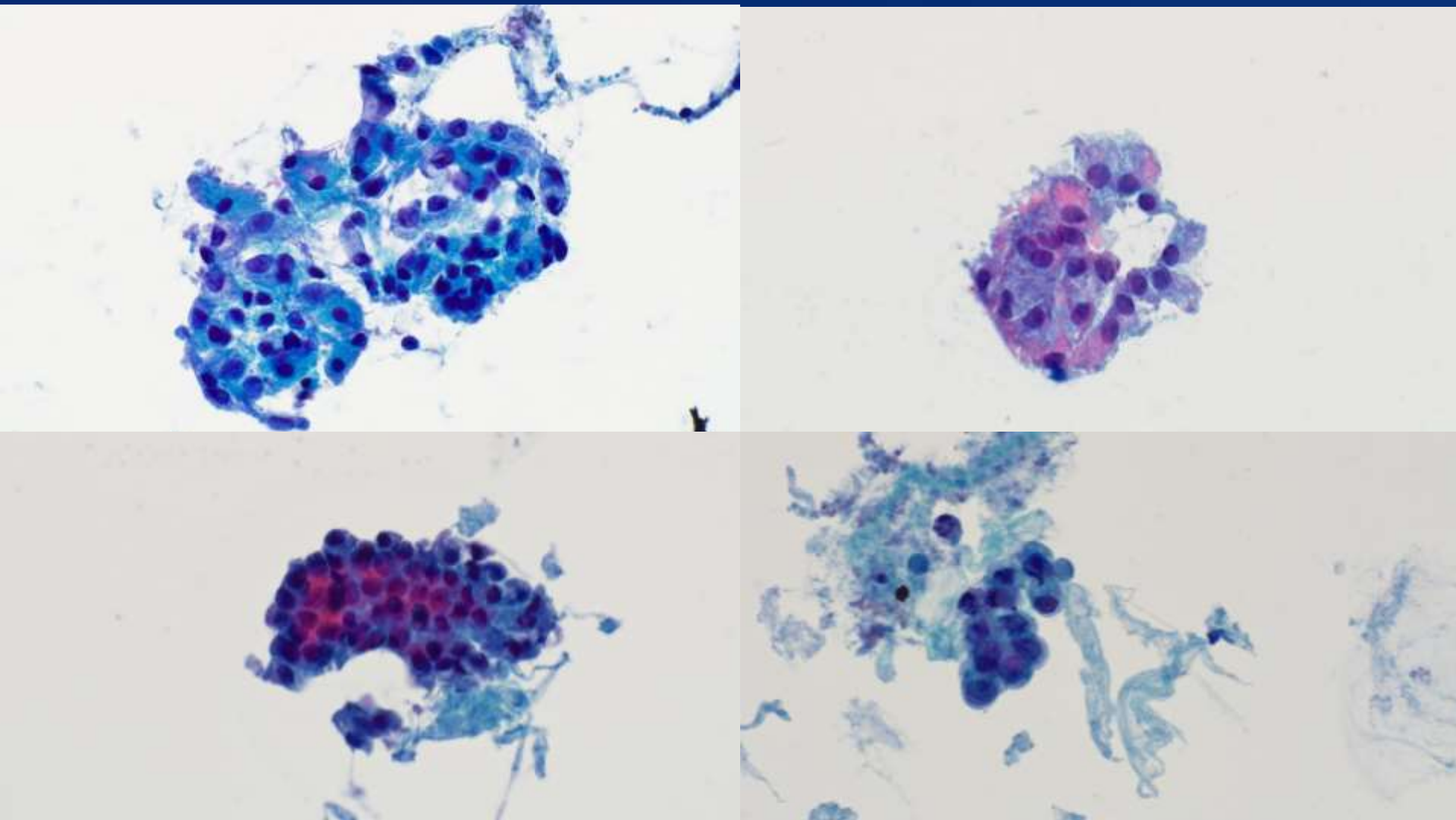




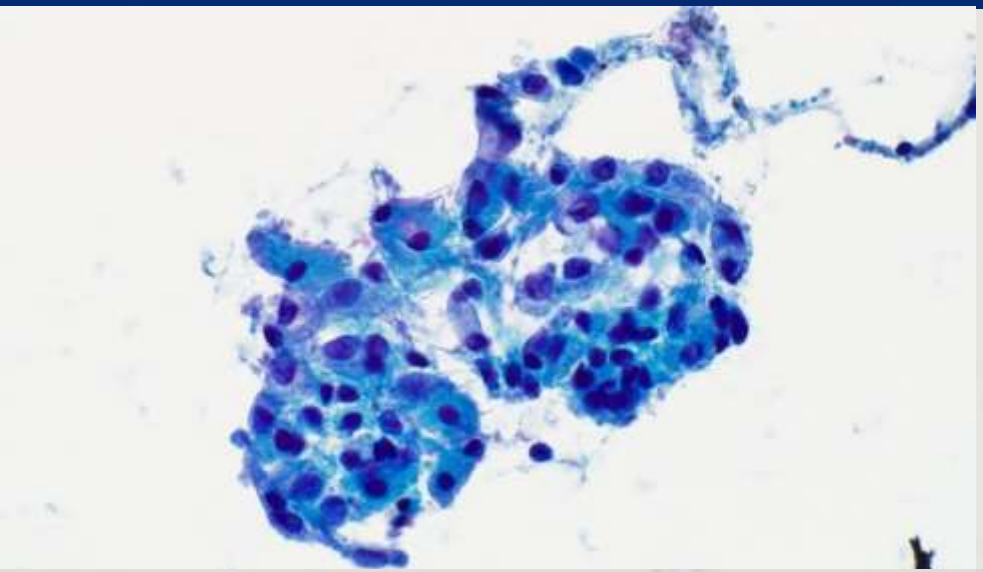
Which of the following is IPMN?
All of them

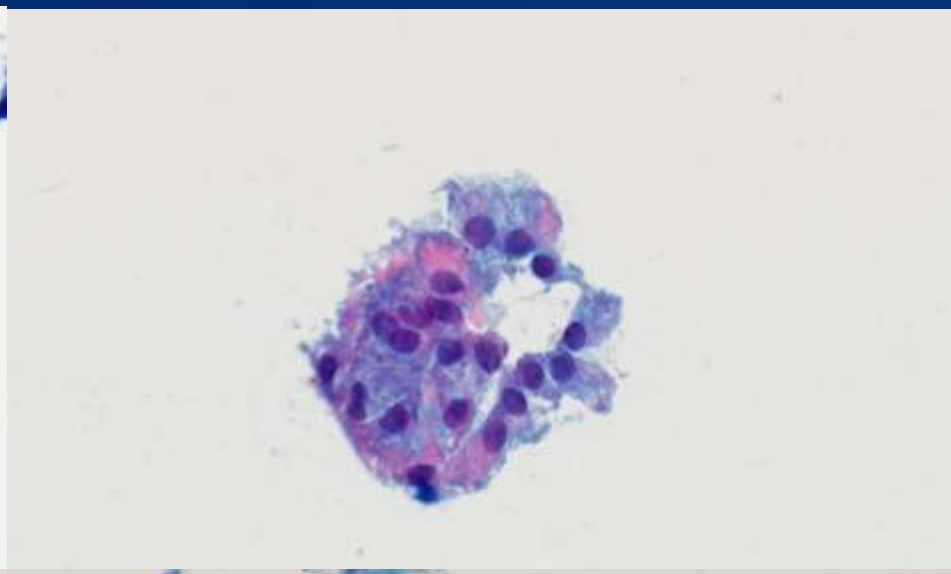


Which of the following is IPMN?
All of them, but…

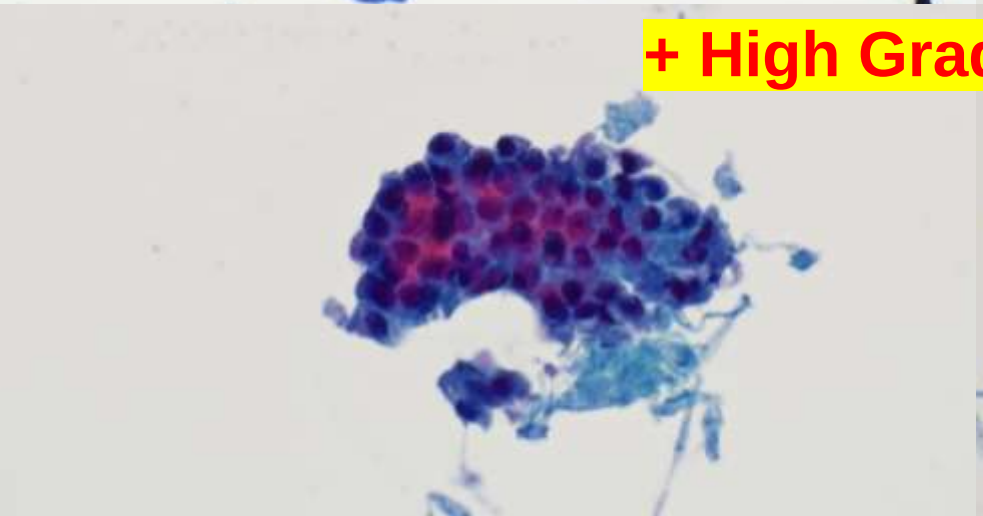


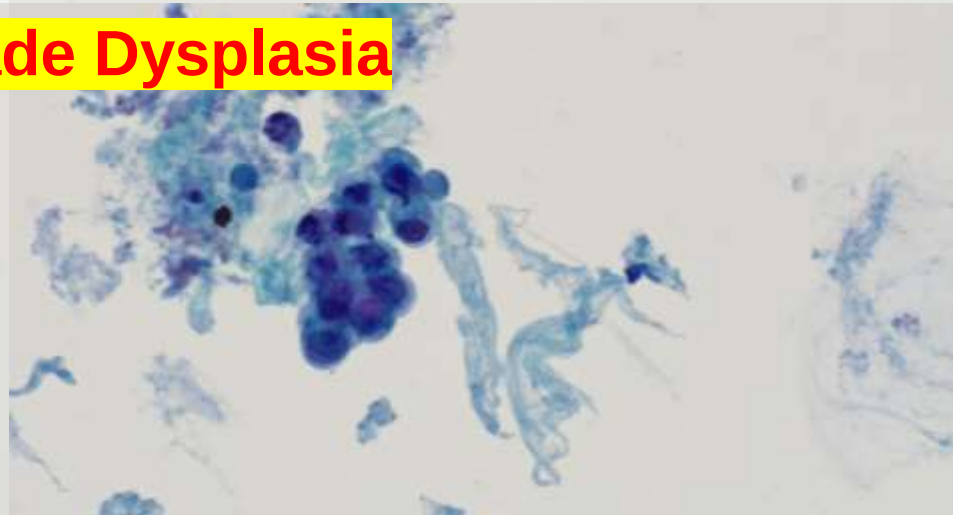
Which of the following is IPMN? All of them, but…





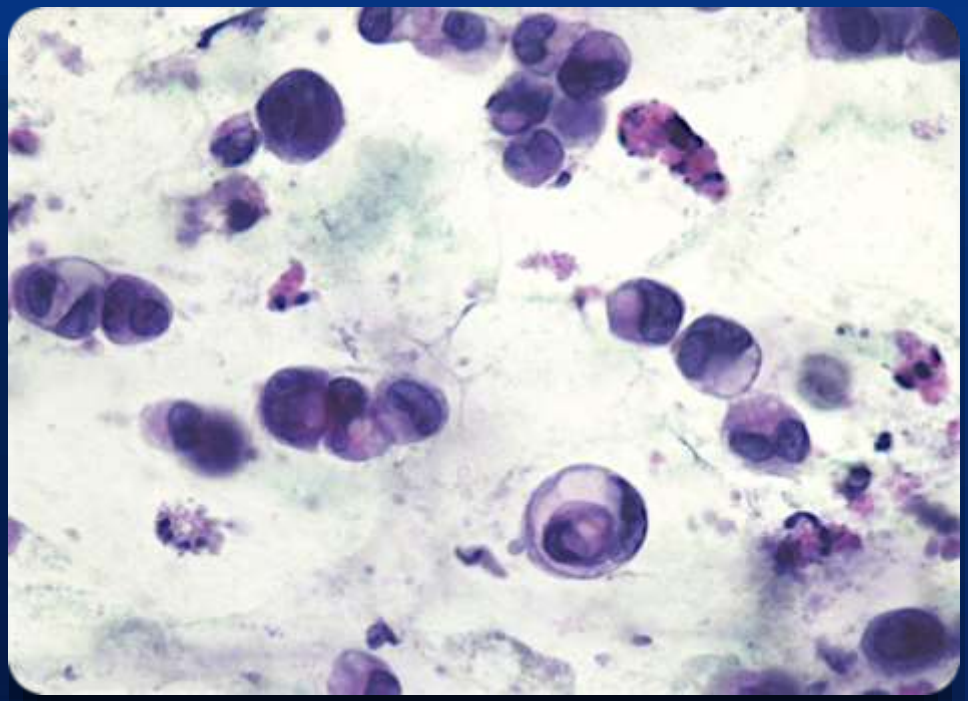
+ High Grade Dysplasia

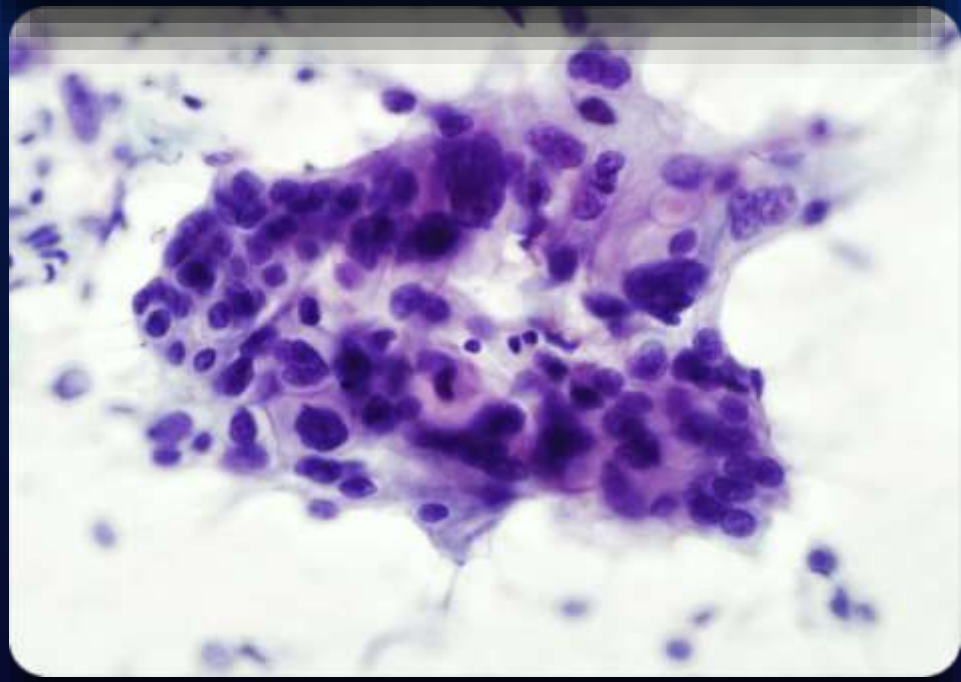




High Grade Dysplasia

- High N/C ratio (variable amount of cytoplasm w or w/o mucin or vacuoles)
- Nuclear atypia (irregularity), hypo or hyperchormasia, variable nucleoli)
- Loss of nuclear polarity, small single cells (< duodenal enterocyte)
- Complex architecture (3D, 2-4 tight buds of cells)
- Less/ scant background mucin, -/+ necrosis





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Images by Dr. Matthew Zarka

High Grade Dysplasia (HGD) in IPMN

- HGD Important to distinguish:
  - Resection
- LGD lesions:
  - Followed clinically EUS/ imaging
  - Resected if worrisome imaging findings appear

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High Grade Dysplasia (HGD) in IPMN

- HGD Important to distinguish:
  - Resection
- LGD lesions:
  - Followed clinically EUS/ imaging
  - Resected if worrisome imaging findings appear
- **If not sure: conservative approach**

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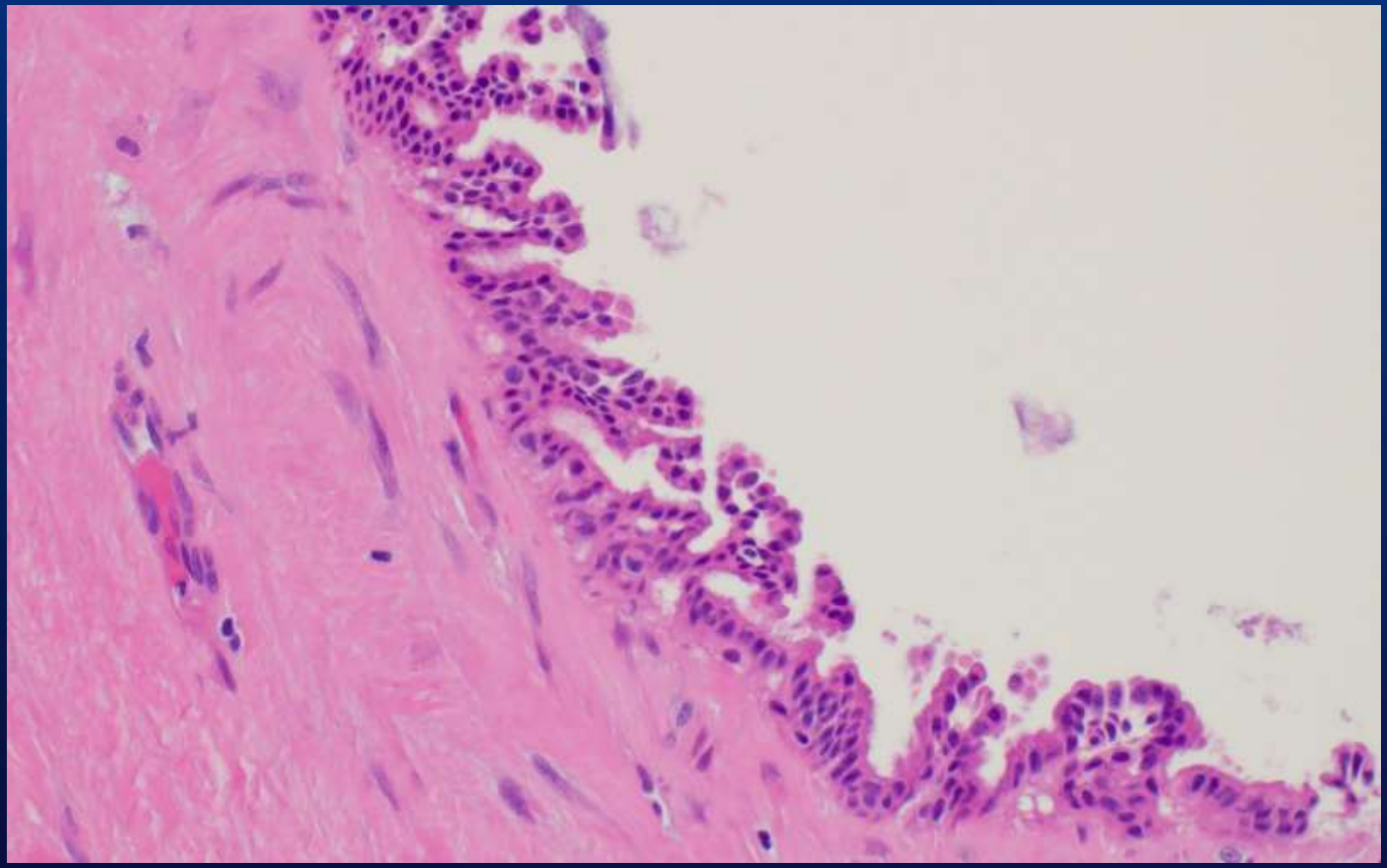
IPMN with High Grade Dysplasia



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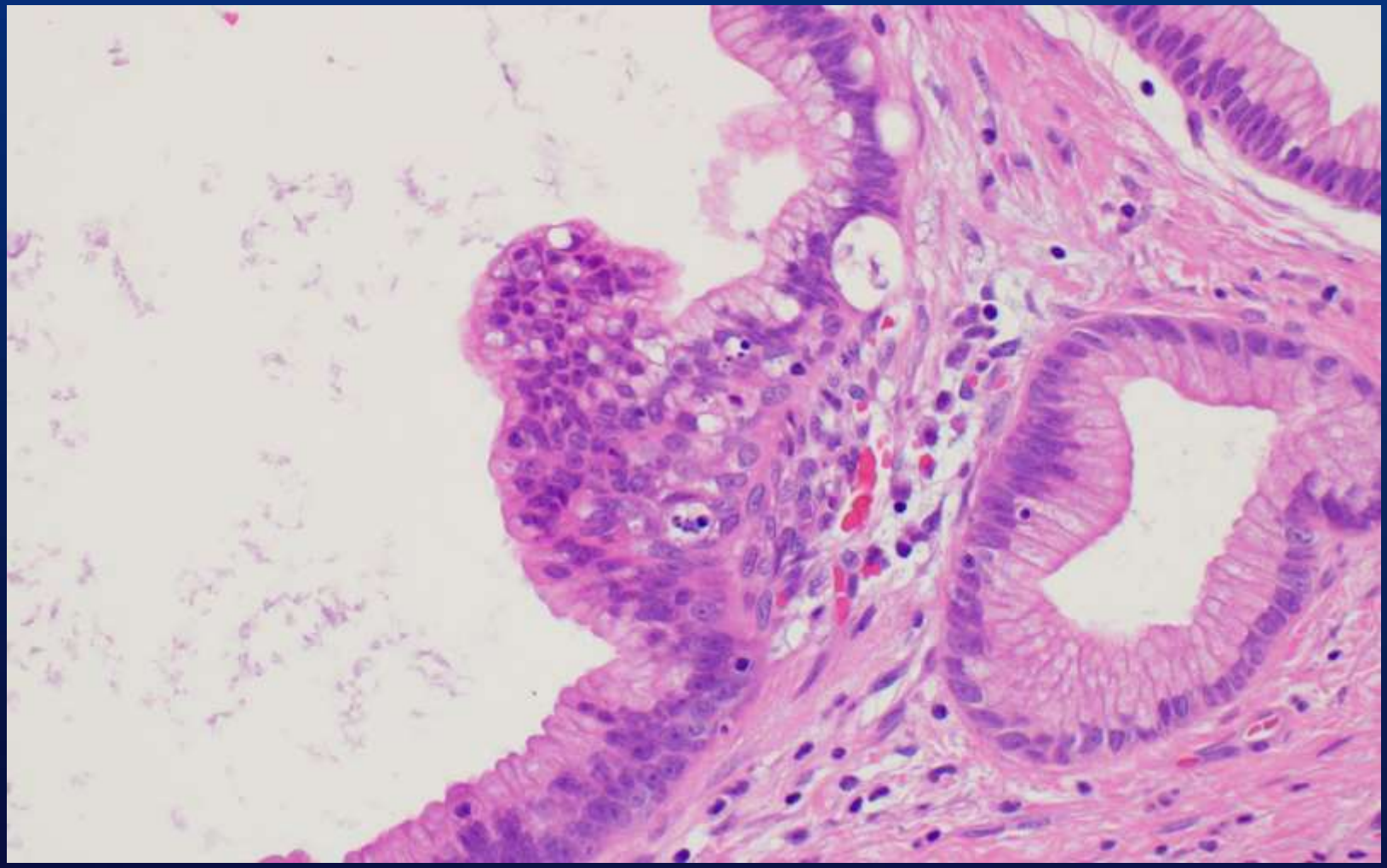
IPMN with High Grade Dysplasia



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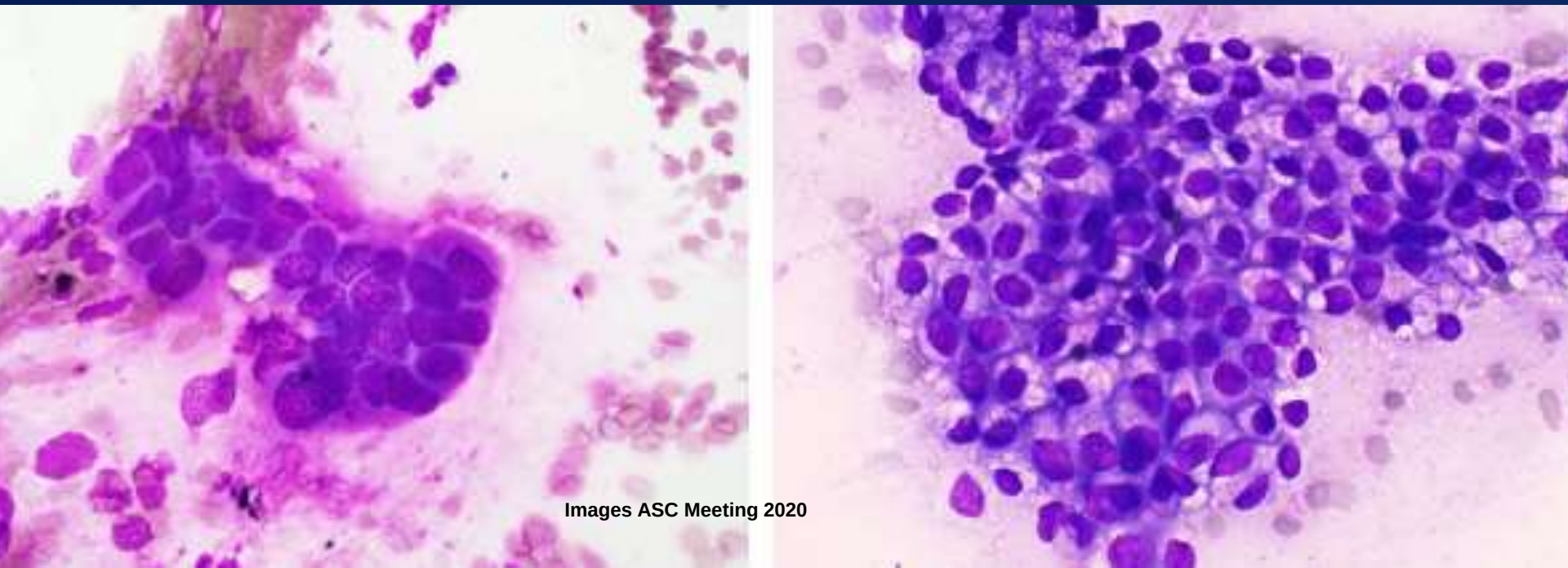
IPMN HG vs LG Dysplasia

- High N/C ratio, “small” cells, variable cytoplasm
- Nuclear atypia (irregularity, hyper or hypochromasia)
- Loss of nuclear polarity
- Single cells or complex architecture (3D, 2-4 tight buds of cells)
- Less/ scant background mucin, -/+ necrosis

- Uniform cells
- Bland or mild nuclear atypia
- No architectural complexity
- Intracytoplasmic mucin
- Abundant extracellular mucinous material



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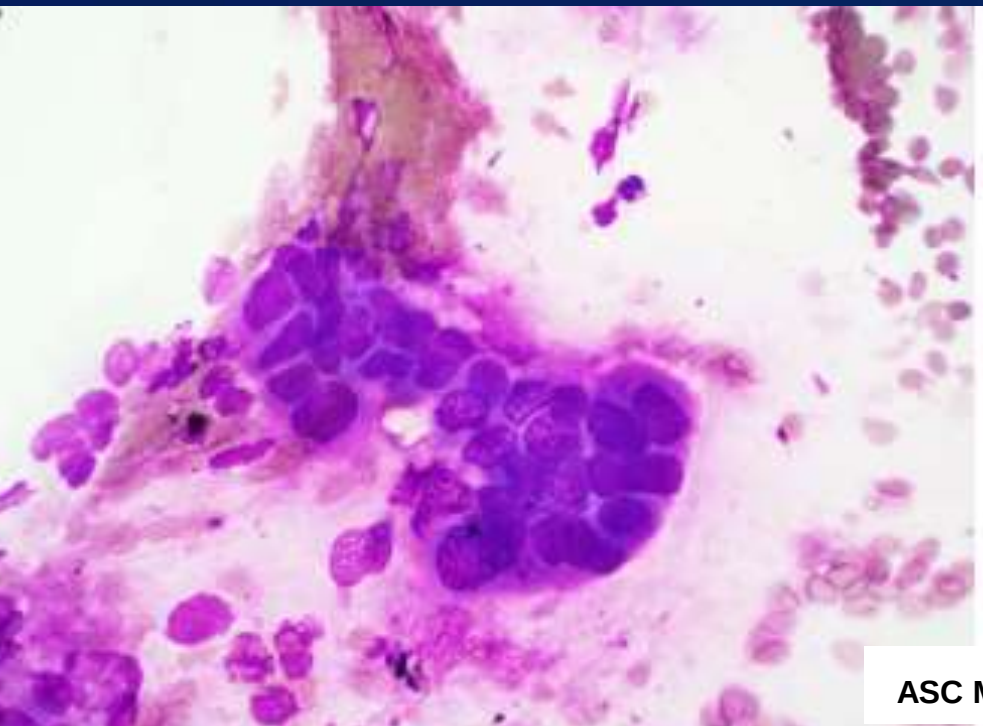
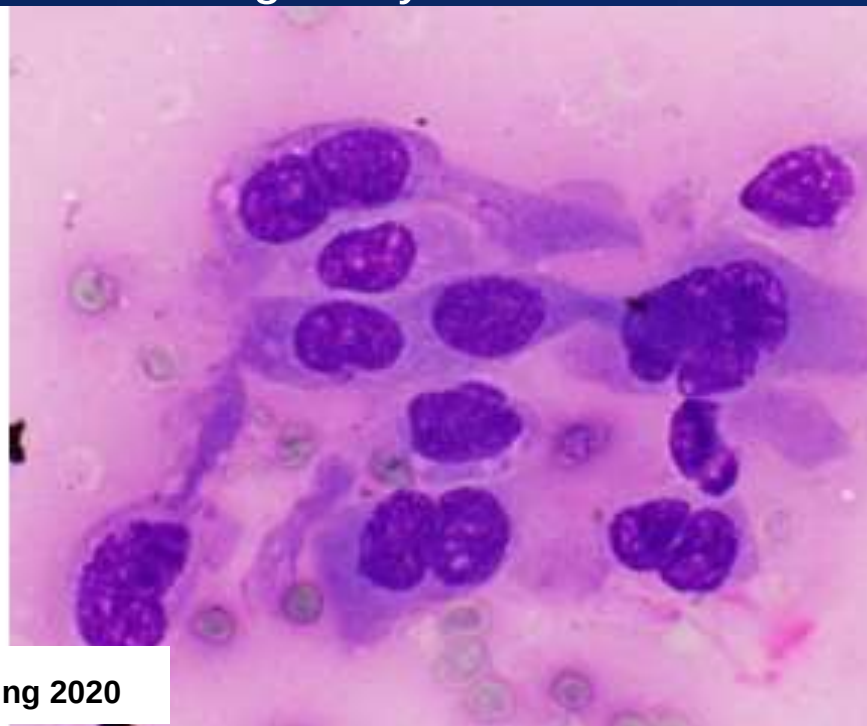
IPMN with HGD

- Increased N/C ratio
- Nuclear atypia
- Loss of nuclear polarity
- Complex architecture
- Less/ scant mucin

Adenocarcinoma

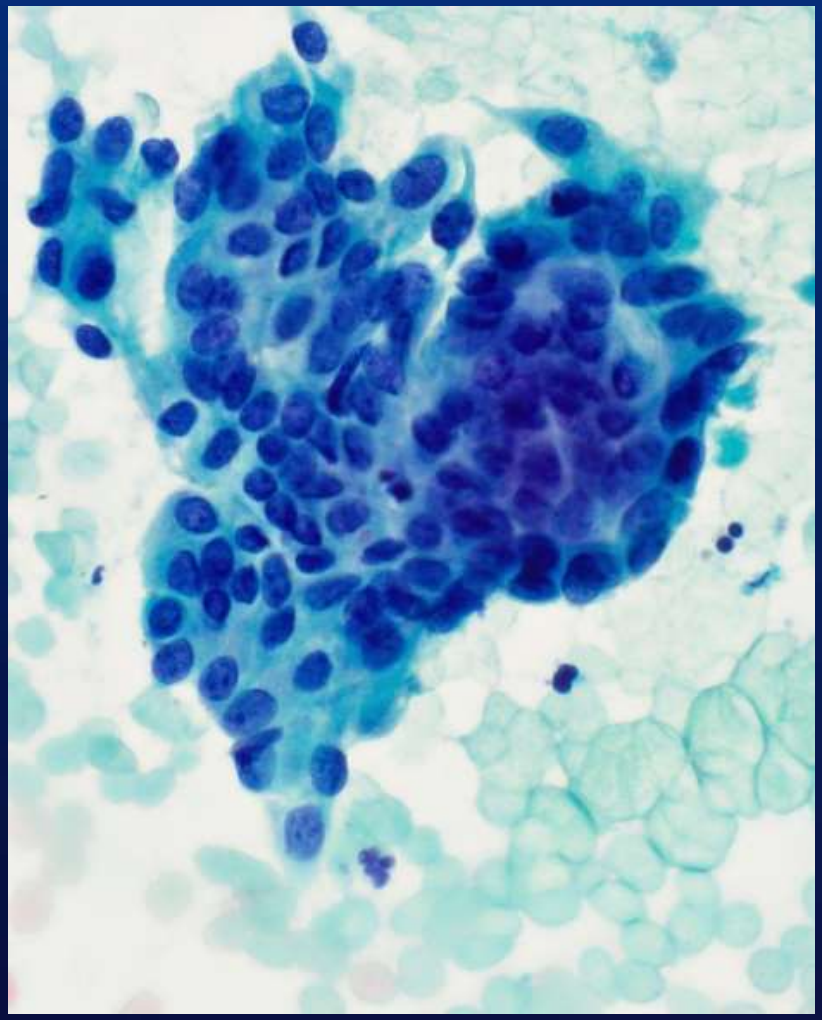
- Discohesion, many single tumor cells
- Anisonucleaosis with >4 times variation in nuclear size
- Necrosis
- Pleomorphism with nuclear outline irregularity

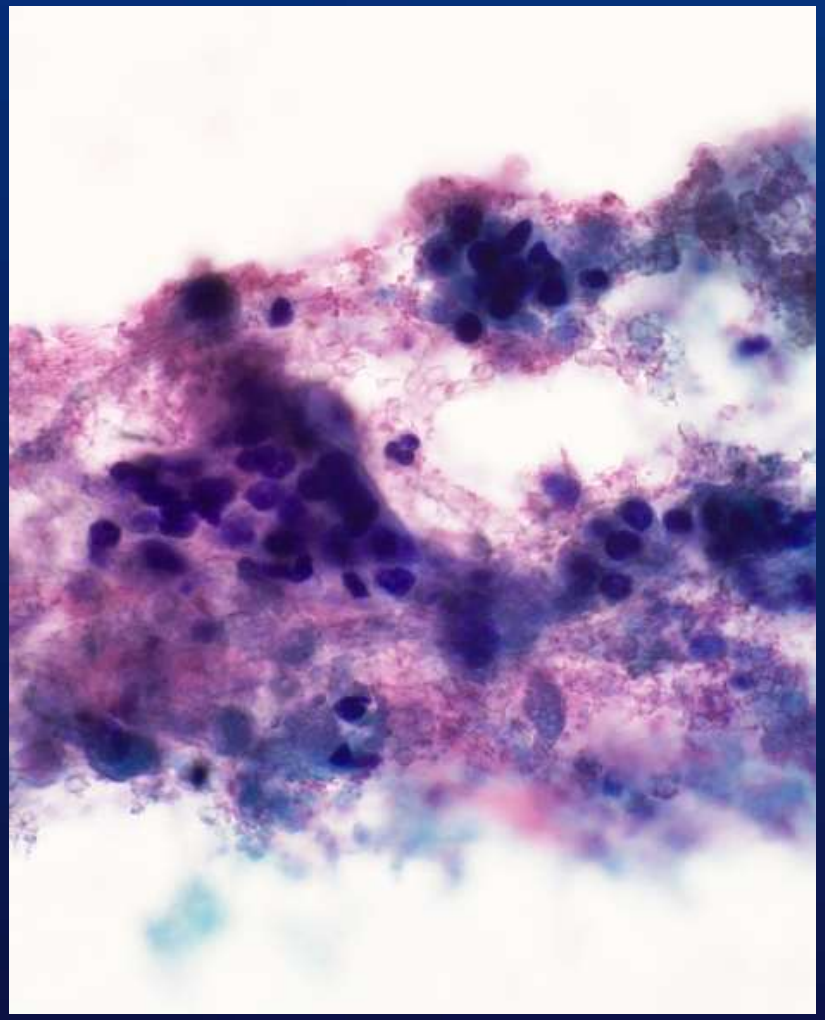




Case 3

Provided information “Suspicious for IPMN”



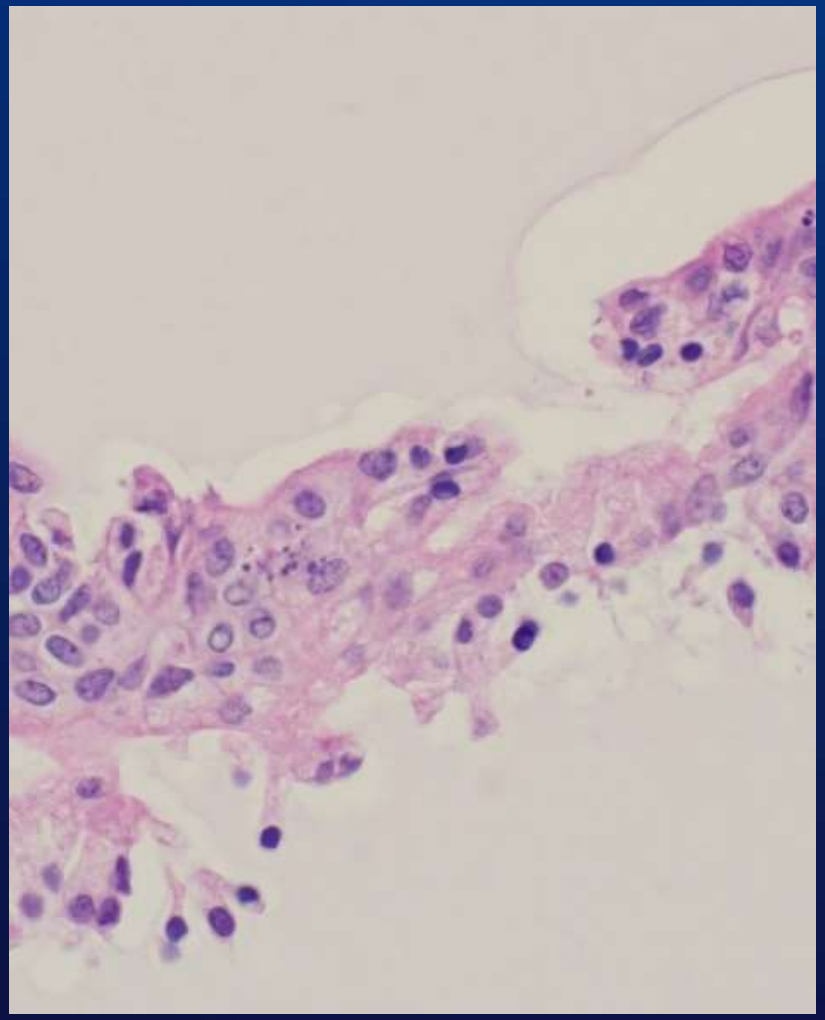


MAYO CLINIC

Positive for Neoplasm

Mucinous epithelium present, suggestive of IPMN
No high-grade dysplasia or malignancy

CB: Is this IPMN???



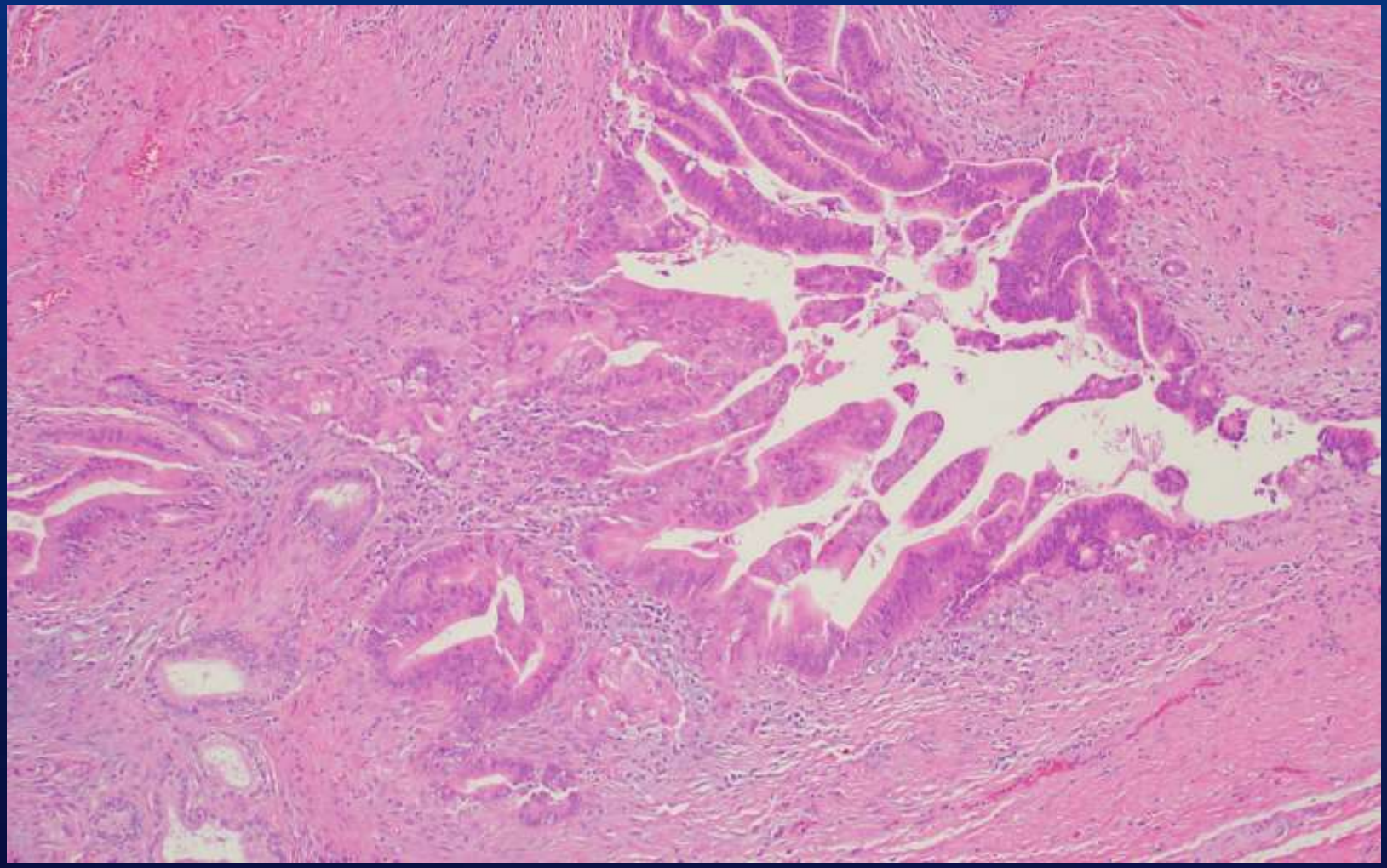
MAYO CLINIC

Follow up:
Lesion not cystic, but mostly SOLID

- Final Report:
- Atypical
  - Markedly paucicellular sample with atypical mucinous cells cannot exclude malignancy

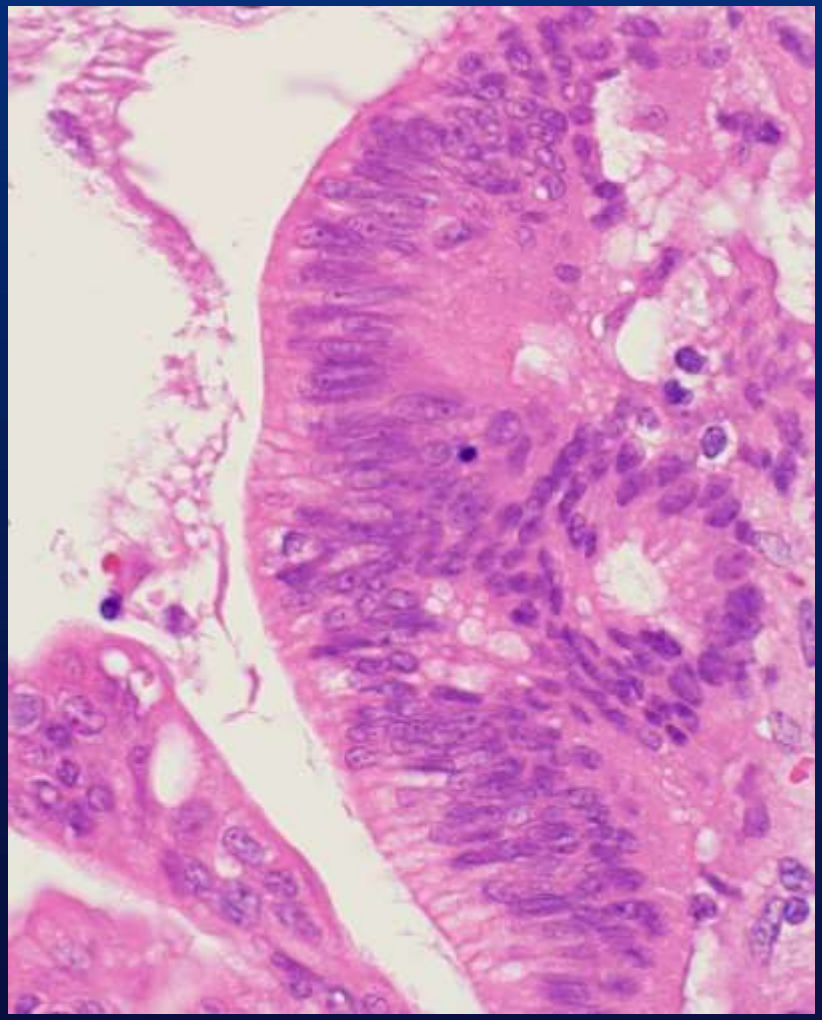
MAYO CLINIC

Resection: Adenocarcinoma arising from IPMN with high grade dysplasia



MAYO CLINIC

Resection vs CB



MAYO CLINIC

Adenocarcinoma vs Mucinous Lesions

- It can be extremely challenging to distinguish well- differentiated PDCA and IPMN/MCN on cytology due to:
  - Subtle cytologic atypia and
  - Low N/C that can occur in both cases
- FAVORS Adenocarcinoma:
  - DISTINCT MASS on imaging

MAYO CLINIC

Cytology of Adenocarcinoma

- Crowding/ overlapping/ 3D, single cells, drunken honeycomb
- Nuclear features:
  - Enlargement, anisonucleosis (4:1), membrane irregularity, clearing/ hyperchromasia, macronuclei
- Cytoplasm:
  - Scant or abundant- mucinous
- Necrosis, mitosis, single cells

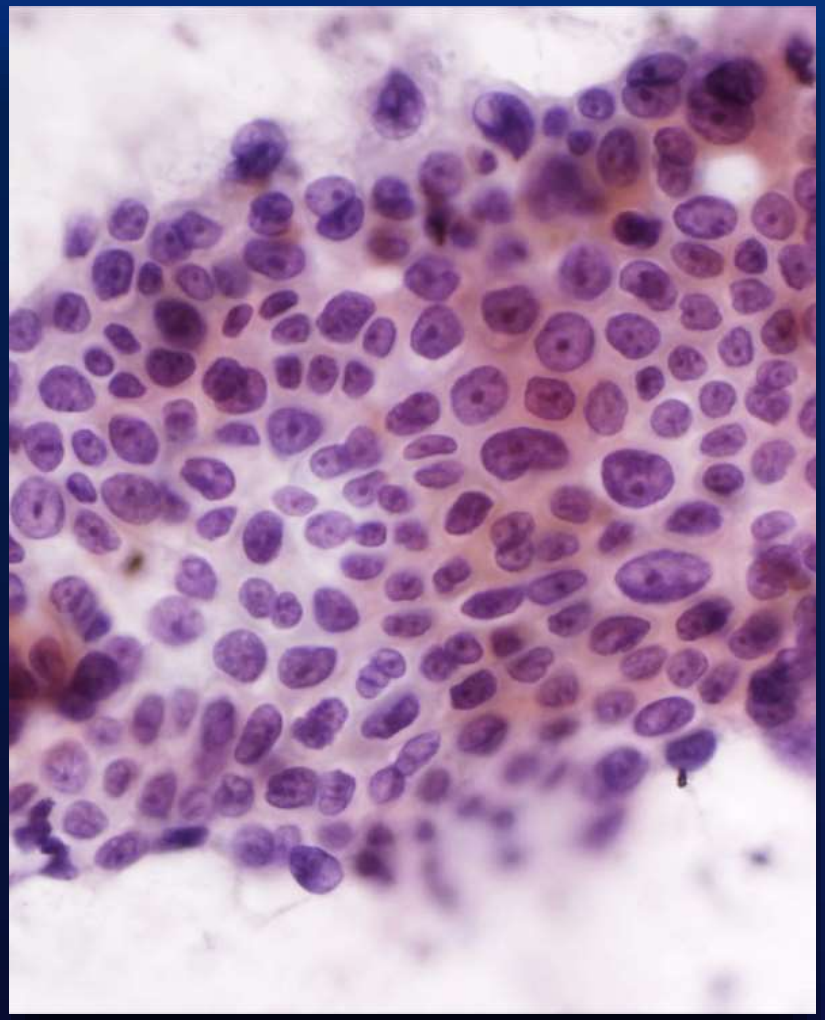
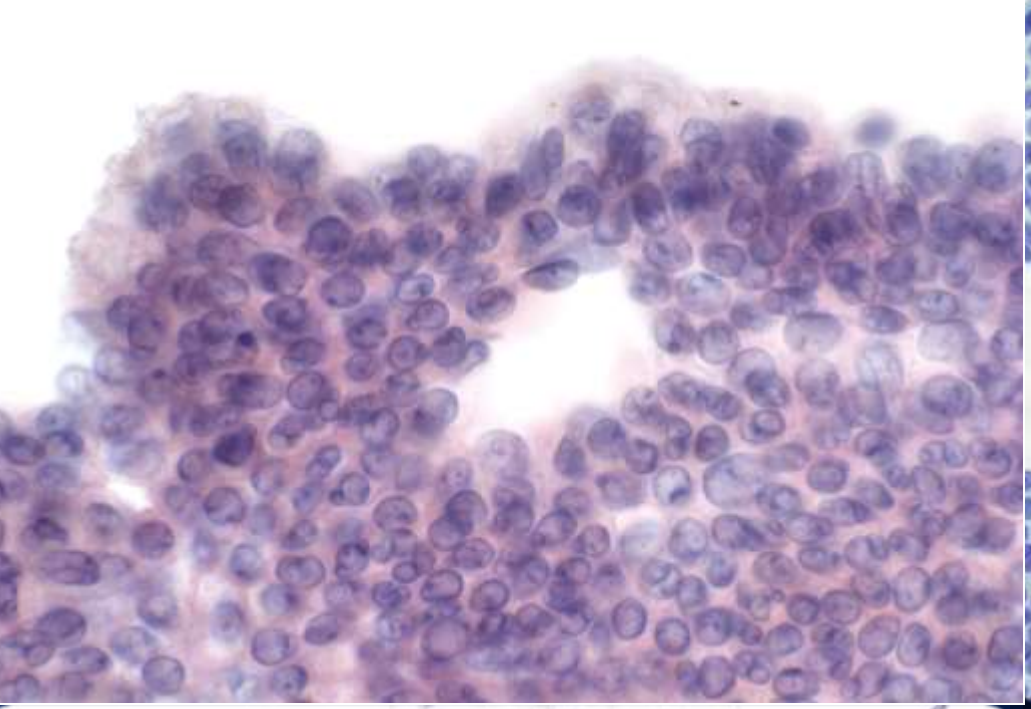
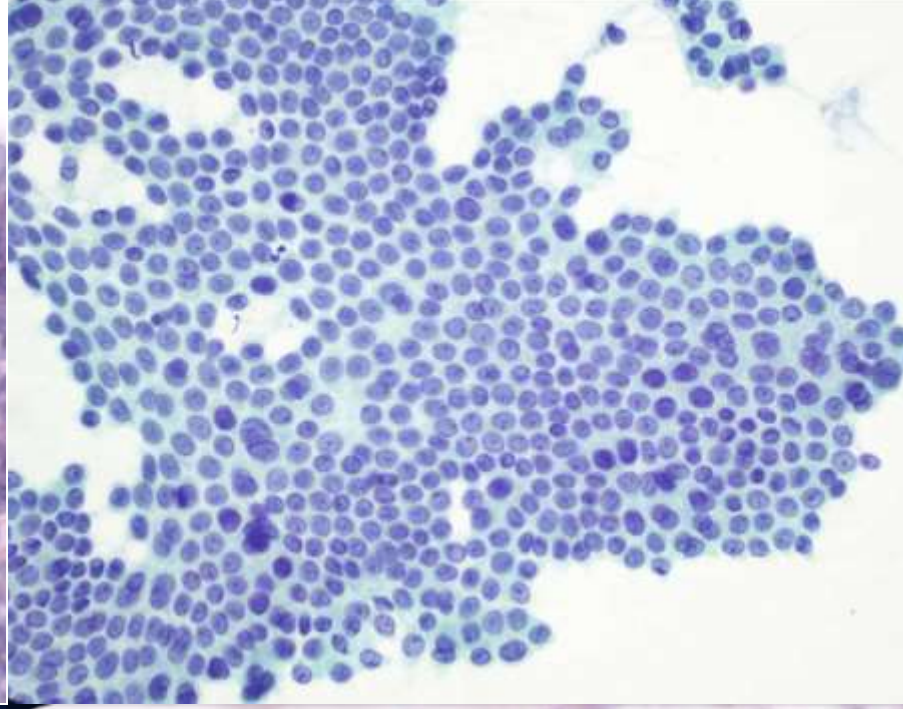
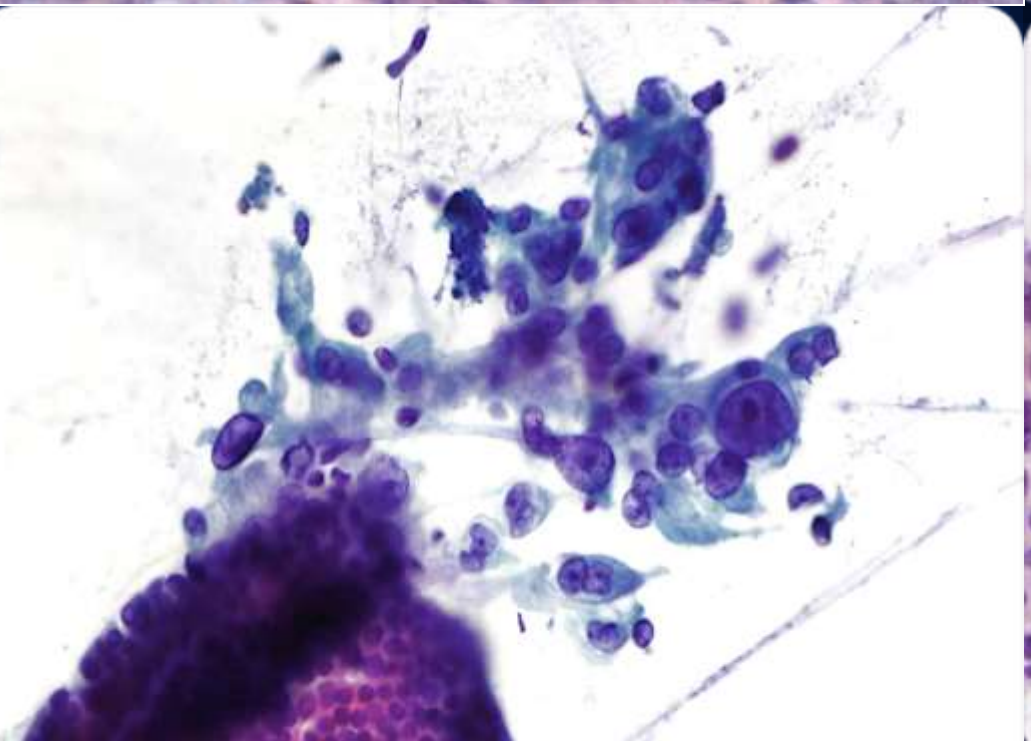


Image by Dr. Matthew Zarka

MAYO CLINIC



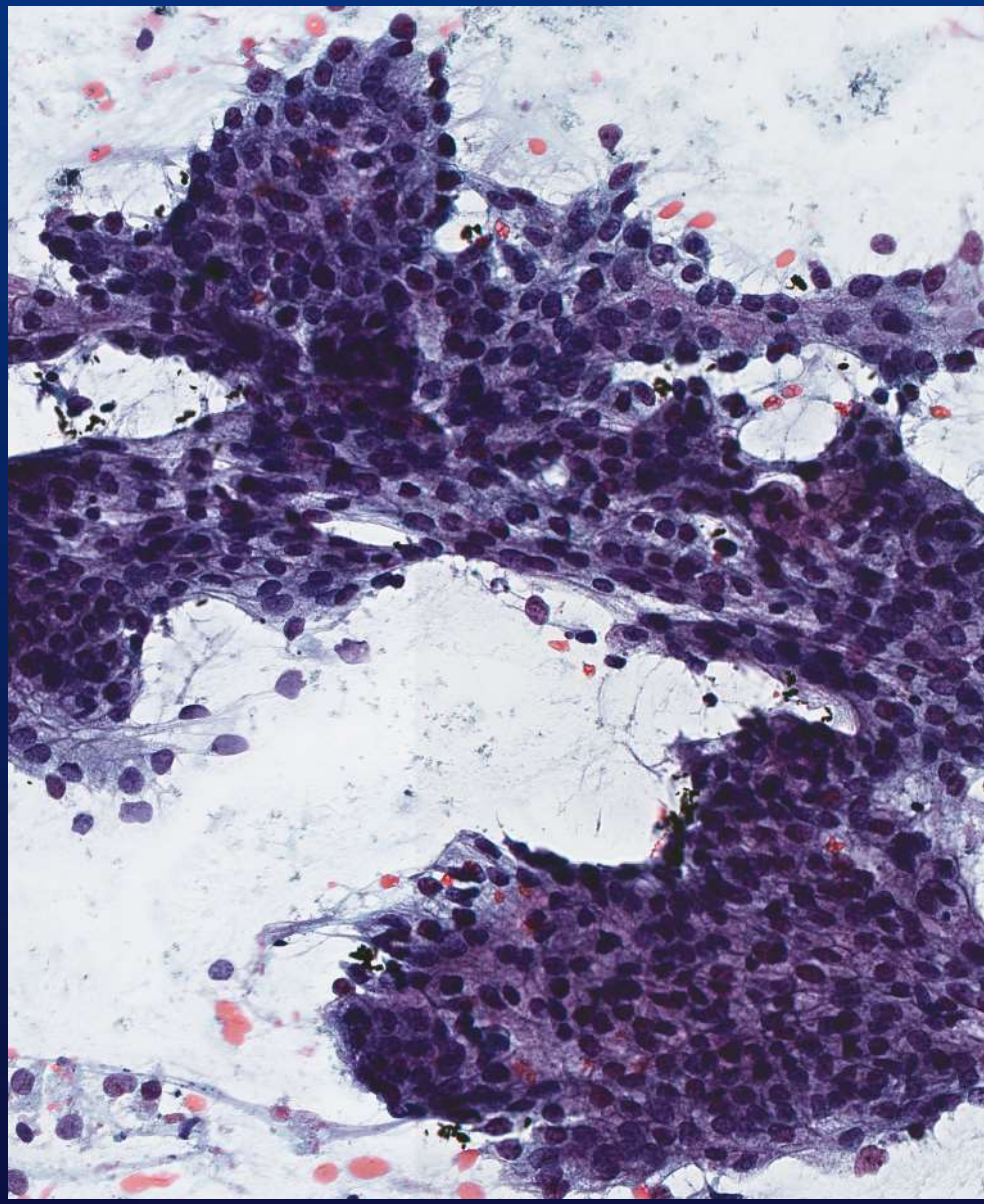




Images by Dr. Matthew Zarka

Adenocarcinoma

- Major criteria
  - Nuclear overlap and crowding
  - Nuclear contour irregularity
  - Chromatin clearing or clumping
- Minor criteria
  - Single epithelial cells
  - Necrosis, mitosis
  - Nuclear enlargement



Acta Cytol, 1995; 39:1-10

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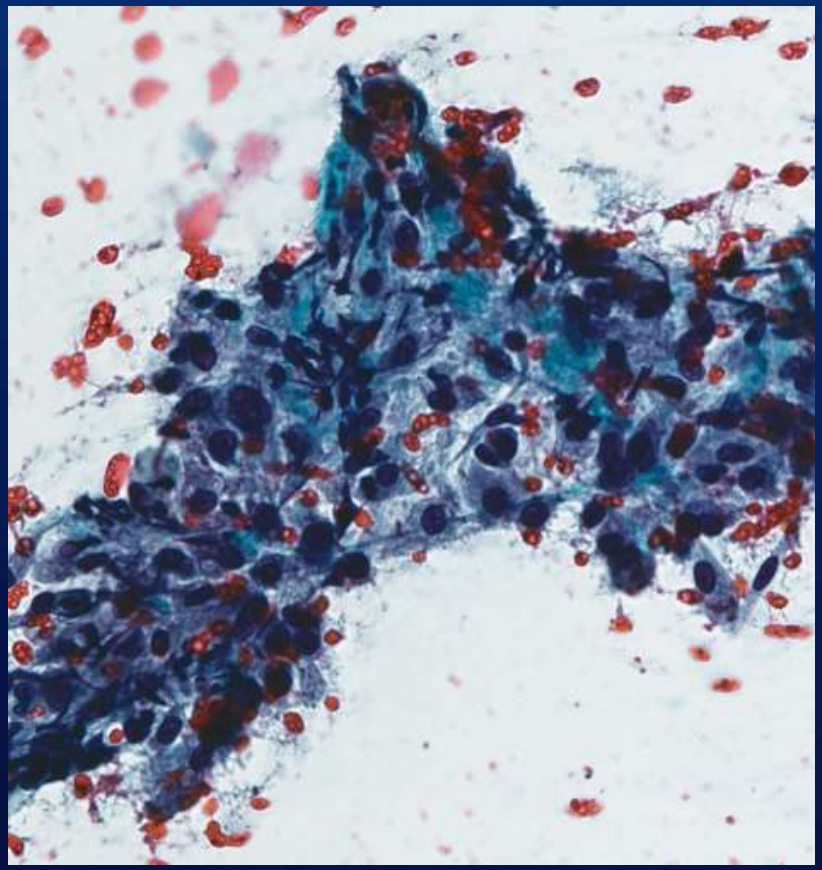
Differential Diagnosis

- Autoimune pancreatitis (AIP)/ chronic pancreatitis (CP)
- Pancreatic Neuroendocrine Tumor (PanNET)

MAYO CLINIC

Autoimmune Pancreatitis (AIP)



- Clinical presentation as mass, mimics malignancy
- Associated with autoimmune diseases
- Responds well to steroids
- Lymphoplasmacytic infiltrate and fibrosis, Increased IgG and IgG4

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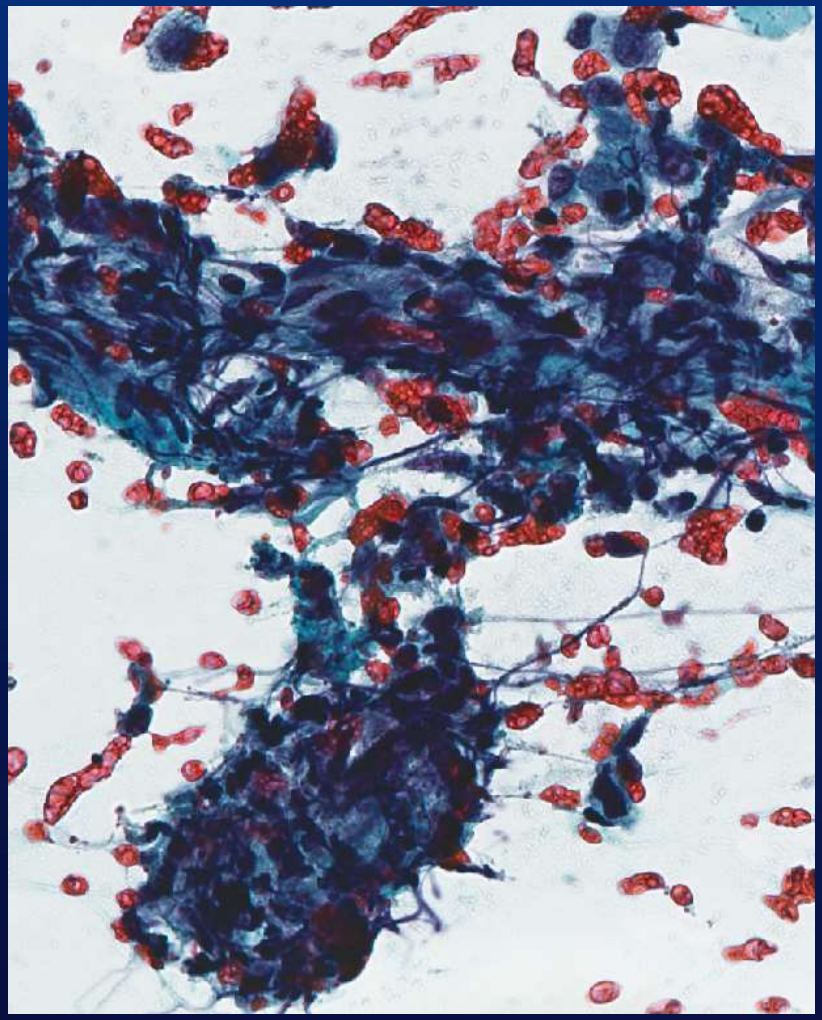
AIP Cytology



- Decreased ductal- type groups, abundant acinar epithelium
- Ductal atypia (nuclear enlargement, prominent nucleoli)
- Cellular stromal fragments rich in lymphocytes or lymphoid tangles
- Variable background inflammation: nil to moderate

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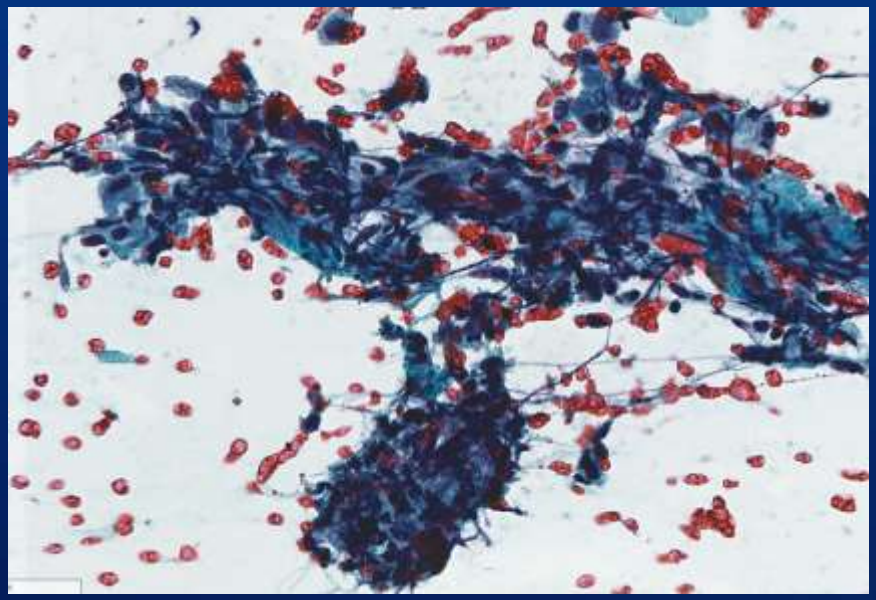
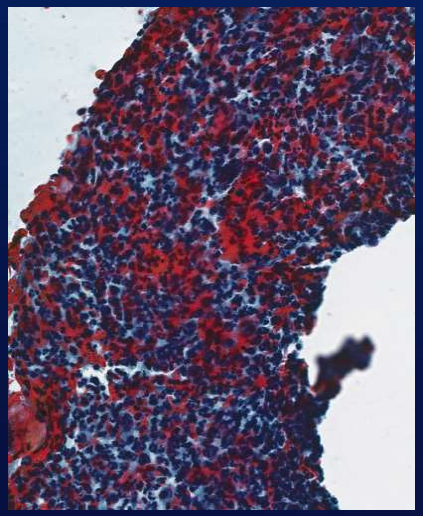
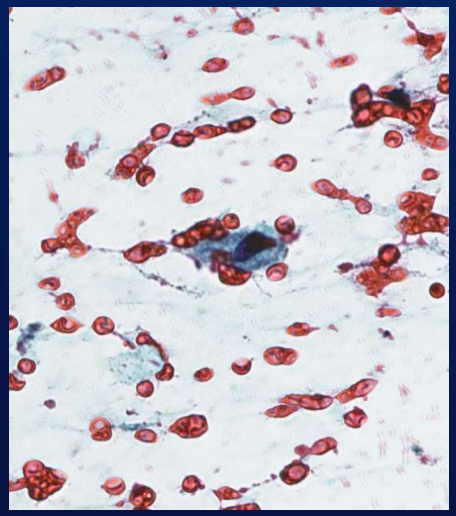
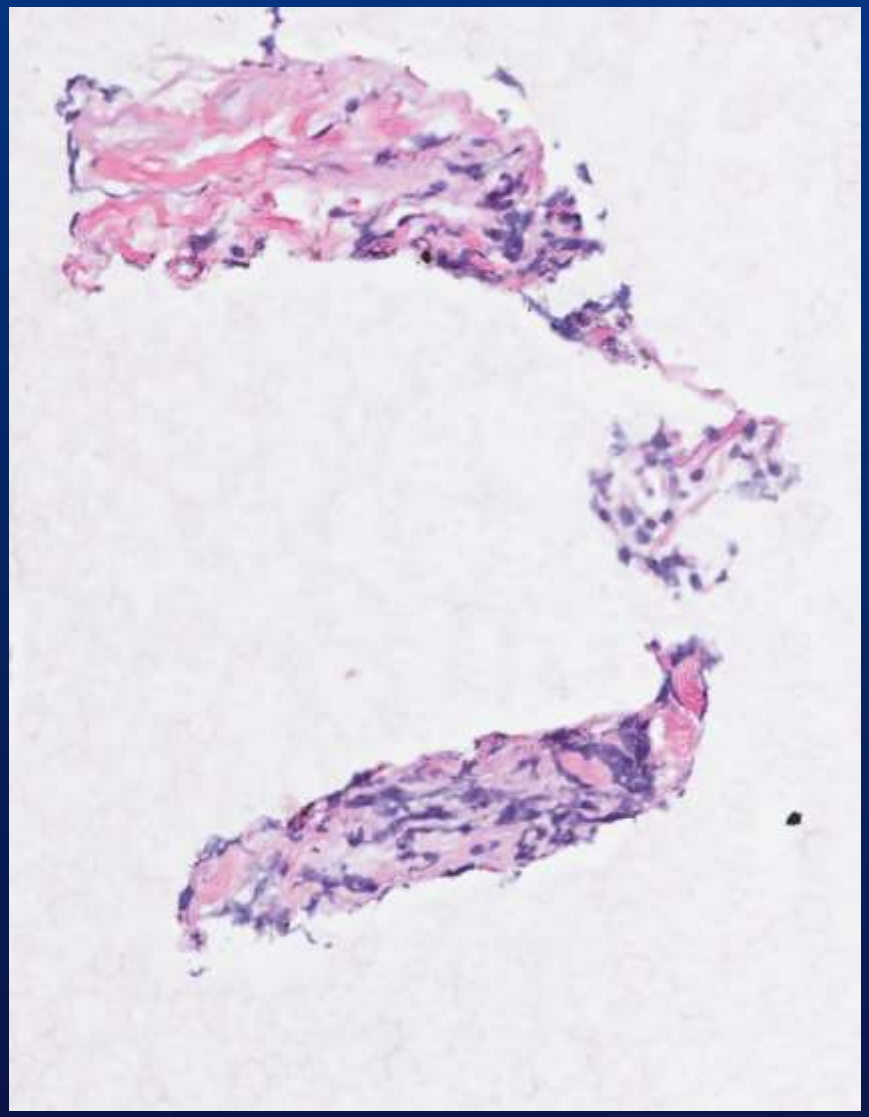
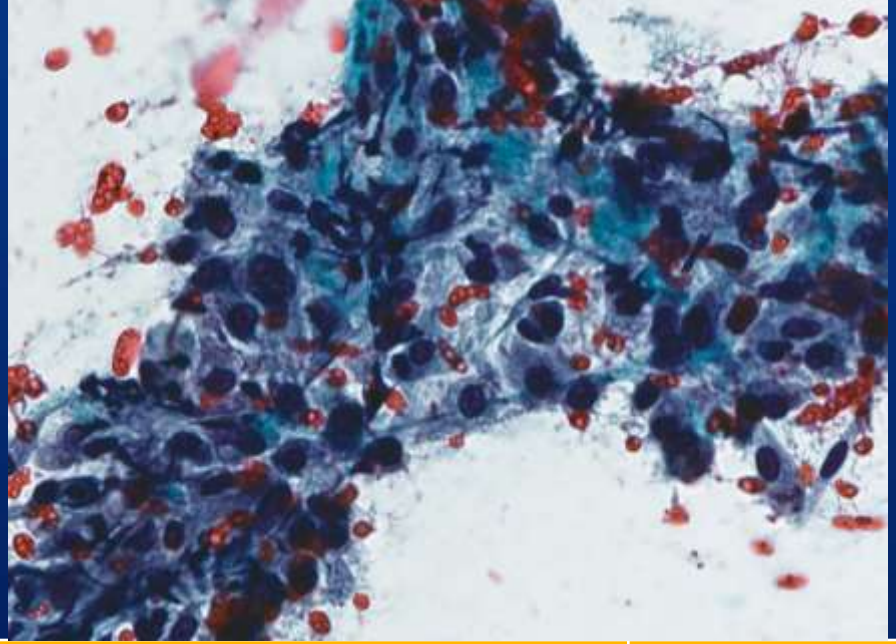
AIP

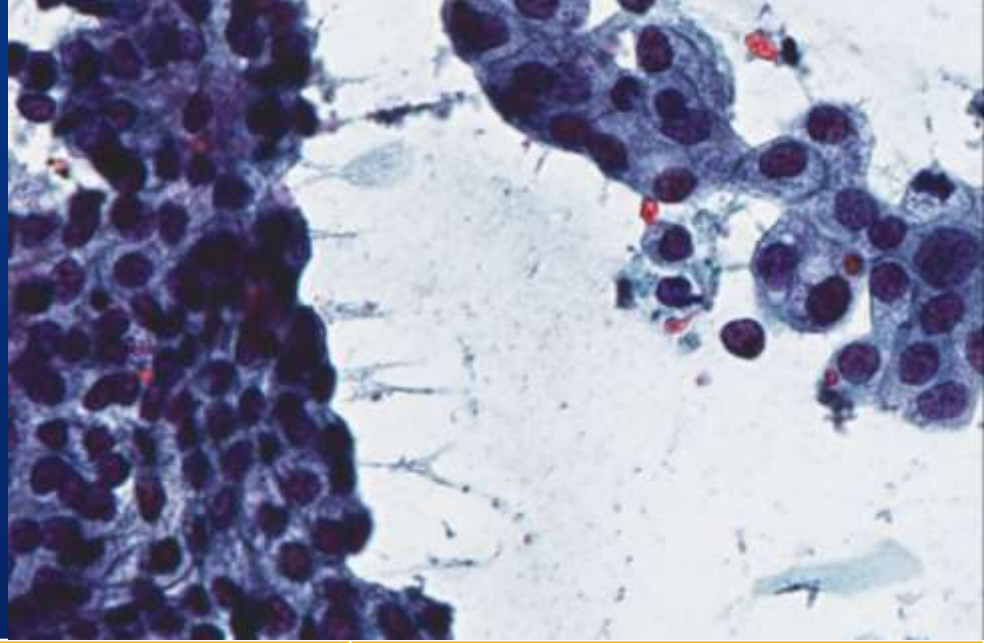








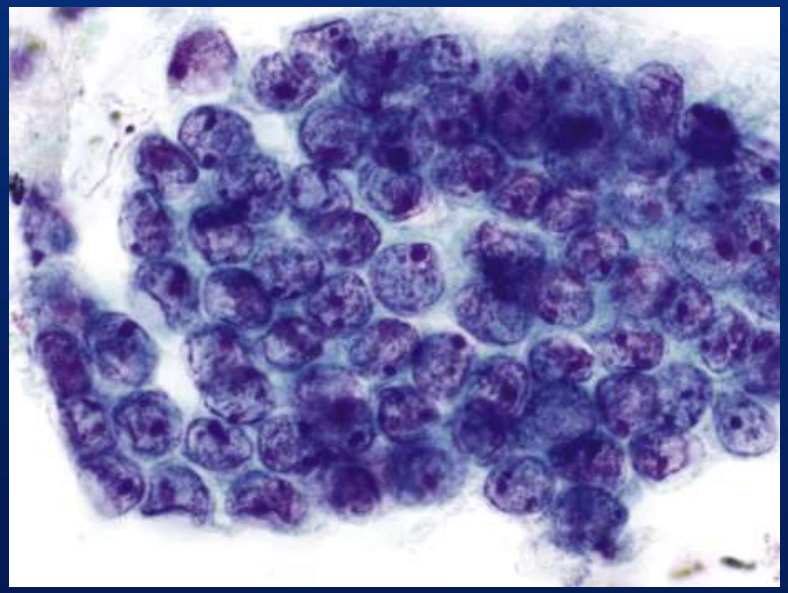


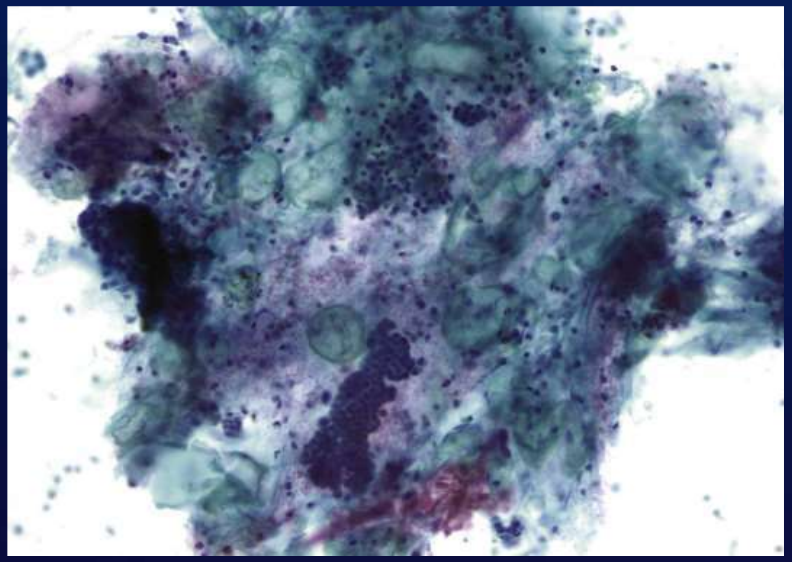


	AIP	Adenocarcinoma
Nuclear atypia	Mild to moderate	Marked
Cell Crowding, 3D	Present	Present
Single cells	Likely GI contamination	Single tumor cells
IgG4/ IgG positive cells	May be elevated	Not elevated
Serum IgG4	May be elevated	Not elevated
Serum ANA	May be elevated	Not elevated

Goyal et al. Pancreas and Biliary Tract Cytohistology. Springer 2019.

Chronic Pancreatitis (CP)





- Low cellularity
- Flat cohesive sheets, slight crowding
- Low N/C ratio
- Slightly enlarged nuclei w little variation in size (<4x)
- Round smooth nuclear membranes
- Prominent nucleoli
- Background: fat necrosis and calcific, inflammatory stroma or saponified debris

Images by Dr. Miguel- Perez

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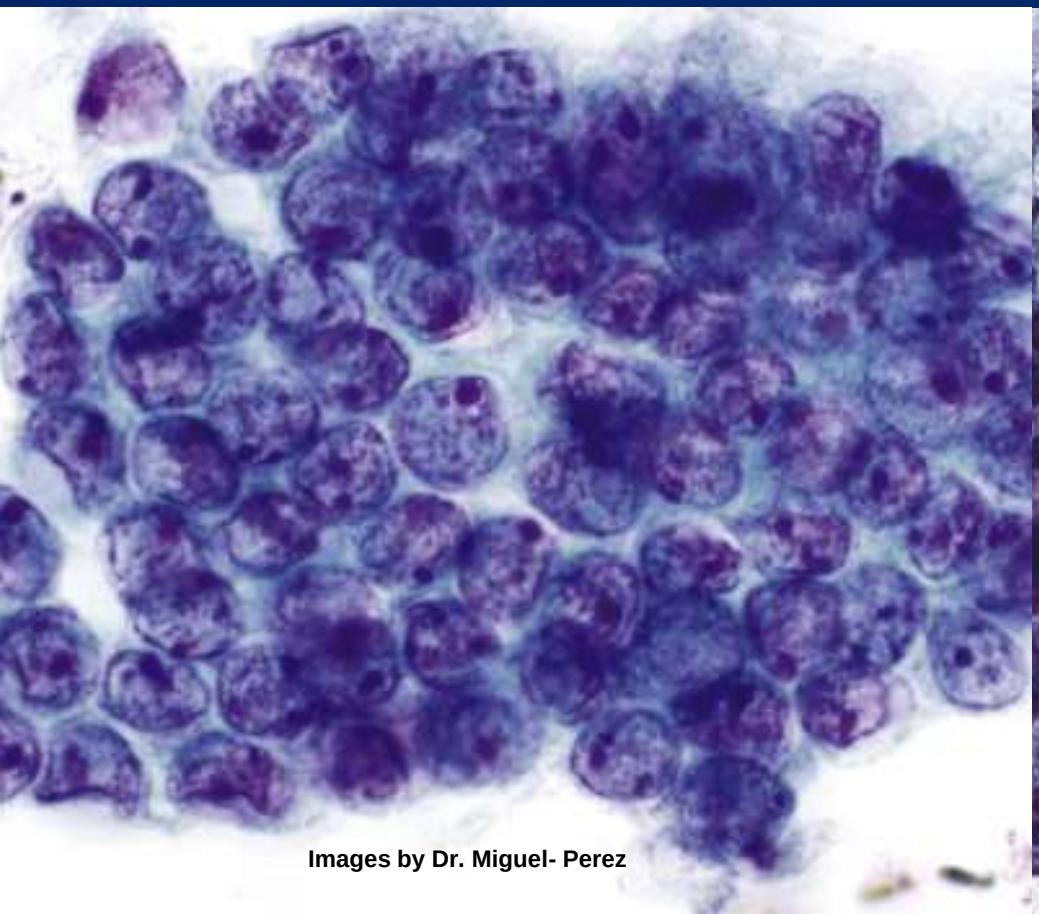
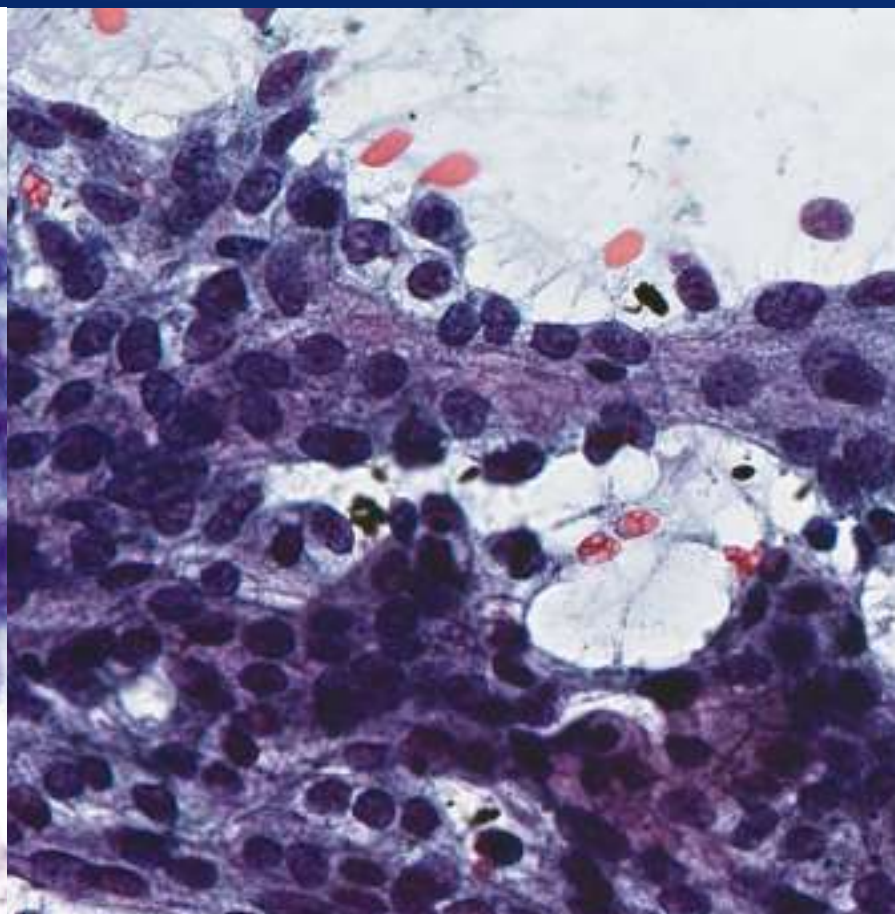
CP vs Adenocarcinoma

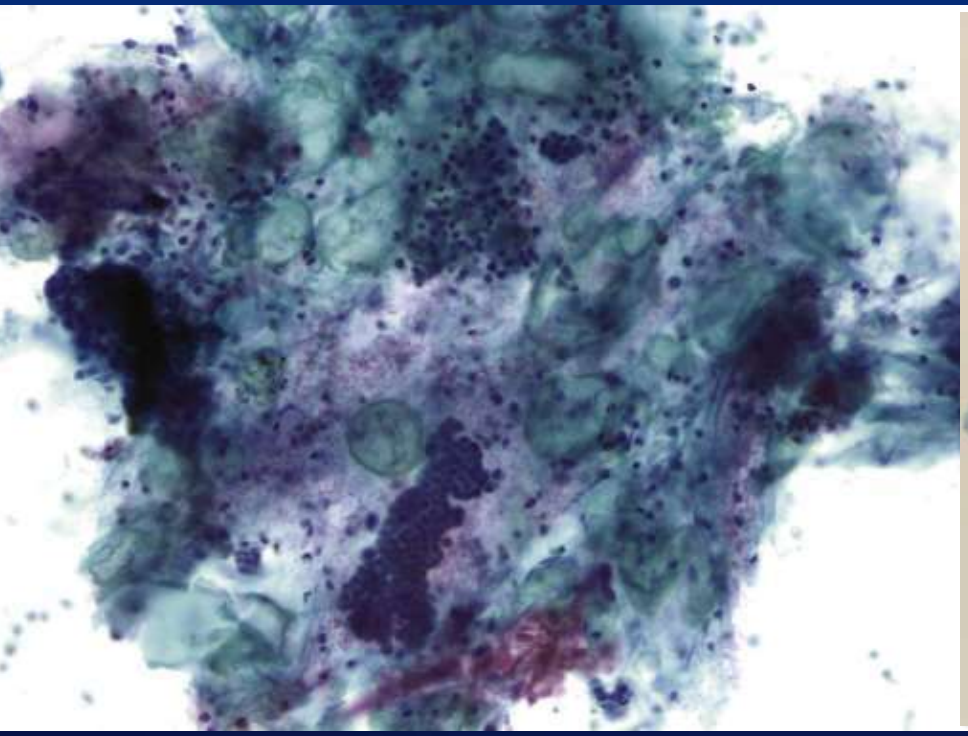
- **Round smooth** nuclear membranes
- **Irregular** nuclear membranes



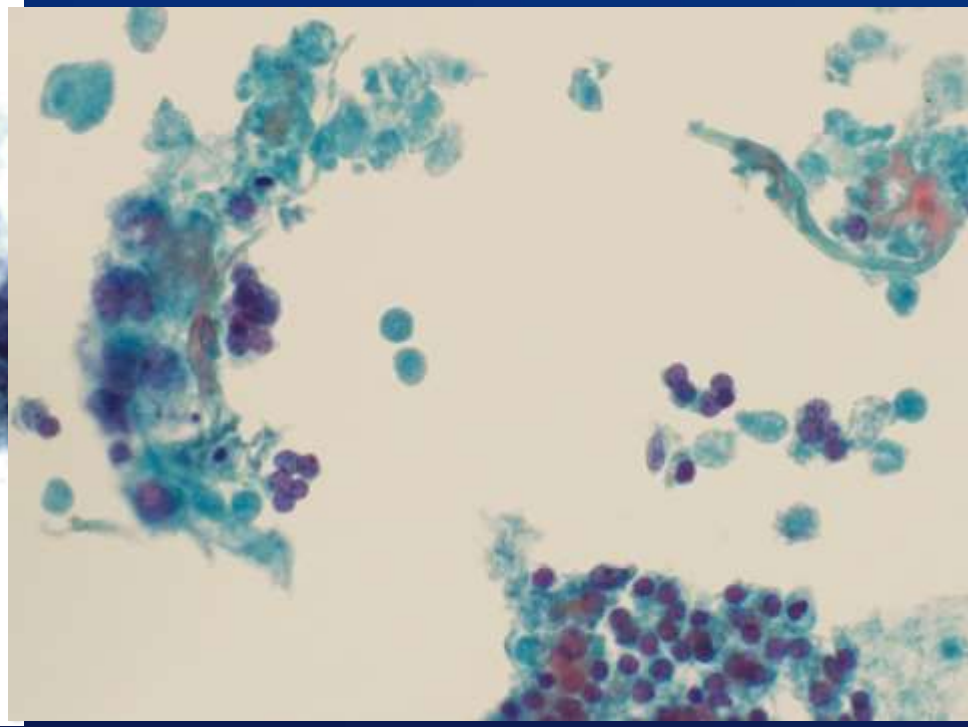
Images by Dr. Miguel- Perez



CP vs Adenocarcinoma



- Background: fat necrosis, “grundgy material”, calcification, inflammatory stroma, saponified debris



- Coagulative necrosis

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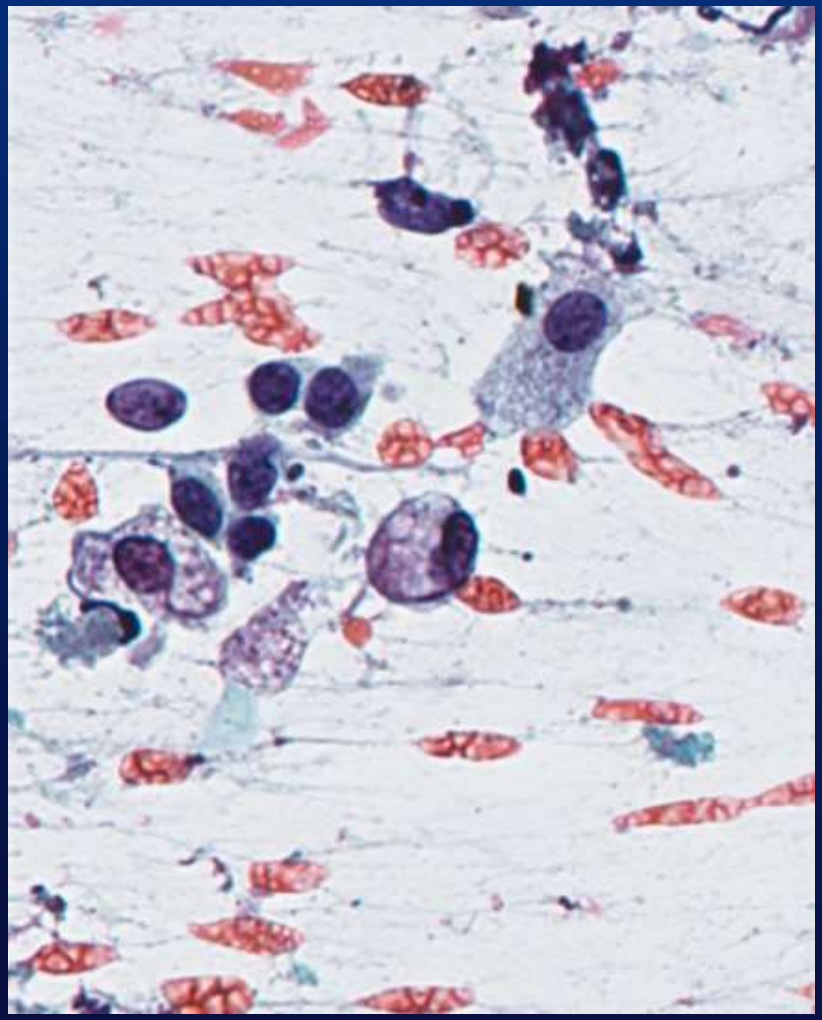
Left side image by Dr. Miguel Perez

	CP	Adenocarcinoma
Nuclear enlargement	Present	Present
Prominent nucleoli	Present	Present
Mitosis	Present	Present
Anisonucleosis	<4x	>4x
Chromatin pattern	Even	Clumpy, paranucleolar clearing
Amylase, lipase	Elevated	Normal
SMAD4 IHC	Retained	Lost in up to 50% of cases
Nuclear membrane contour	**Slightly irregular**	**Markedly irregular**

Goyal et al. Pancreas and Biliary Tract Cytohistology. Springer 2019.

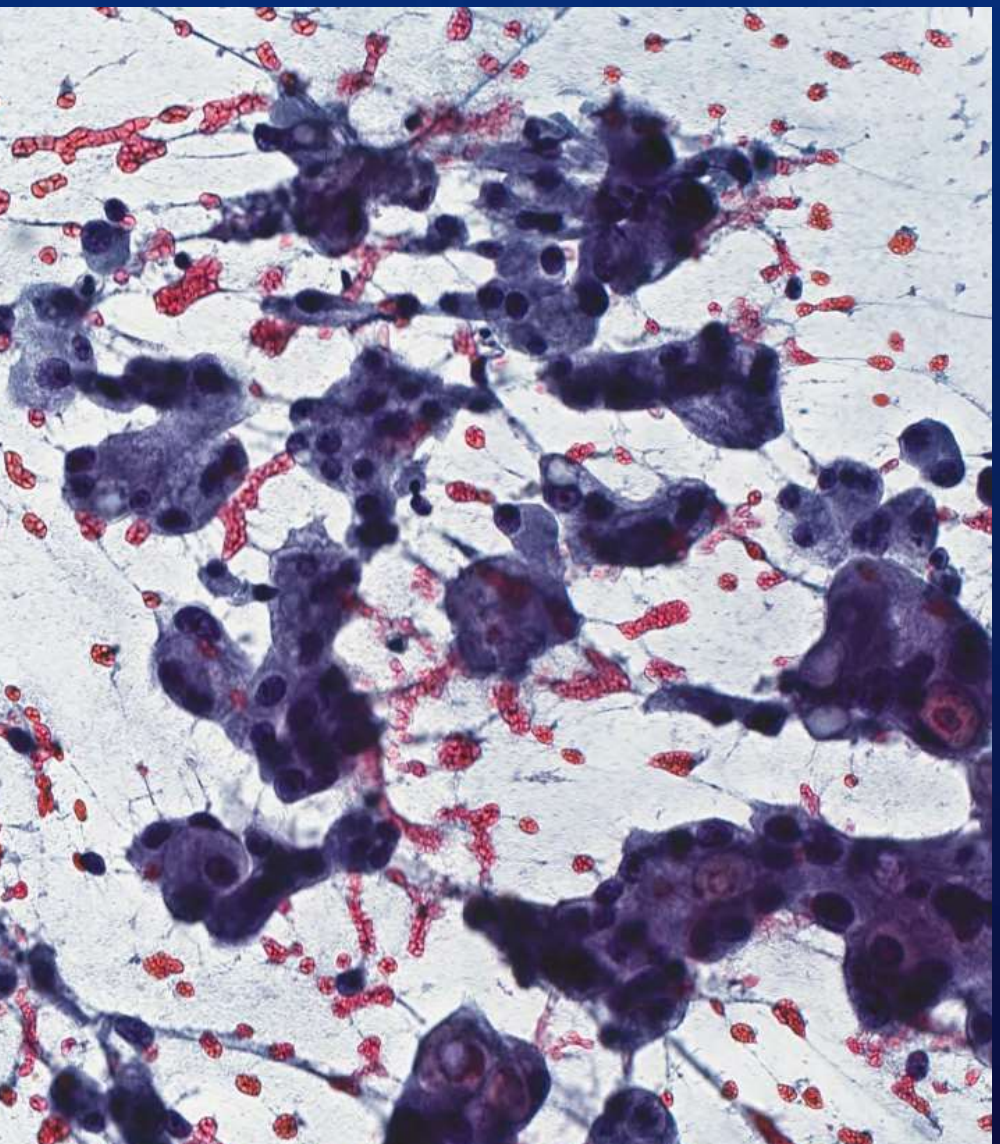
Adenocarcinoma



- **AVOID a definitive diagnosis**:
  - Scant atypical cells
  - Acute or chronic inflammation in the background
  - Fibrotic fragments with lymphoid tangles

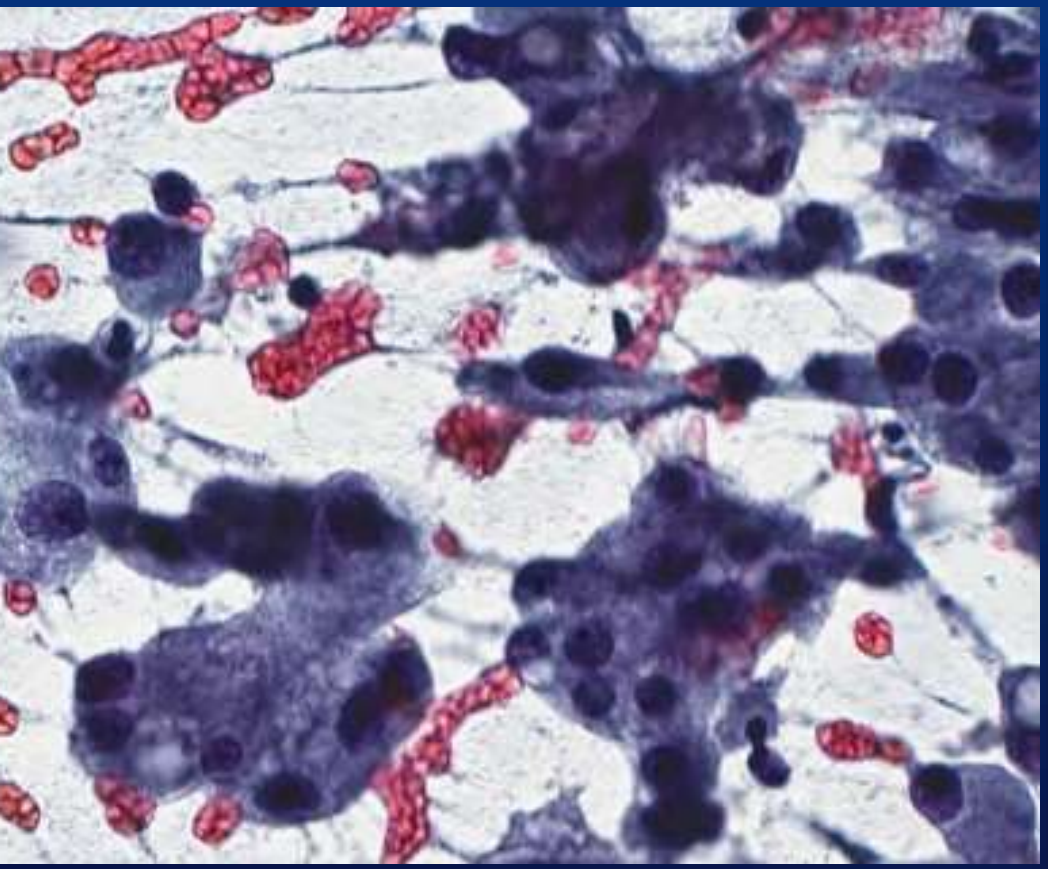
MAYO CLINIC

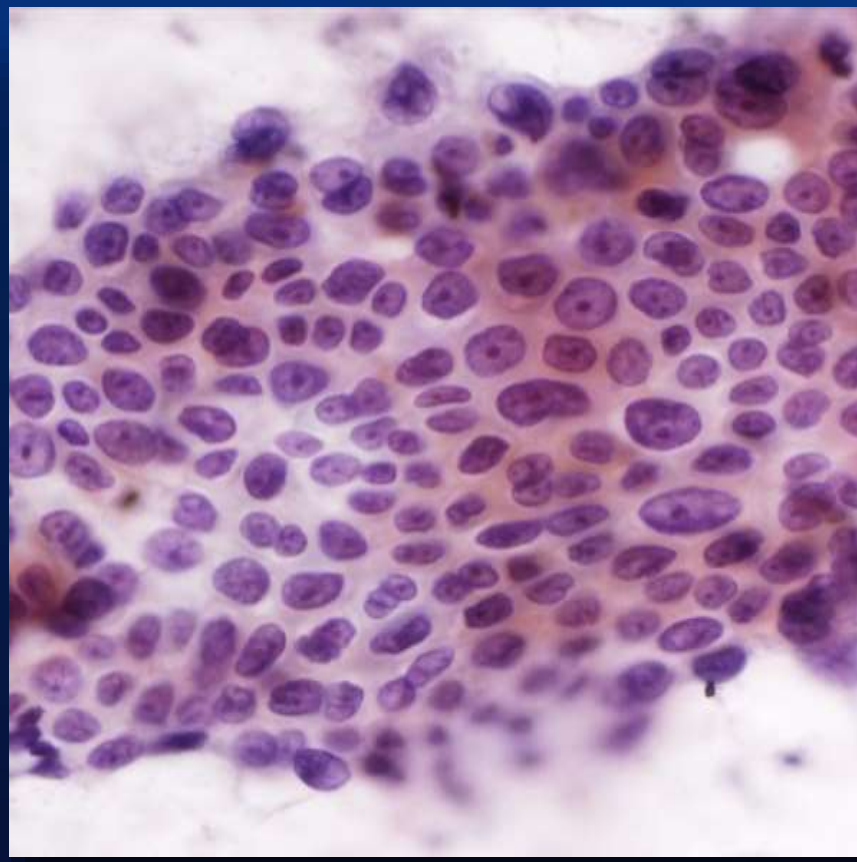
PanNET challenges



- Nuclei may be pleomorphic due to endocrine atypia
- Pseudorosettes may be confused with glands
- Lipid rich variant: foamy/ vacuolated cytoplasm
- Oncocytic variant: abundant granular, oncocytic cytoplasm, prominent nucleoli

PanNET vs Adenocarcinoma





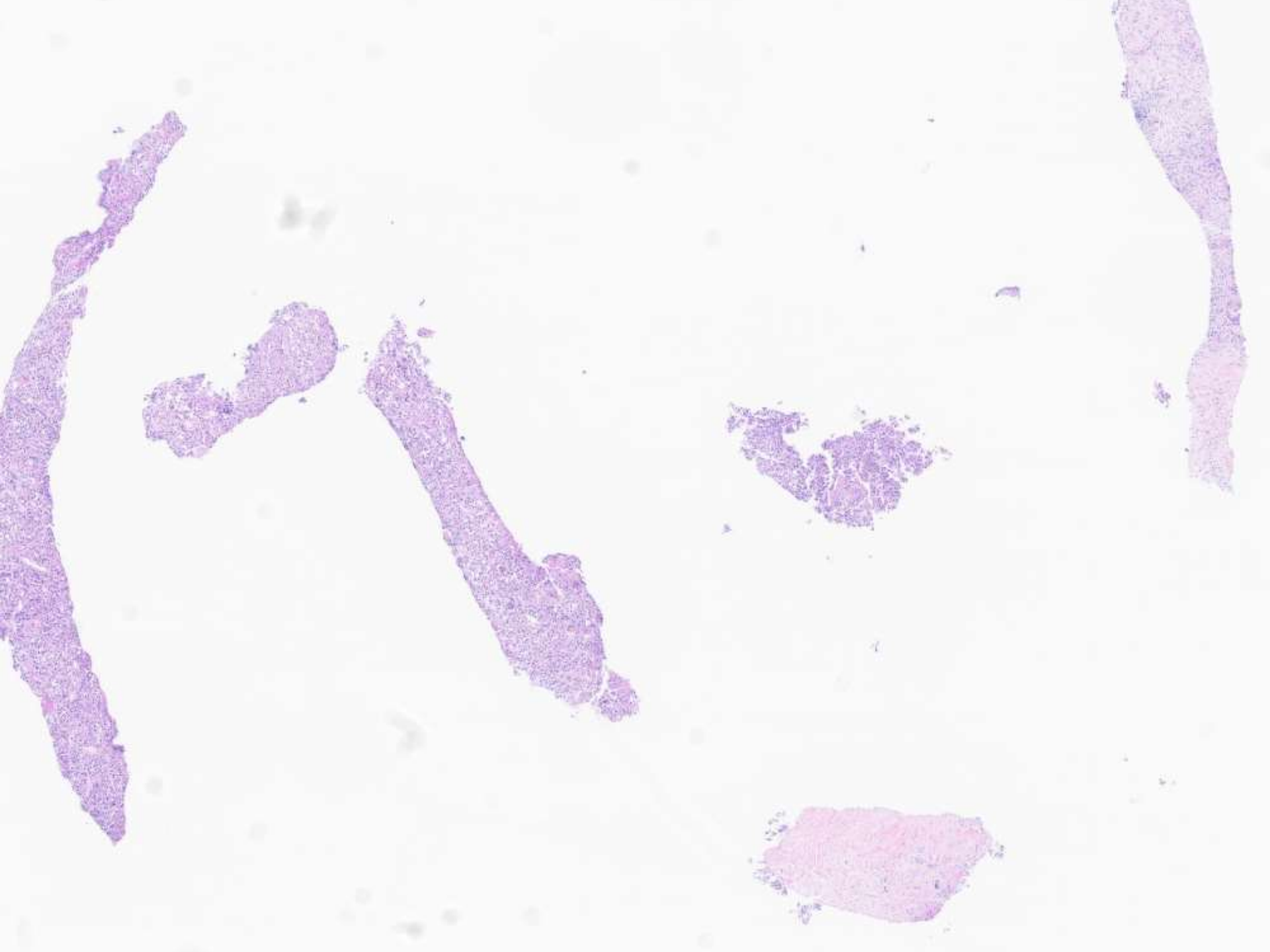
- Nuclei: “salt and pepper” chromatin, elongated, plasmacytoid, spindled
- Even in the presence of atypia, retain uniformity of the nuclei

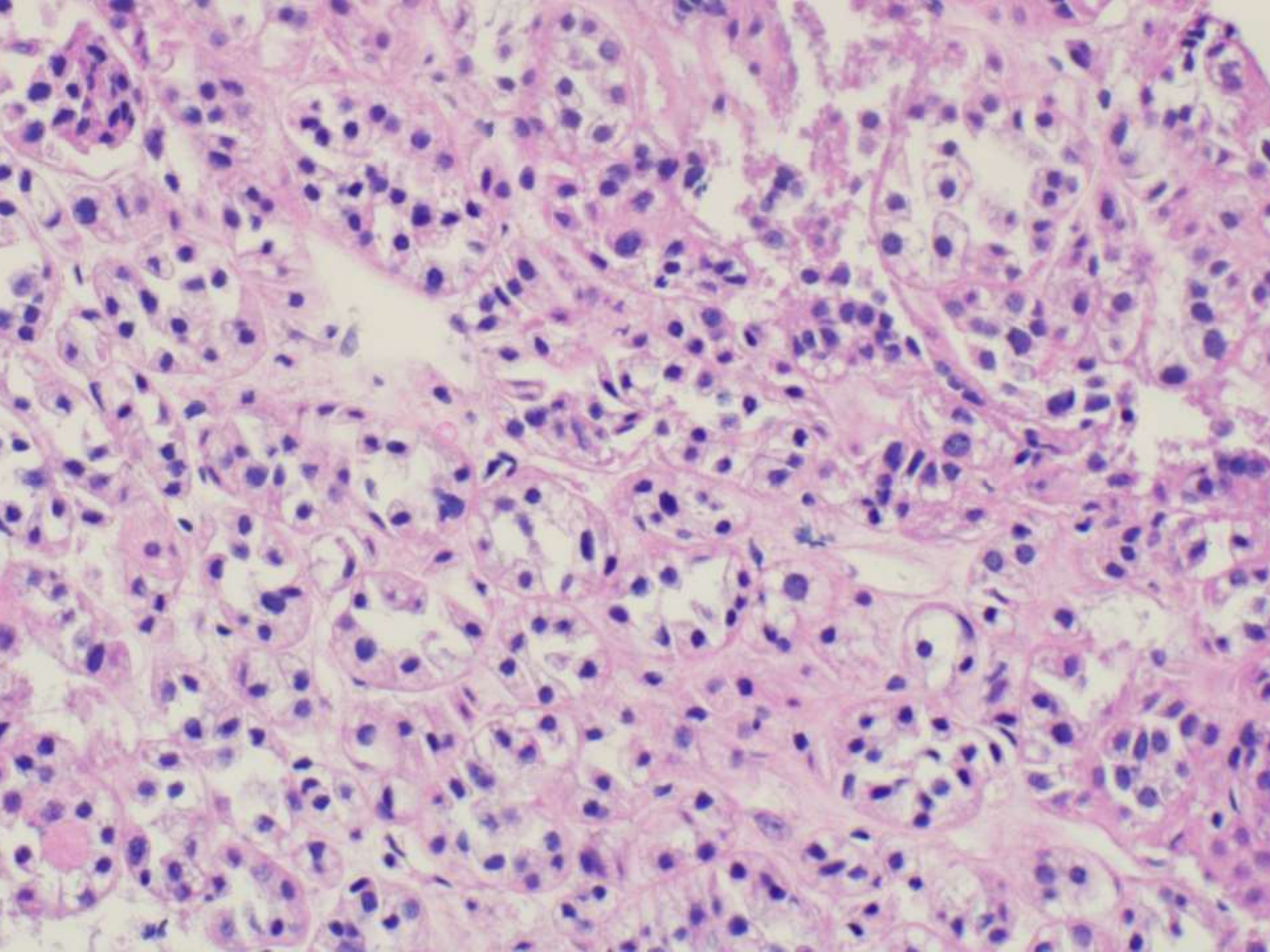
- More cohesive fragments, glandular differentiation
- More pleomophism and nuclear atypia, mitosis, necrosis

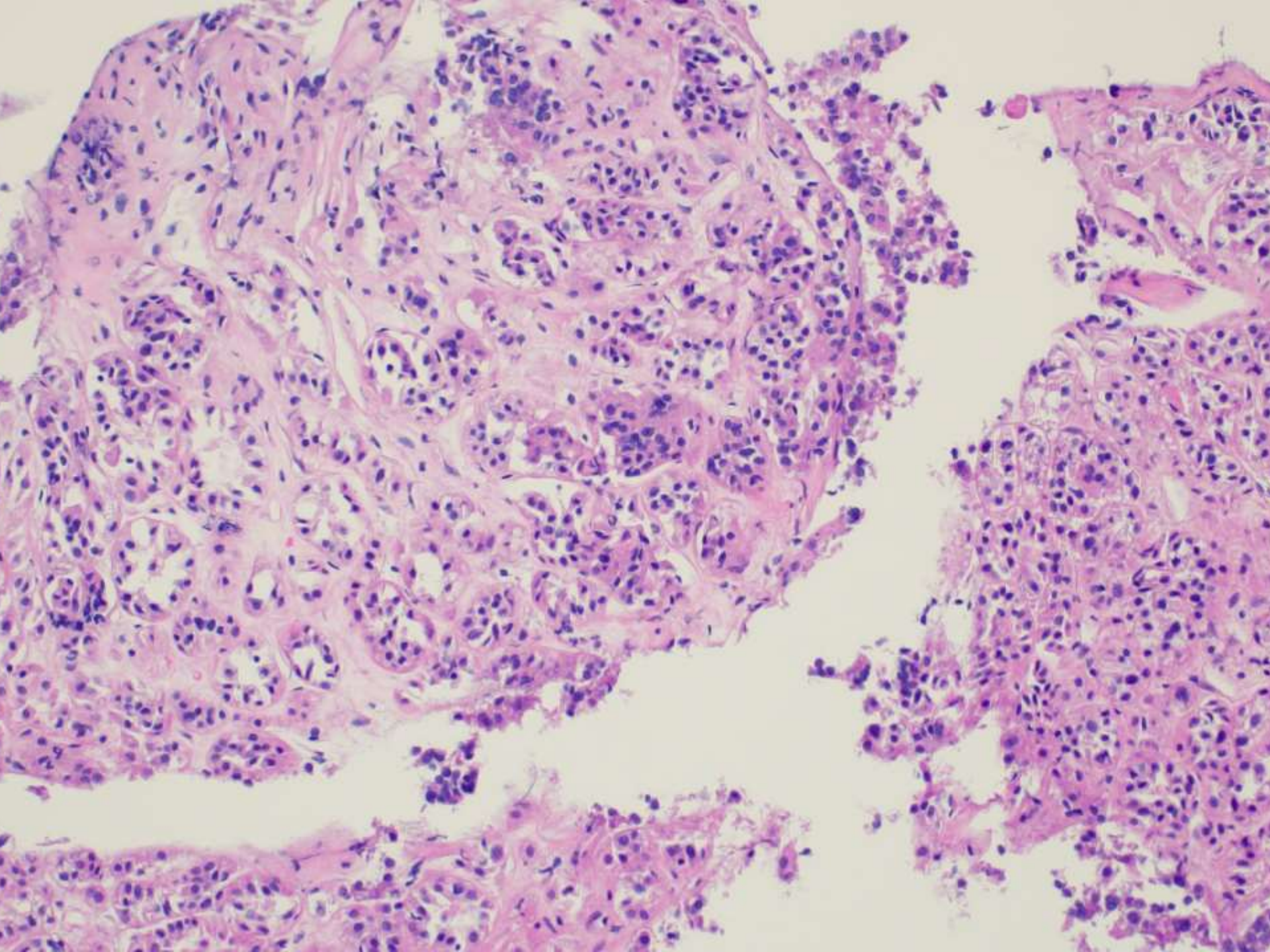
Right side image Dr. Matthew Zarka

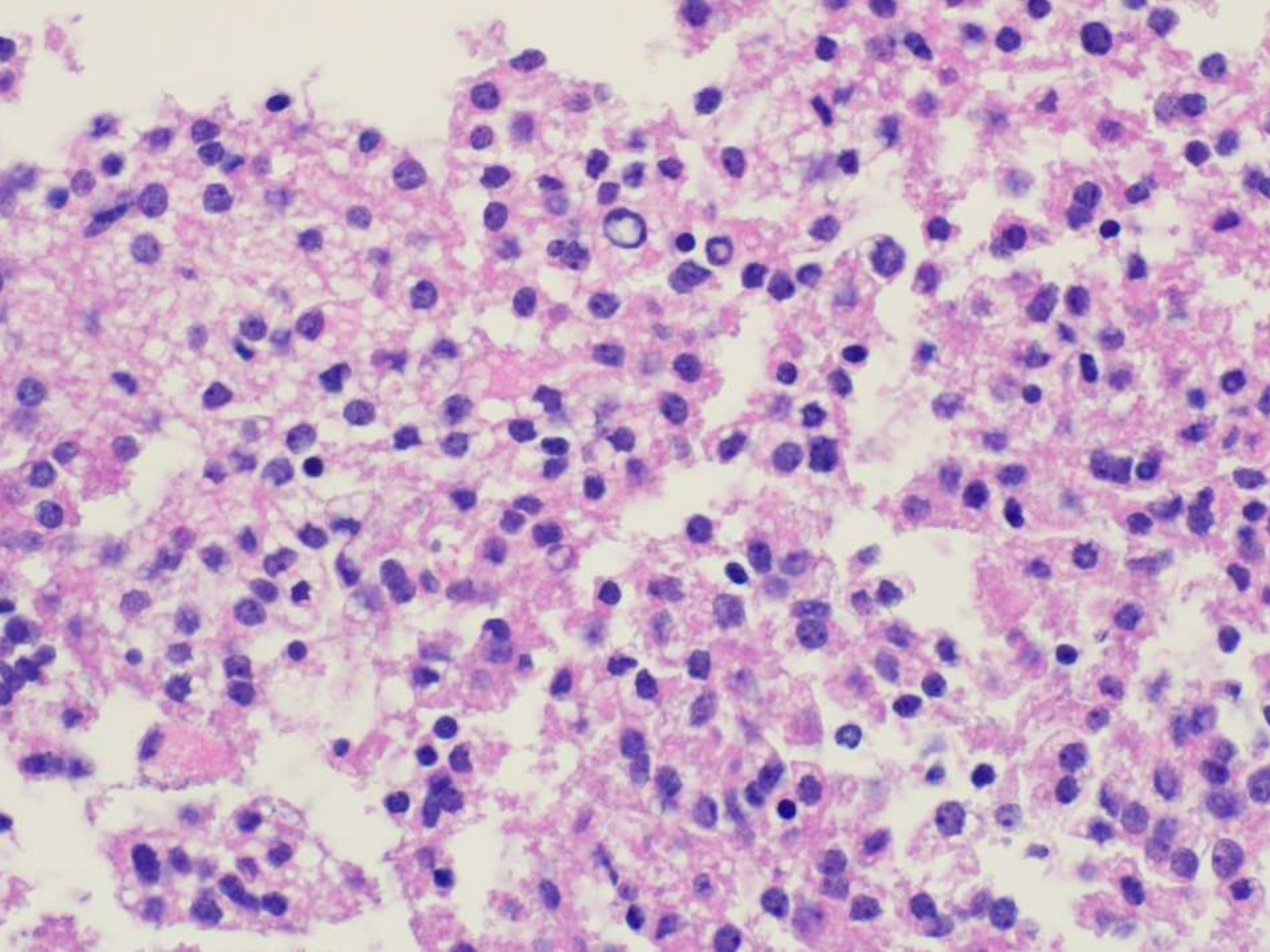
Extra/ Final Case: Outside consult for Second Opinion- Surgeon's Request

81 year old male with a large solid mass
Unresectable pancreatic mass at presentation
Patient very ill and another EUS- FNA not feasible









Outside Diagnosis

- Suspicious for neoplasm
- Differential diagnosis
  - Low grade neuroendocrine tumor
  - Serous cystadenoma

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IHC

- Negative:
  - PASD
  - Mucin
  - CK7/ CK20
  - PAX8
  - TTF1
  - Chromogranin
  - Synaptophysin

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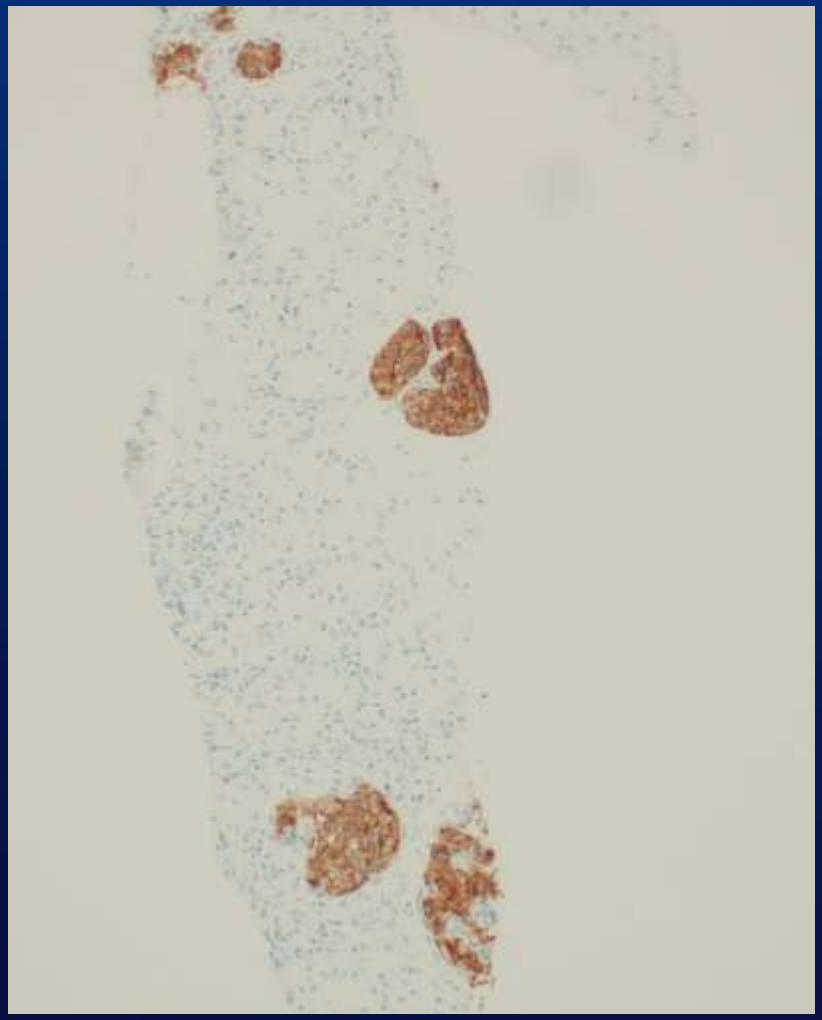
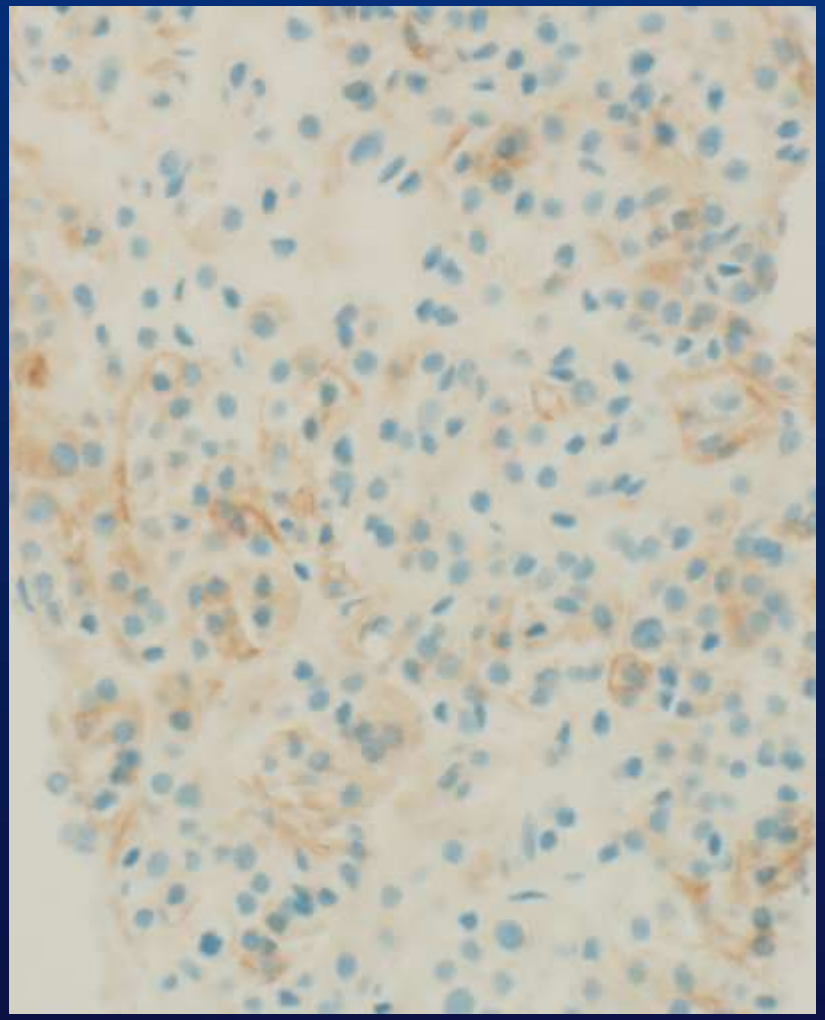
Synaptophysin





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Serous Cystadenoma

- Markedly hypocellular, clear fluid
- Small cuboidal cells
- Imaging: “soap bubble”, central scar, “star burst’ pattern of calcifications

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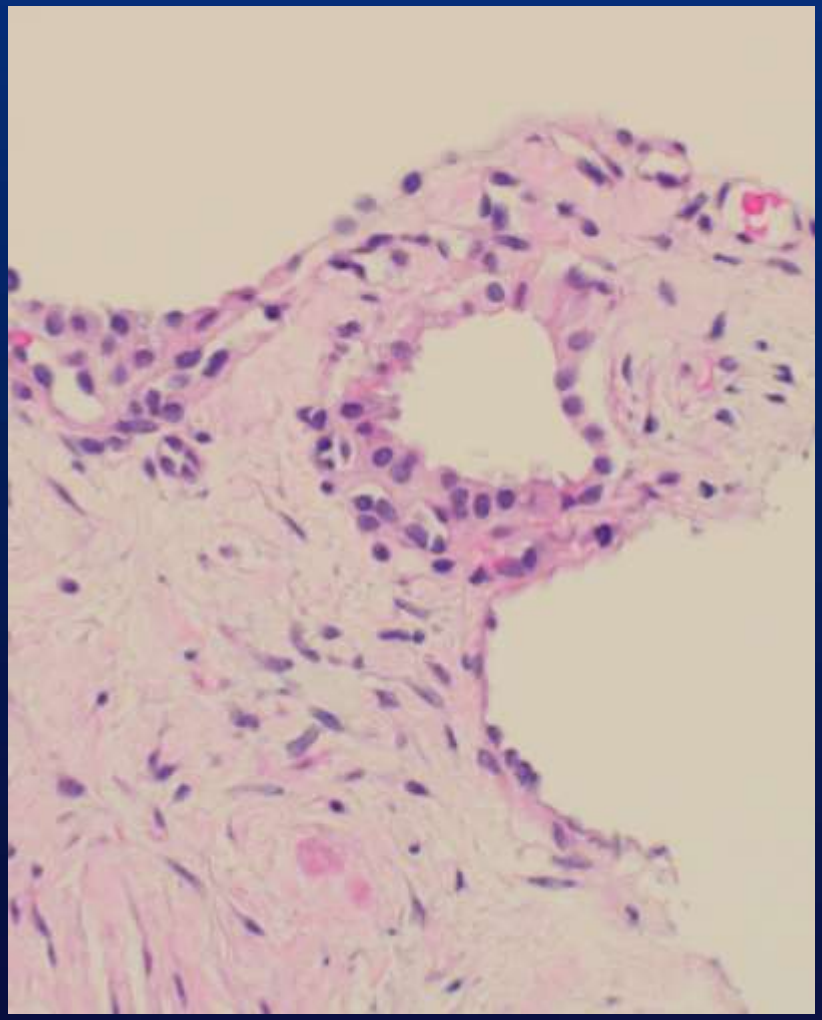
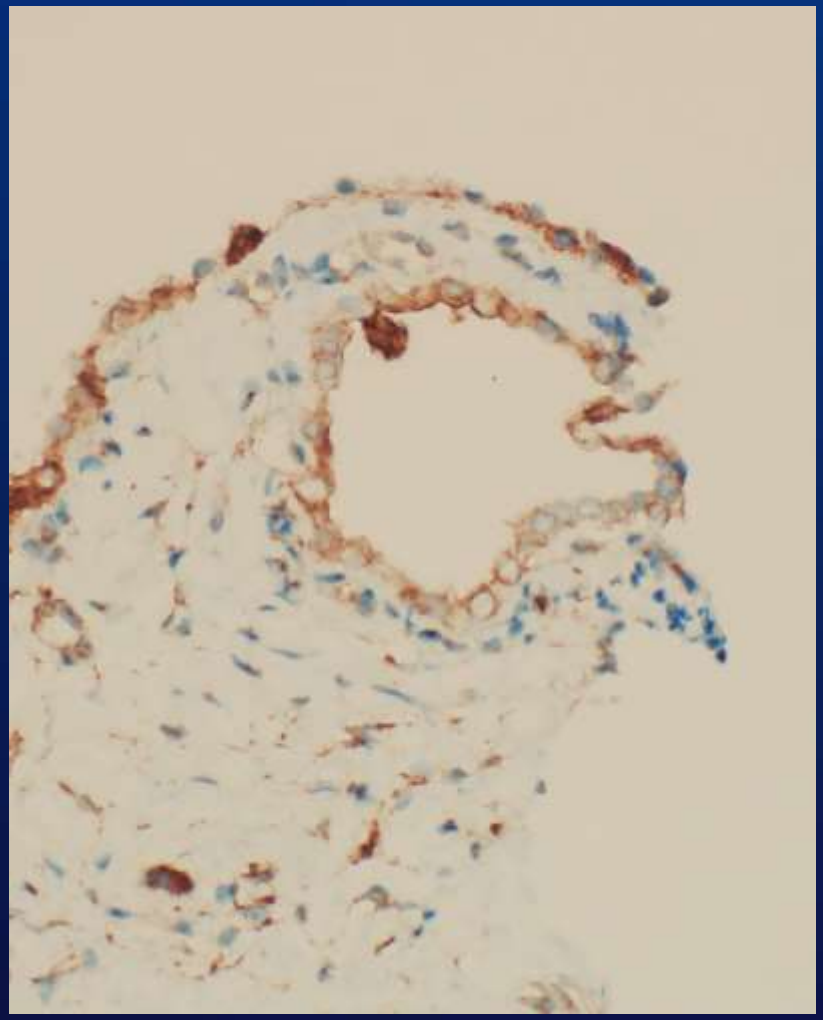
Serous Cystadenoma: Inhibin+





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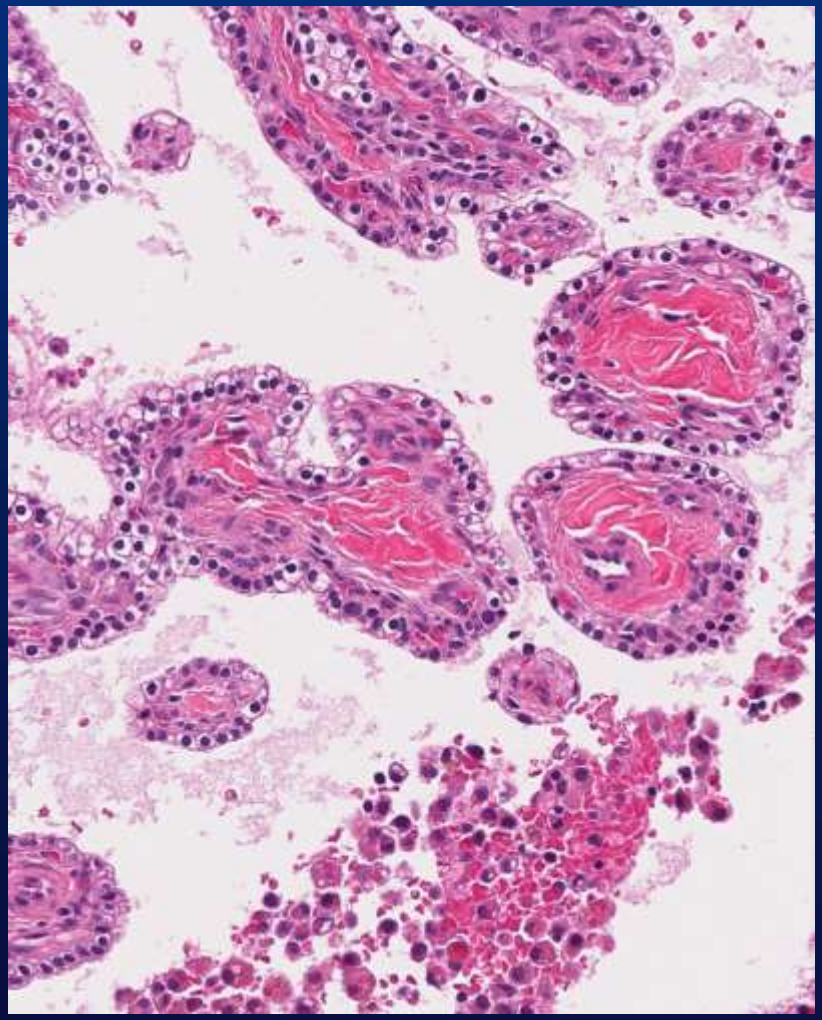
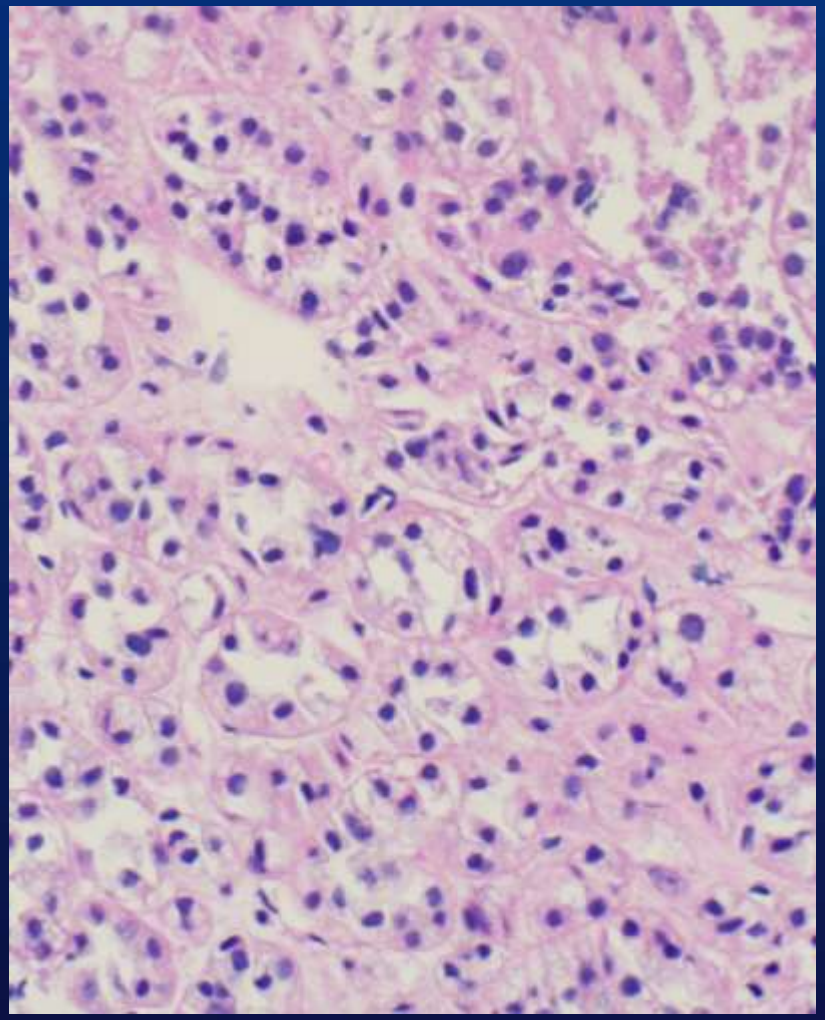
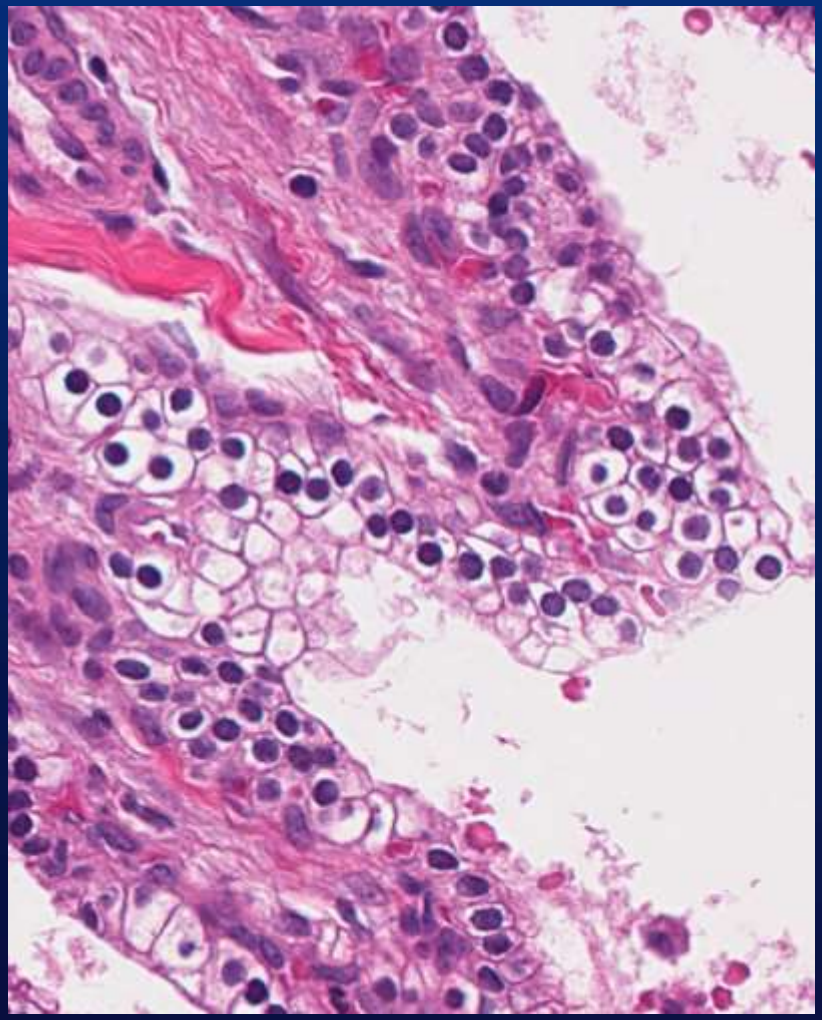
Serous Cystadenoma vs Outside Case

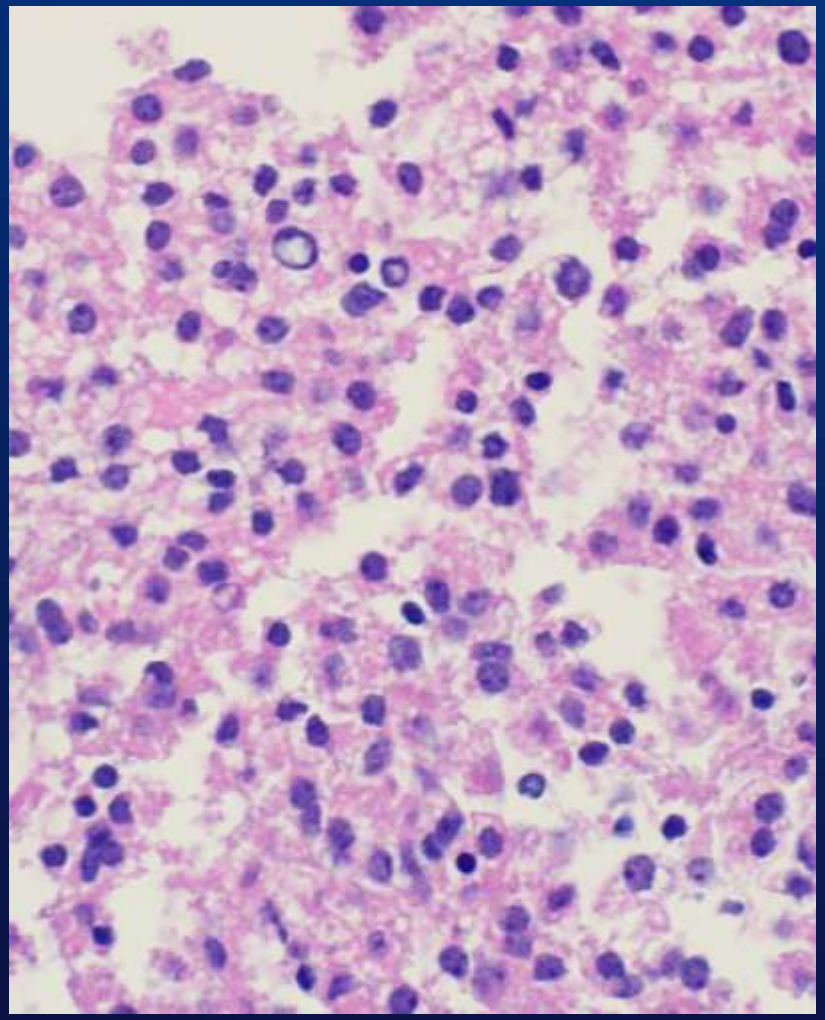




MAYO CLINIC

Serous Cystadenoma vs Outside Case





MAYO CLINIC

MAYO CLINIC

Next steps:

???Request Block and do more stains

IHC Solid Pancreatic Epithelial Neoplasms

Diagnosis	Immunostains
Pancreatic adenocarcinoma	SMAD-4 loss (50%) Mesothelin expression
Neuroendocrine tumor	CK+ve, CD56, synaptophysin, chromogranin, PAX-8*
Acinar cell carcinoma	CK+ve, Trypsin, chymotrypsin
Solid pseudopapillary neoplasm	CK negative, b-catenin (nuclear localization), CD56, CD10, Trypsin, chymotrypsin,

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Next steps:
???Request the Block and do more stains

- OR…
- Look at the case again…

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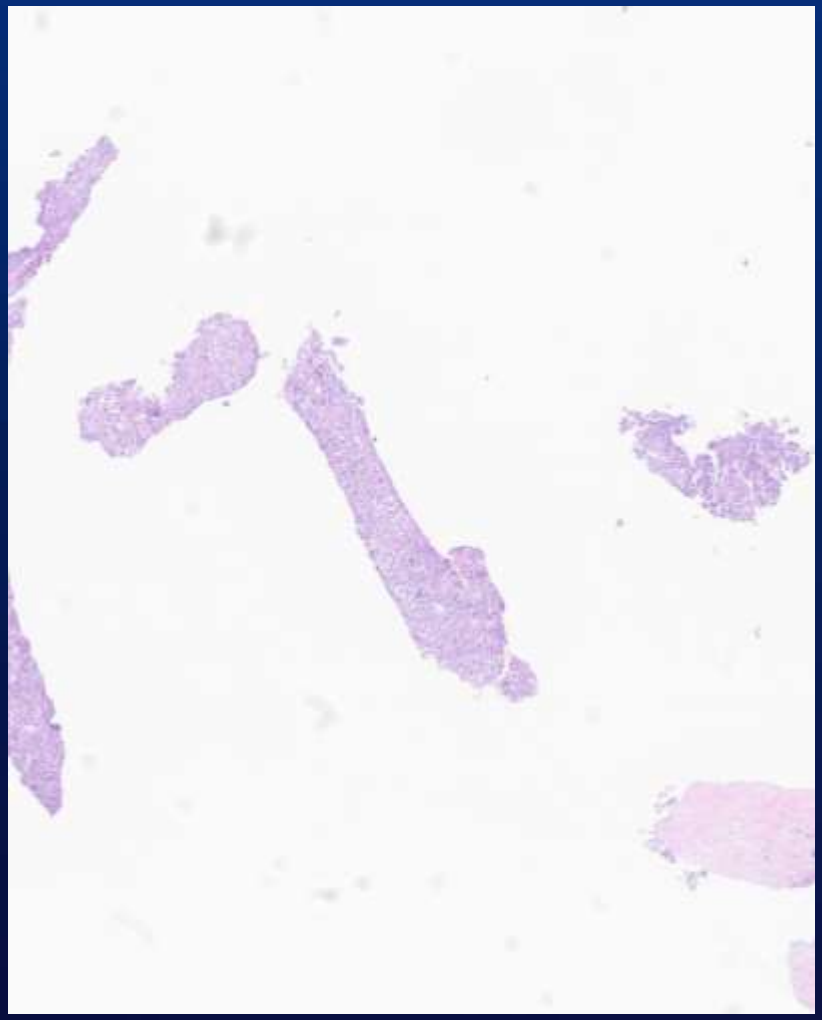
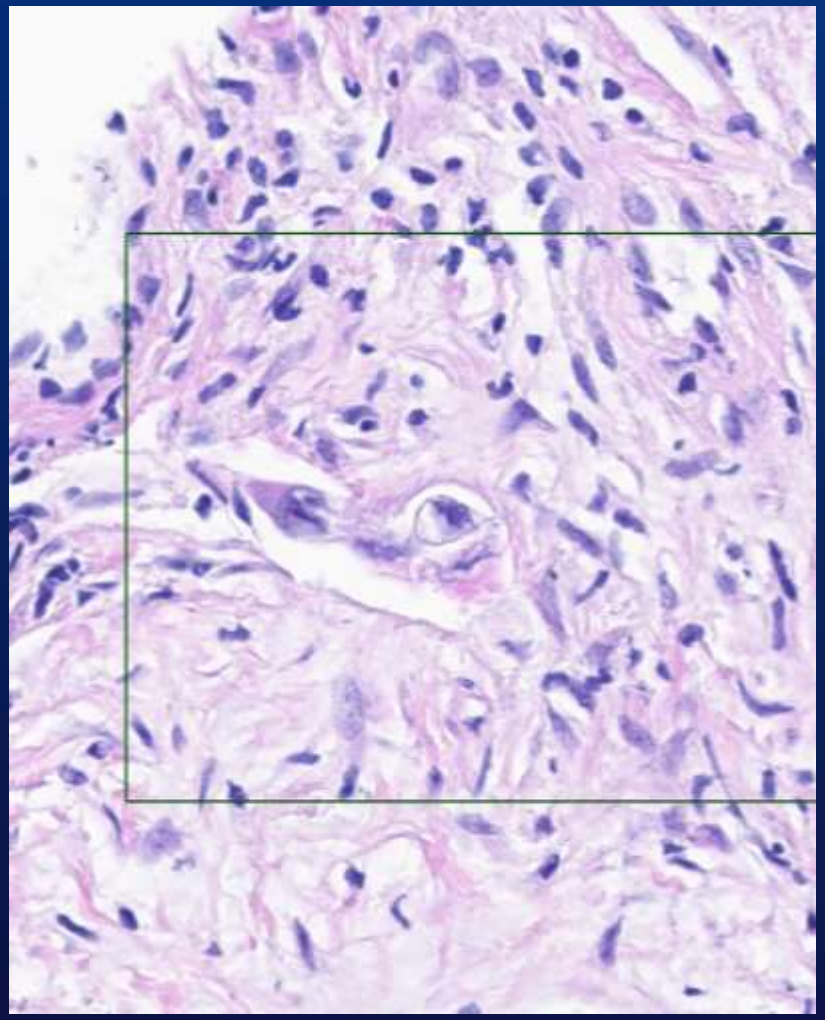
Back to Outside Case: Fibrotic areas





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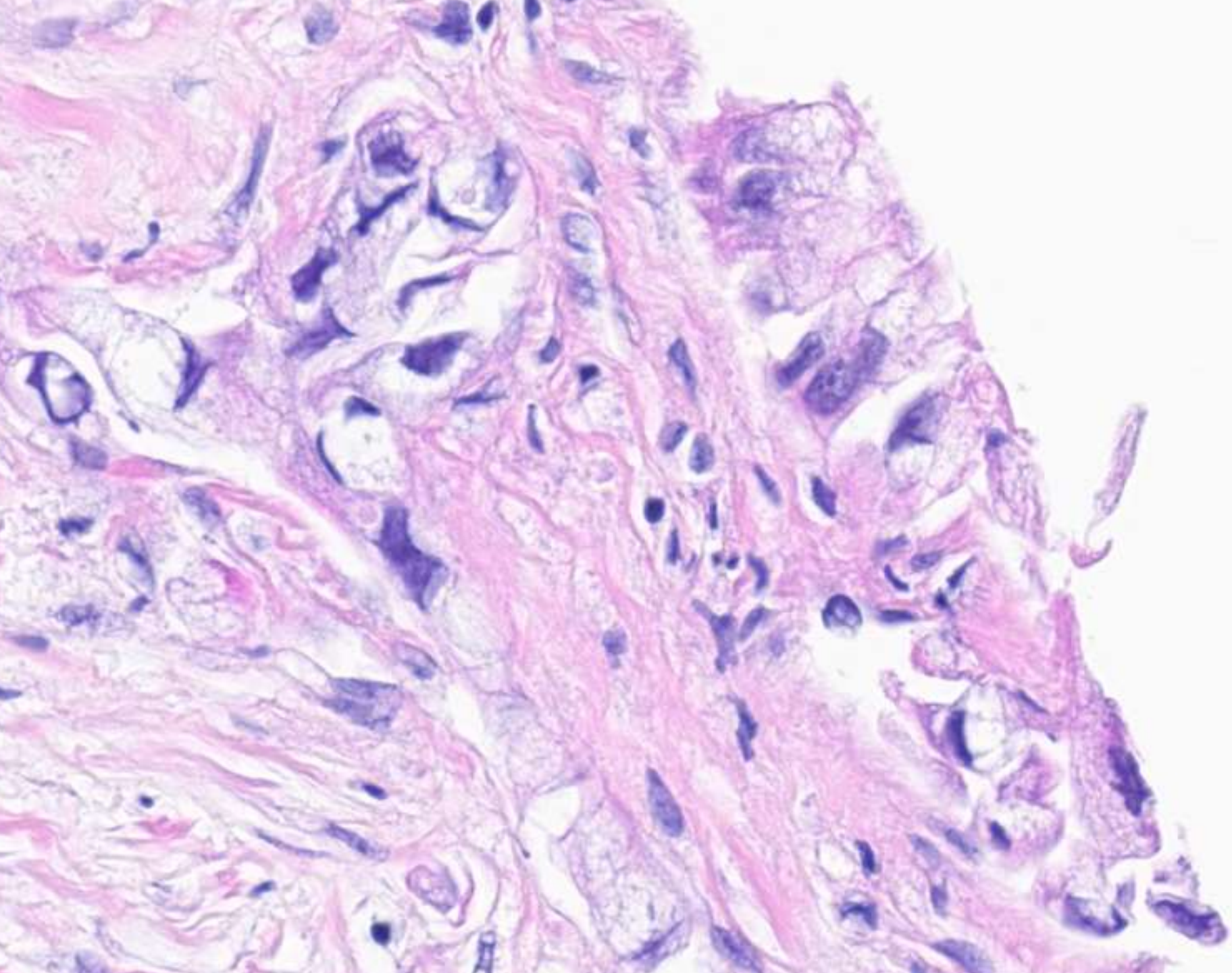
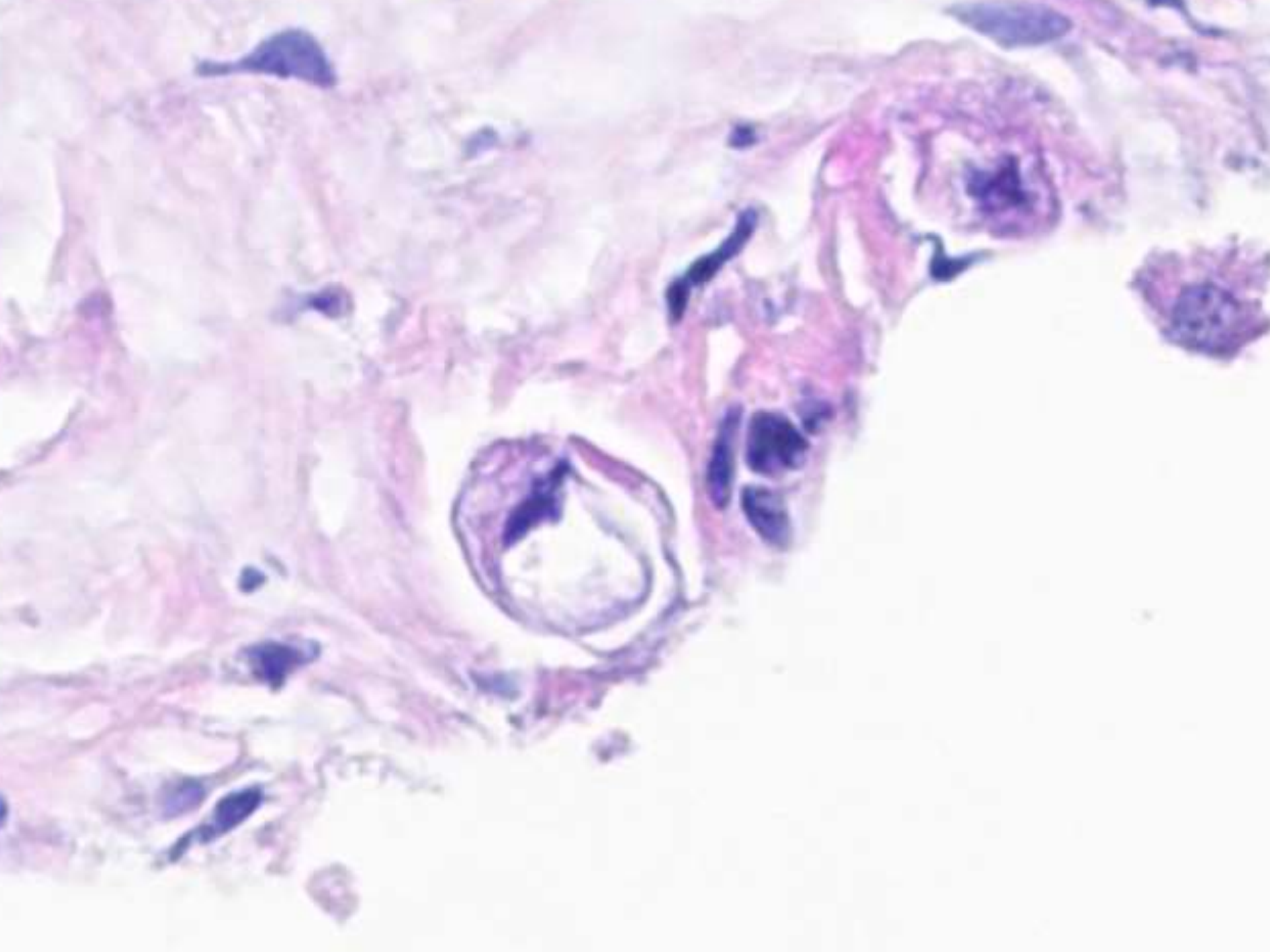
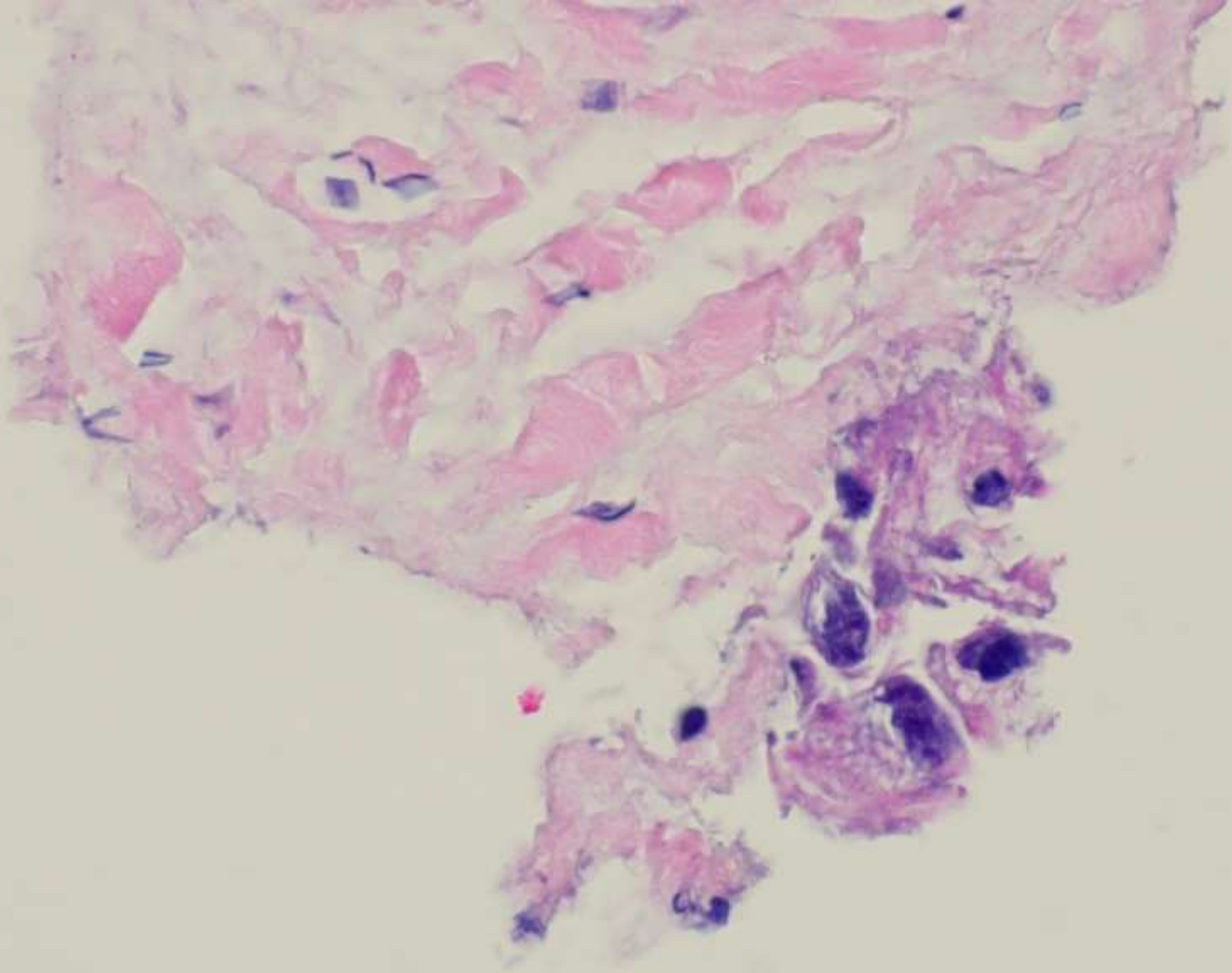
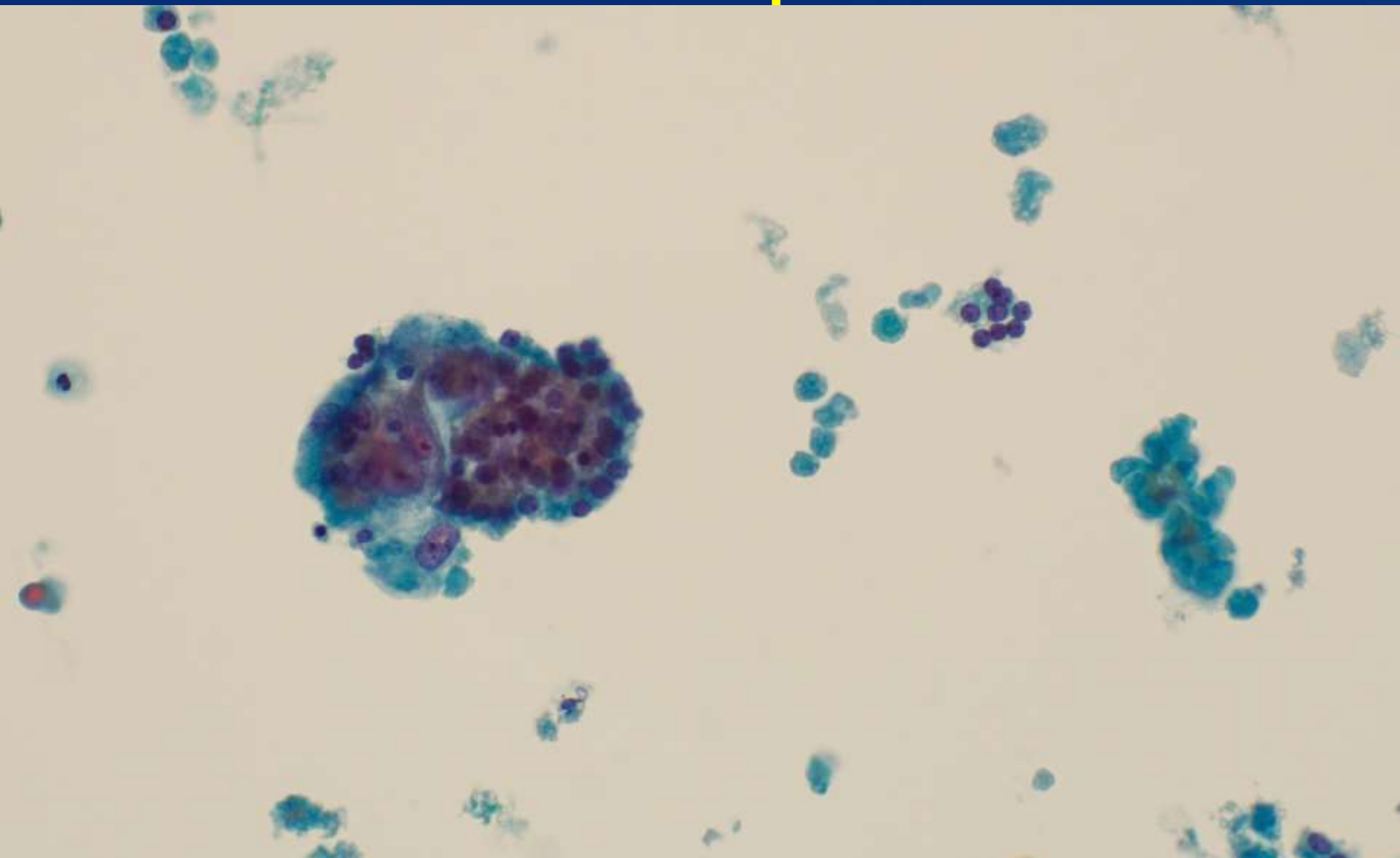
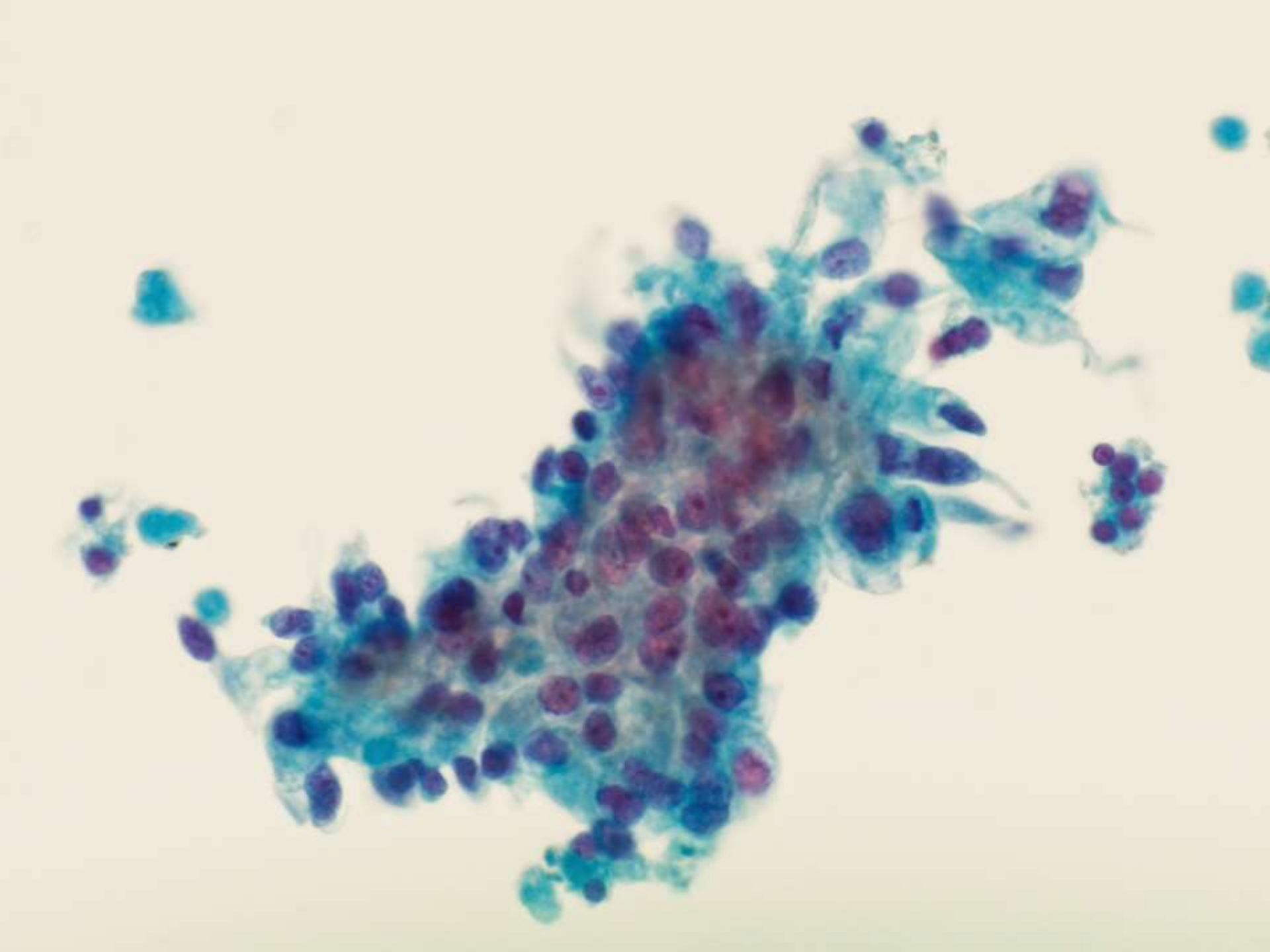


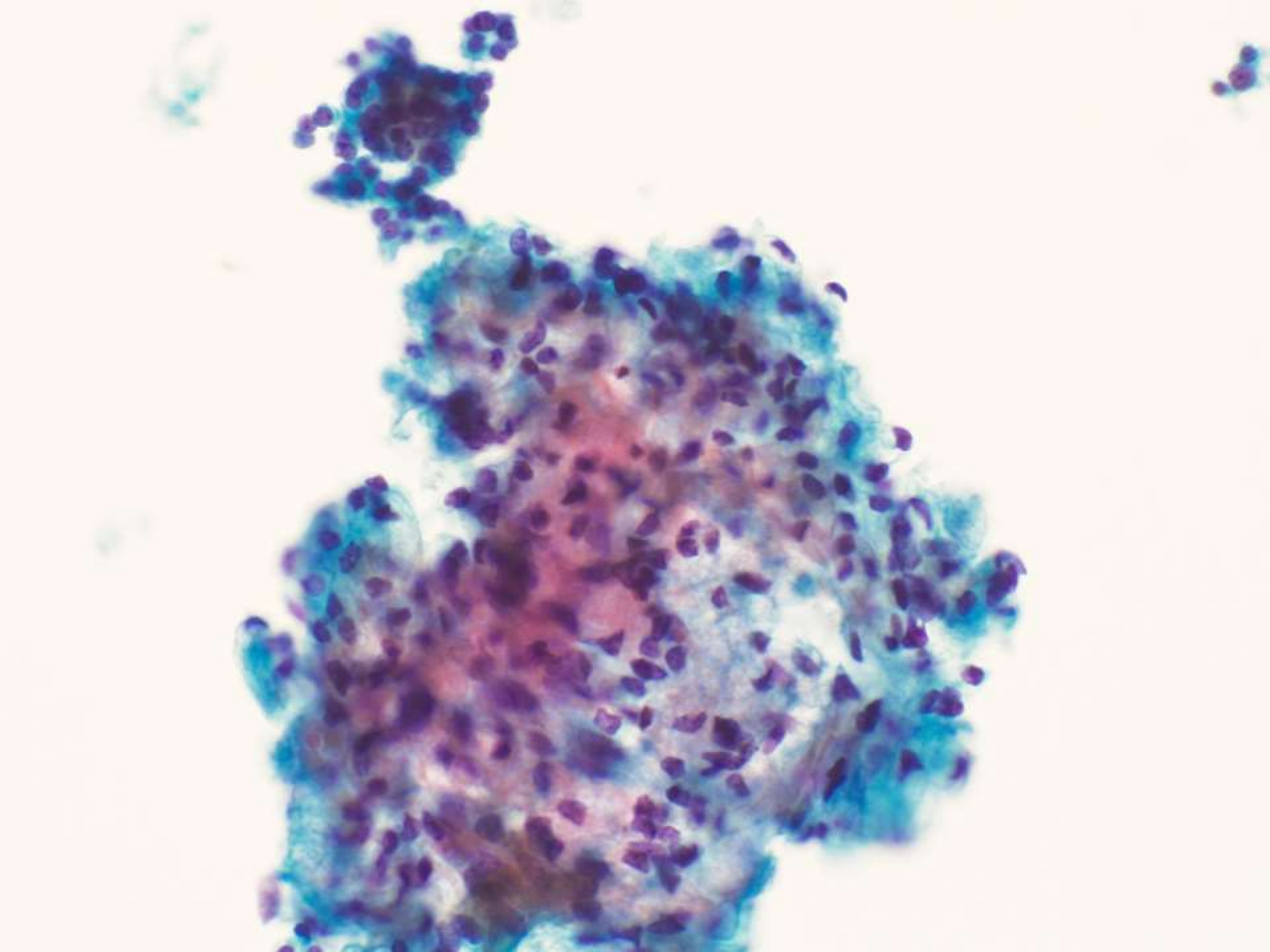


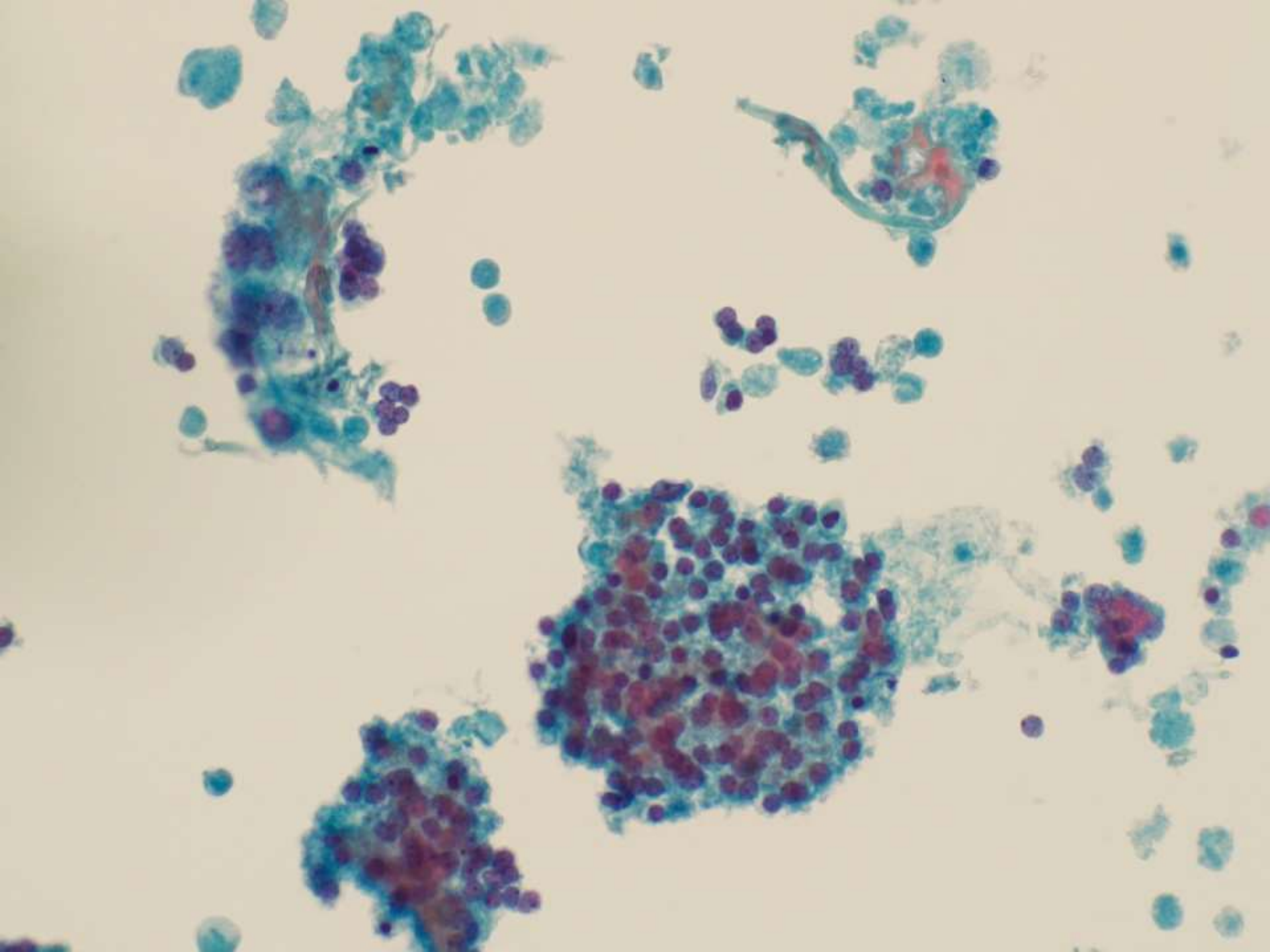


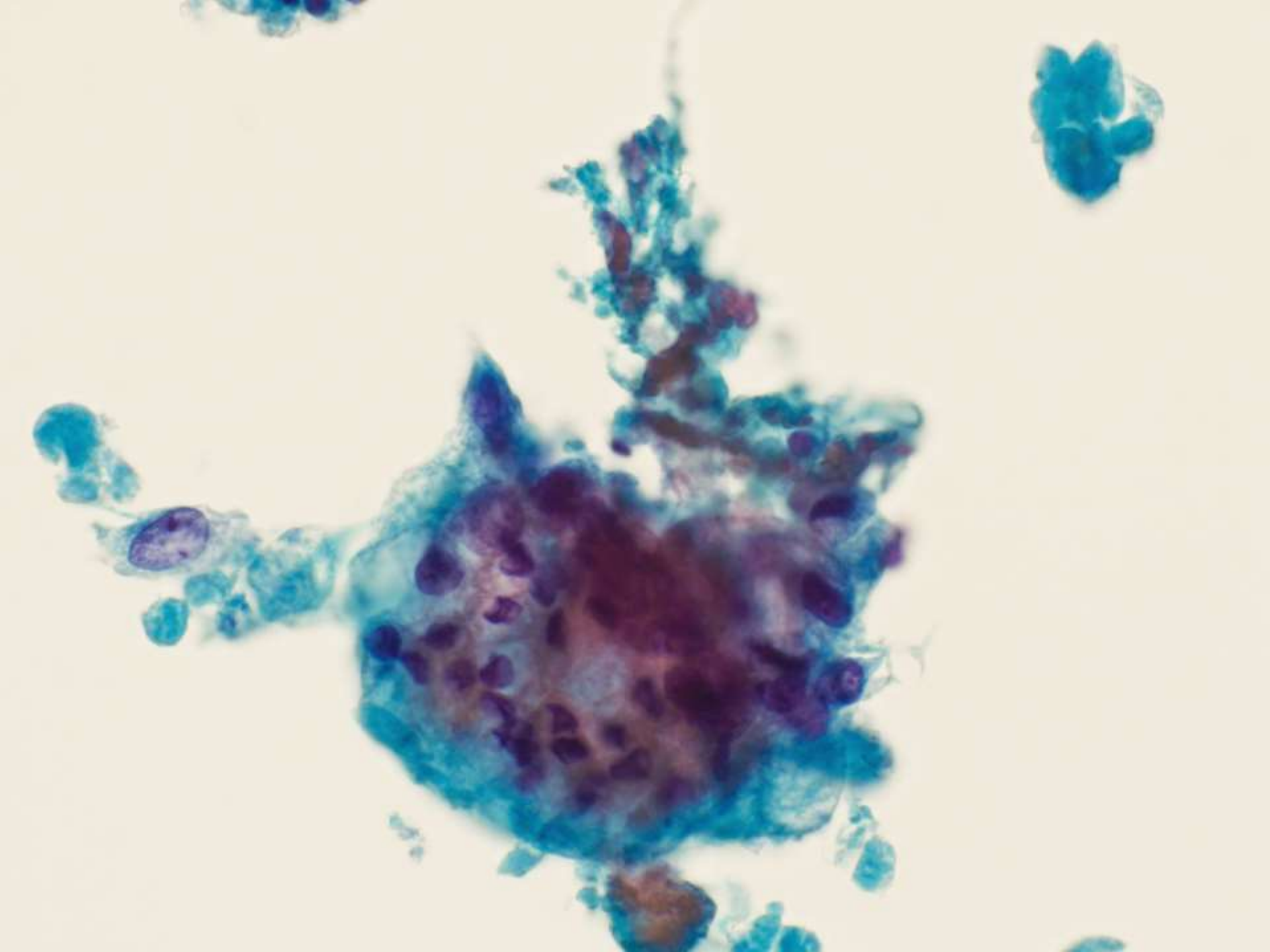
Outside Case: ThinPrep

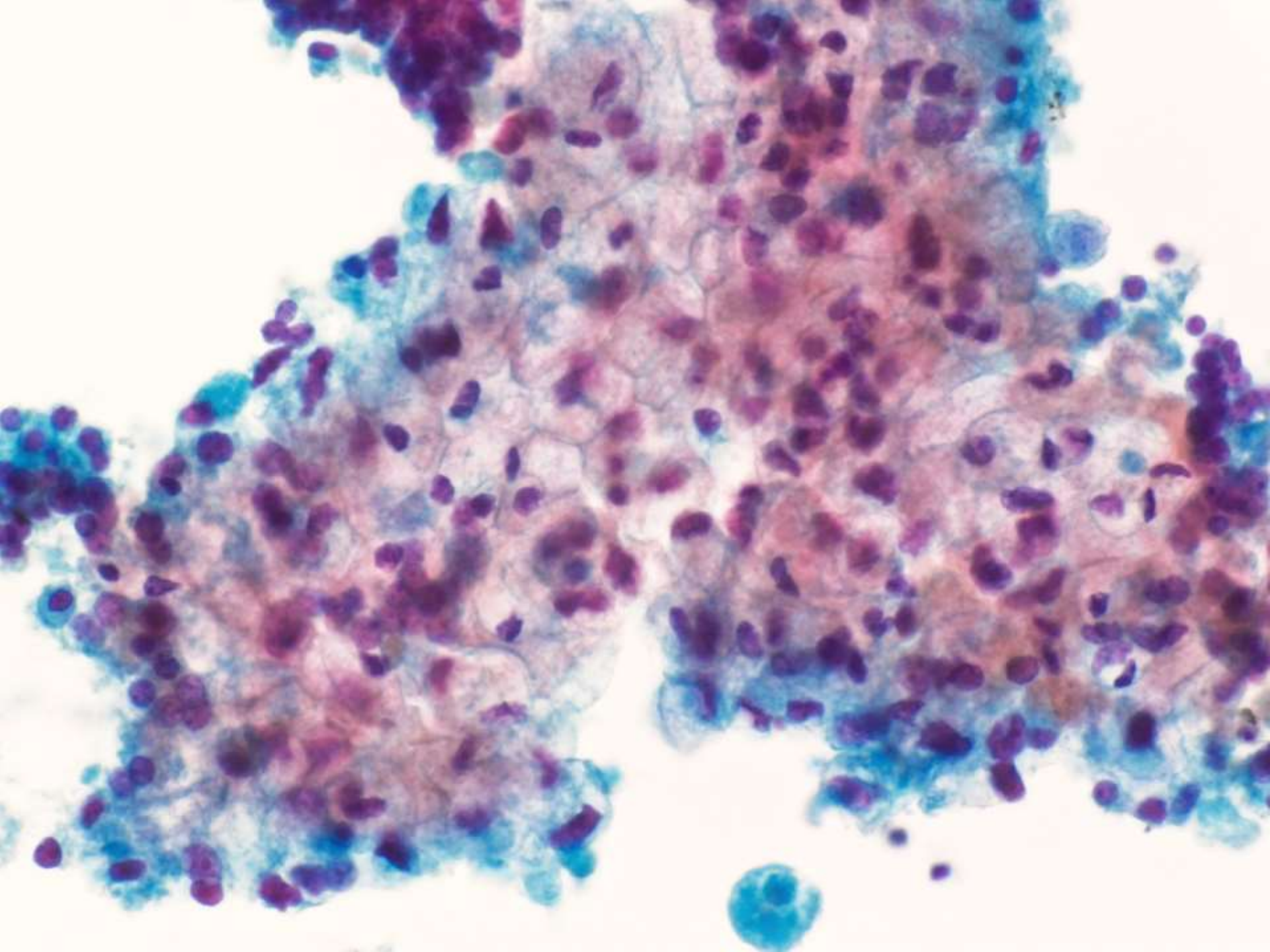


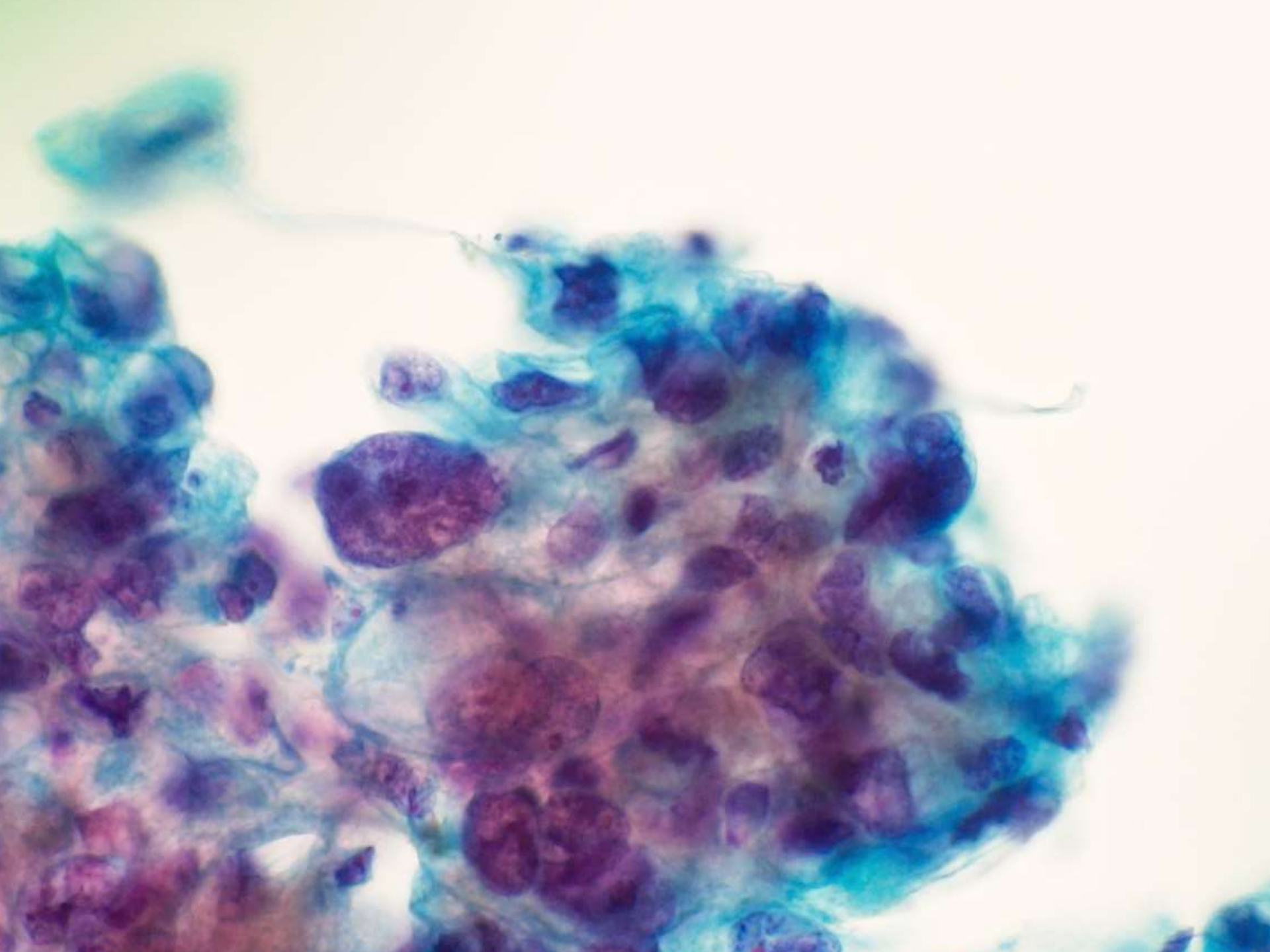












Summary- Pancreas FNA Pitfalls

- Normal Pancreas vs Neoplasm
  - Preserved acinar/ normal lobulated architecture
- Cystic lesions:
  - Low cellularity
  - GI contamination
  - Very helpful:
    - Correlation with imaging, fluid chemistry (CEA, Amylase), molecular analysis
    - Thick colloid like extracellular mucin favors mucinous neoplasm
  - IPMN: LG vs HG very important distinction
- Adenocarcinoma:
  - Low N/C ratio
  - Difficult to distinguish from reactive conditions (AIP, CP)
  - Look for fibrotic fragments, lymphoid tangles
  - Correlation with imaging and clinical findings essential

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Thanks!

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References

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- Sigel CS et al. Cytomorphologic and Immunophenotypical Features of Acinar Cell Neoplasms of the Pancreas. Cancer Cytopathology 2013; 459-470
- Goyal et al. Pancreas and Biliary Tract Cytohistology. Springer 2019.
- ASC Meeting 2020: Images and content
- ASCP Meeting 2021: Images and content

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Normal

- Predominance of acinar cells (except chronic pancreatitis)
- Acinar cells: cohesive, small grape-like clusters of cells, scattered polygonal single cells, occasional stripped nuclei
- Round regular Nuclei, central to eccentric, uniform chromatin, often prominent nucleoli
- Abundant granular cytoplasm (DQ: small vacuoles)
- Architecture: Key to differentiate B9 acinar cells from neoplasm (small uniform grape- like)

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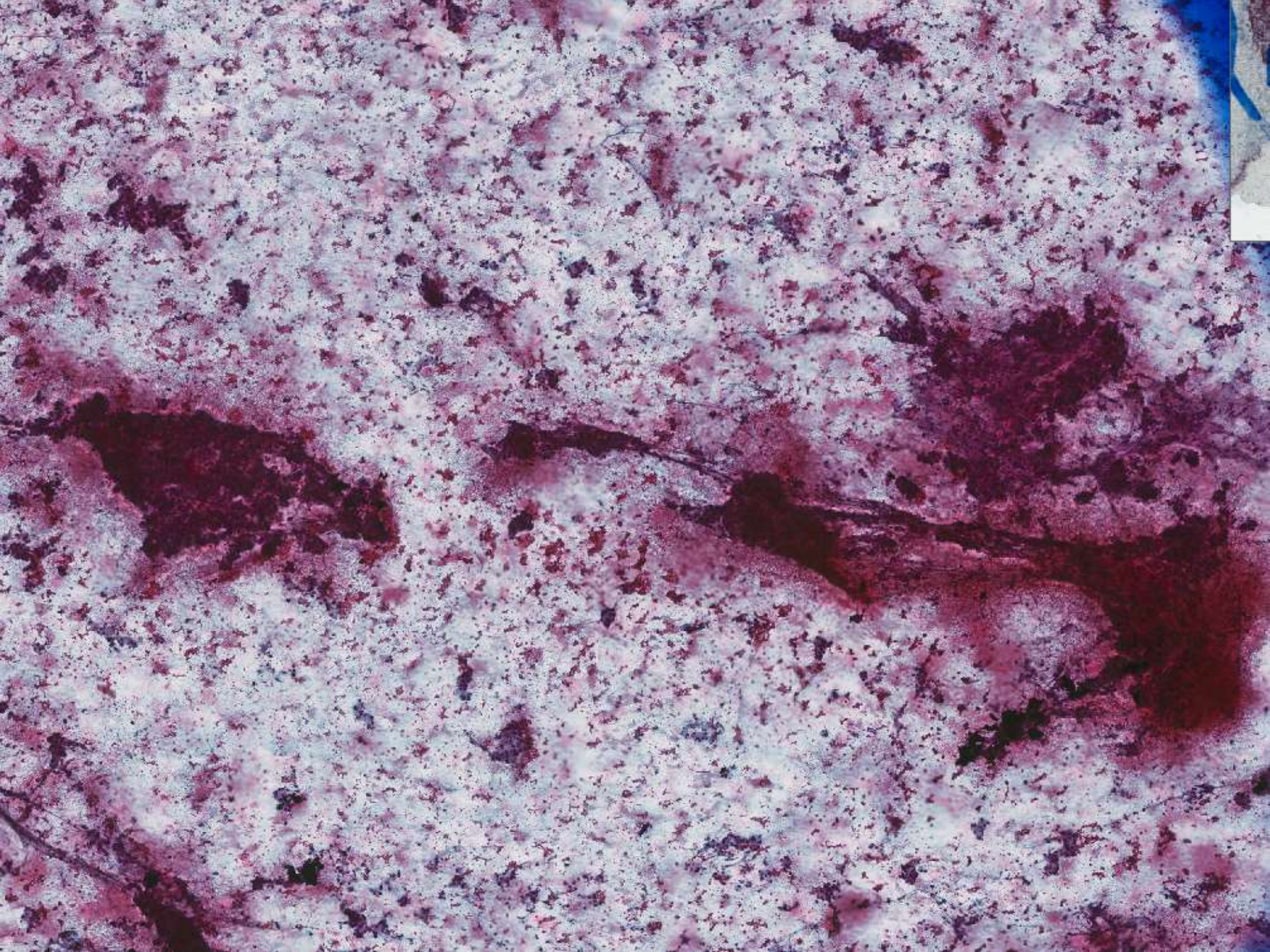
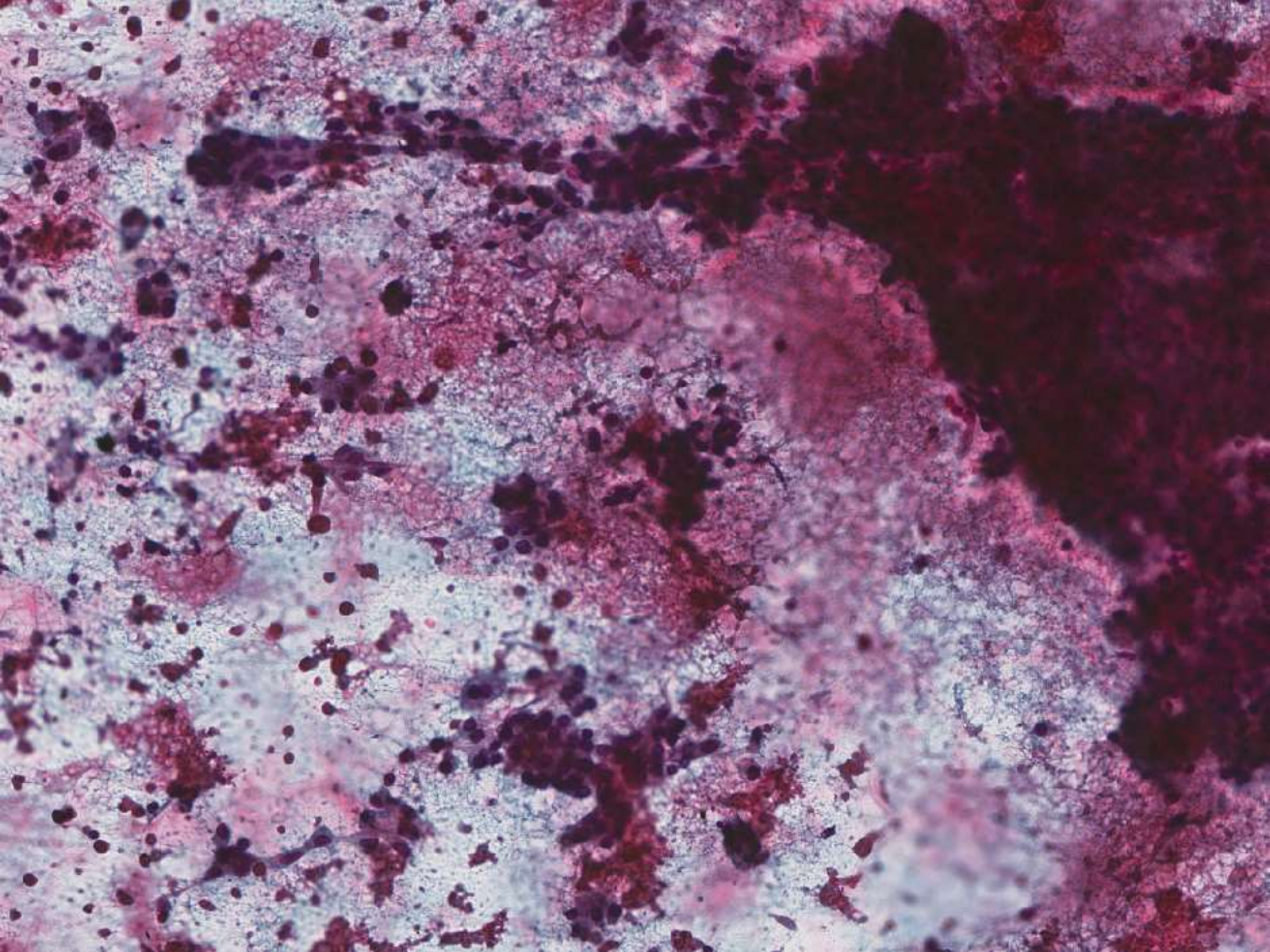
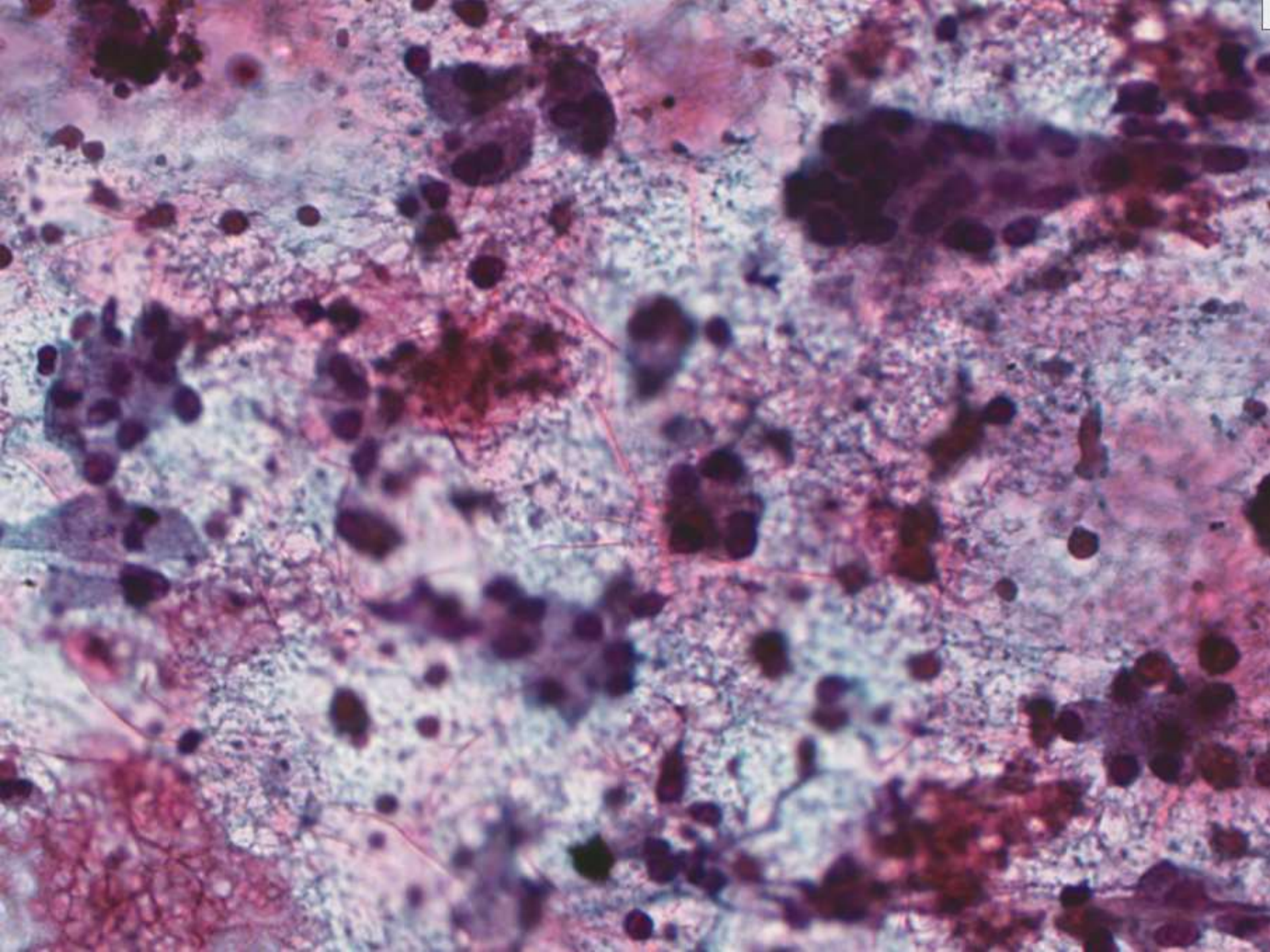
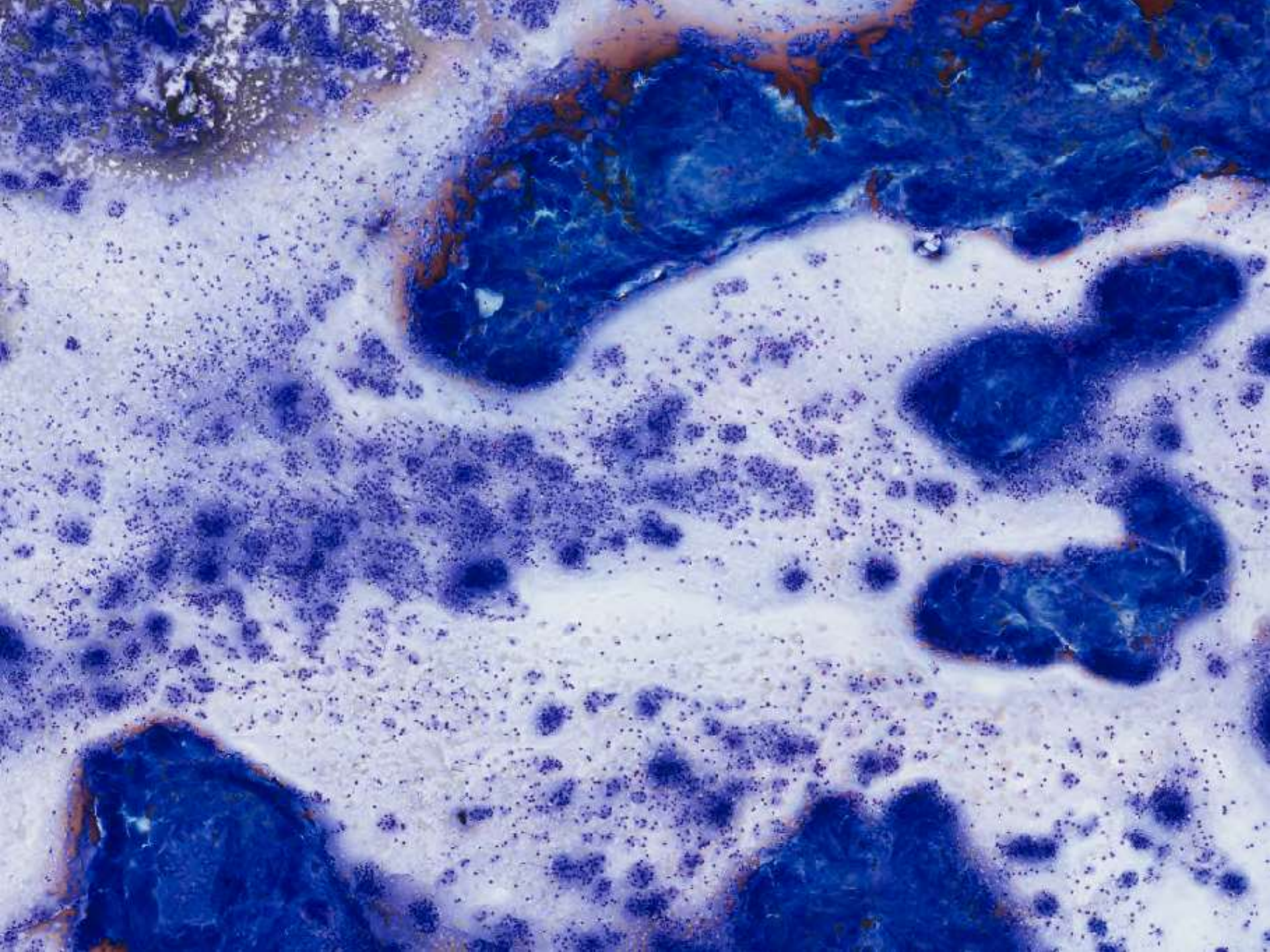
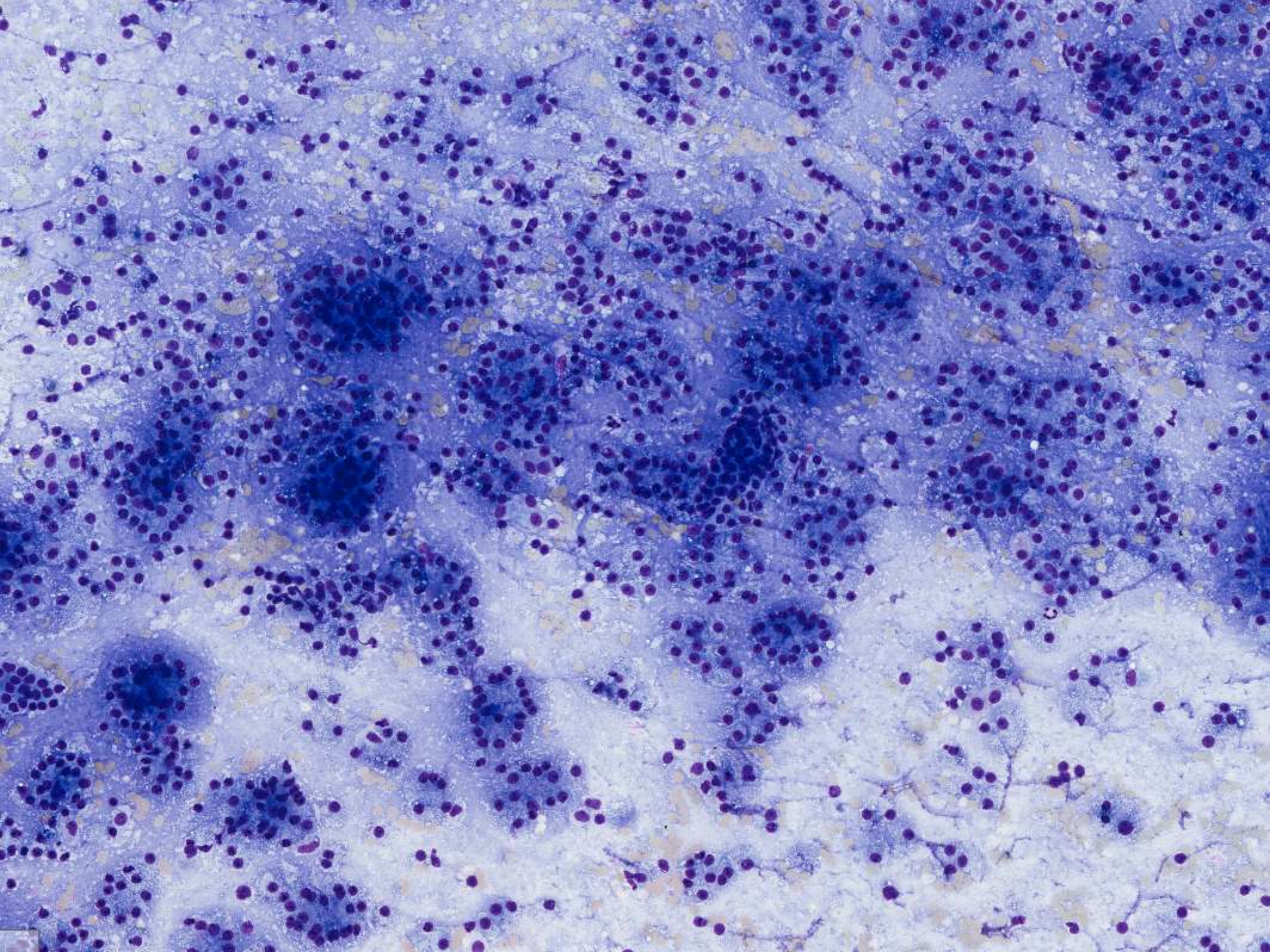
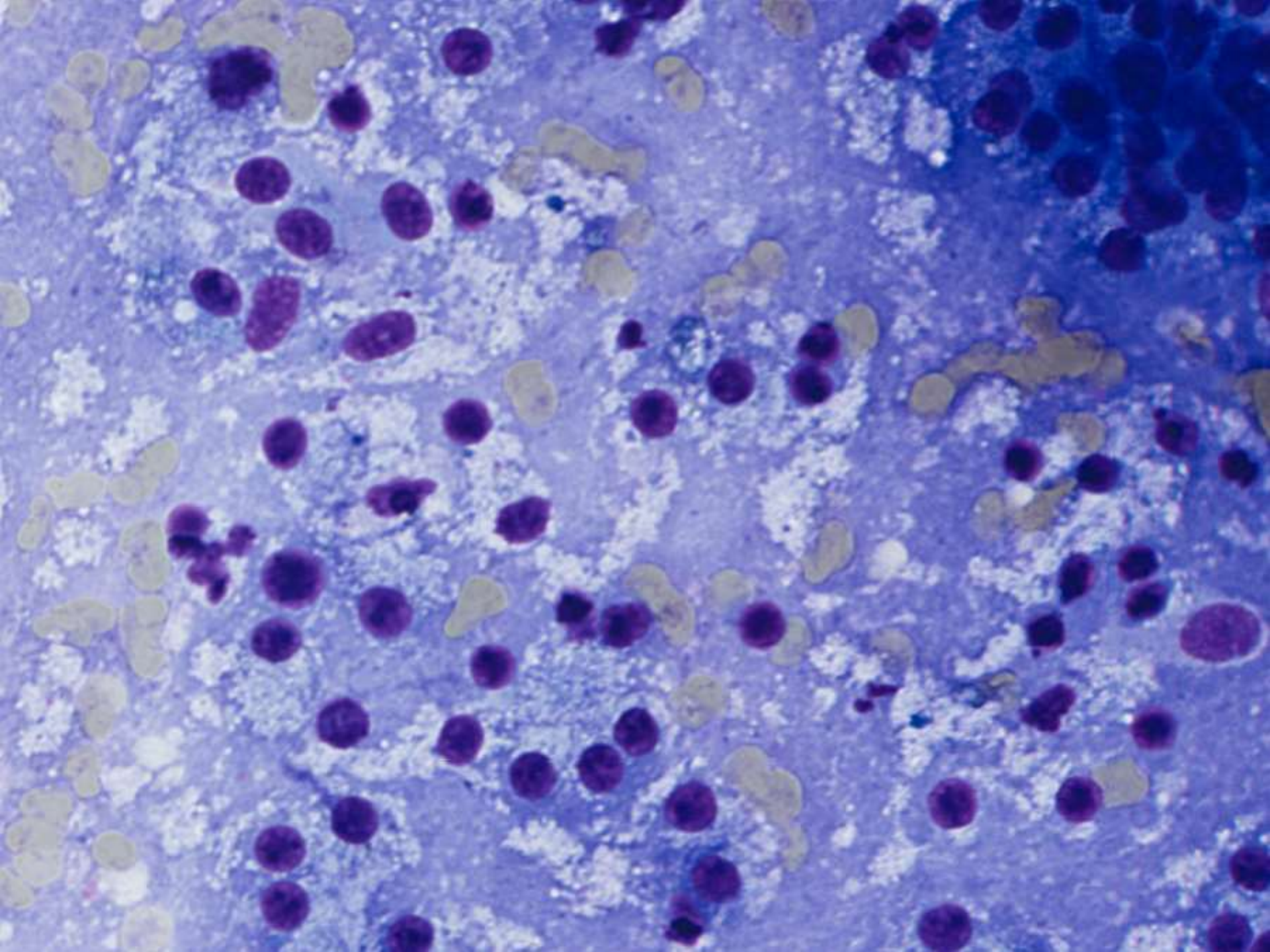


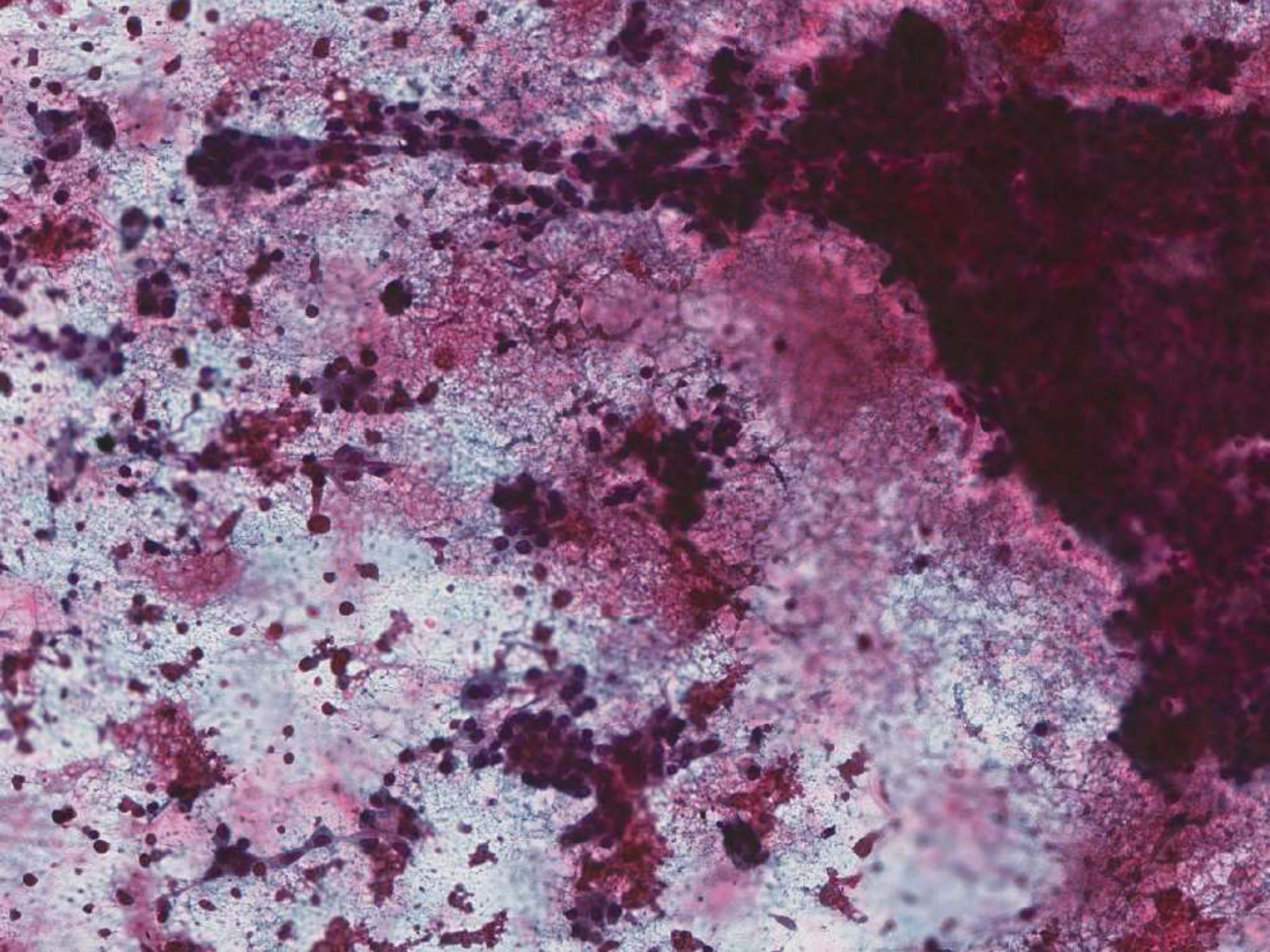


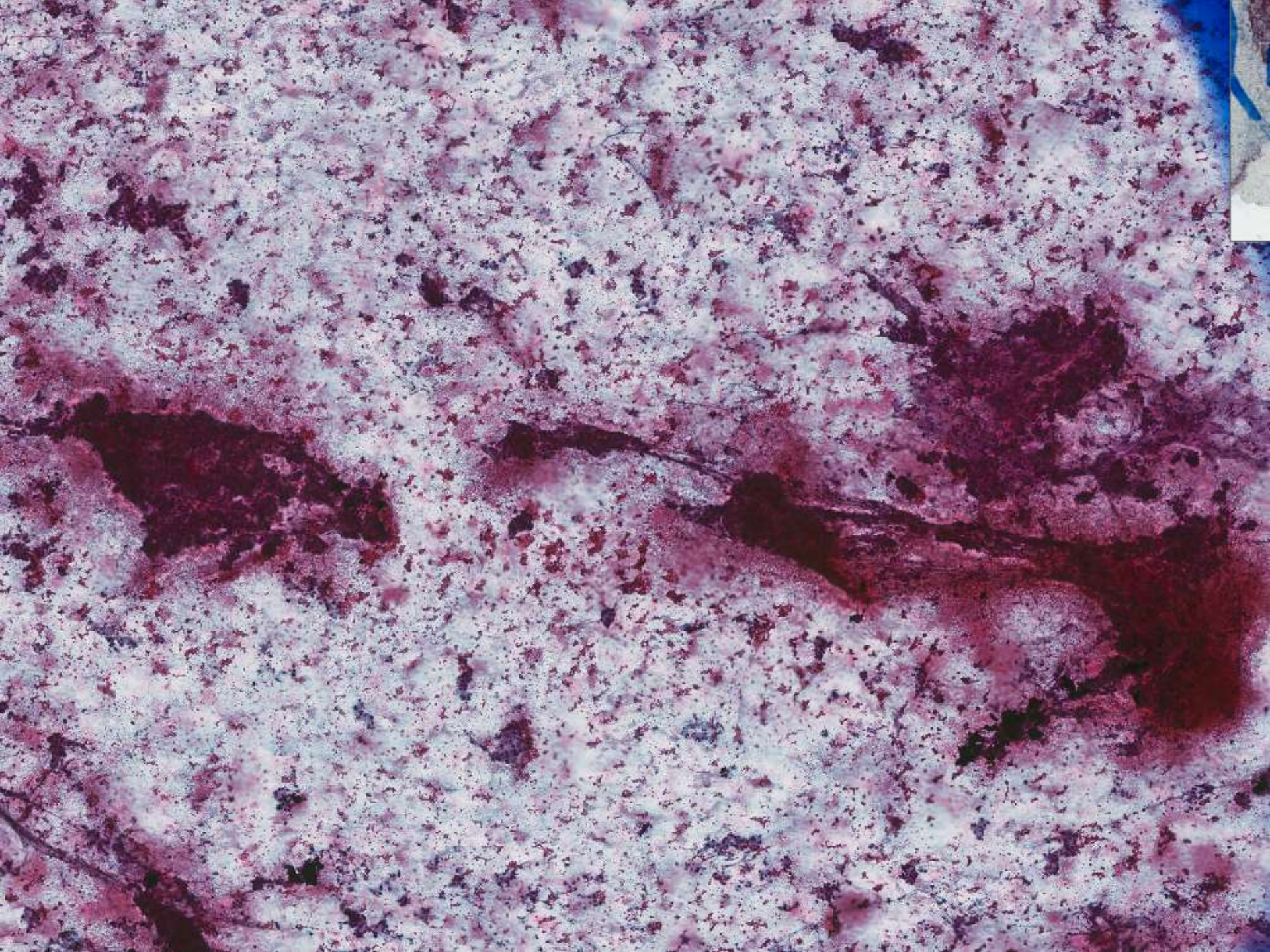












IVA Neoplastic Benign

Serous cystadenoma

Cystic teratoma

Schwannoma

Lymphangioma

Benign behavior

IVB Neoplastic Other

Intraductal papillary mucinous neoplasm

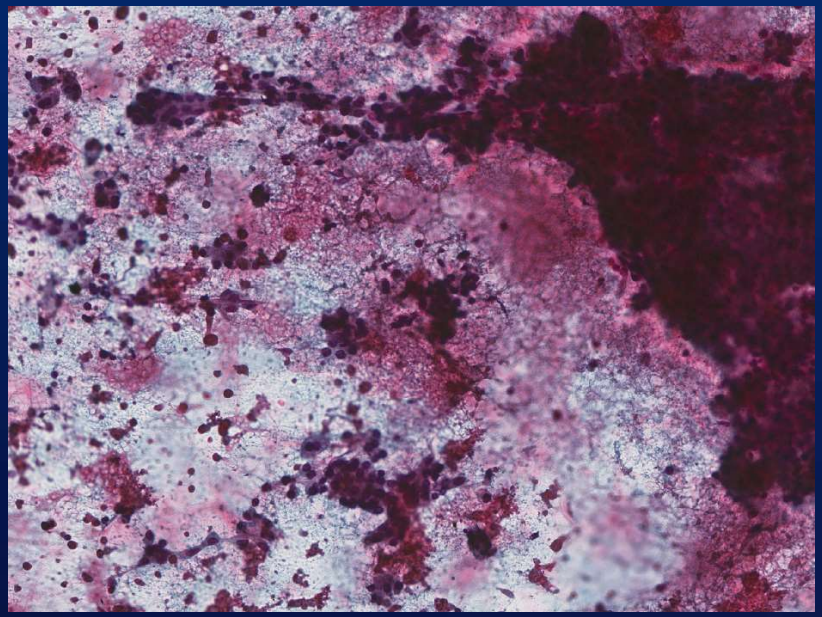
Mucinous cystic neoplasm

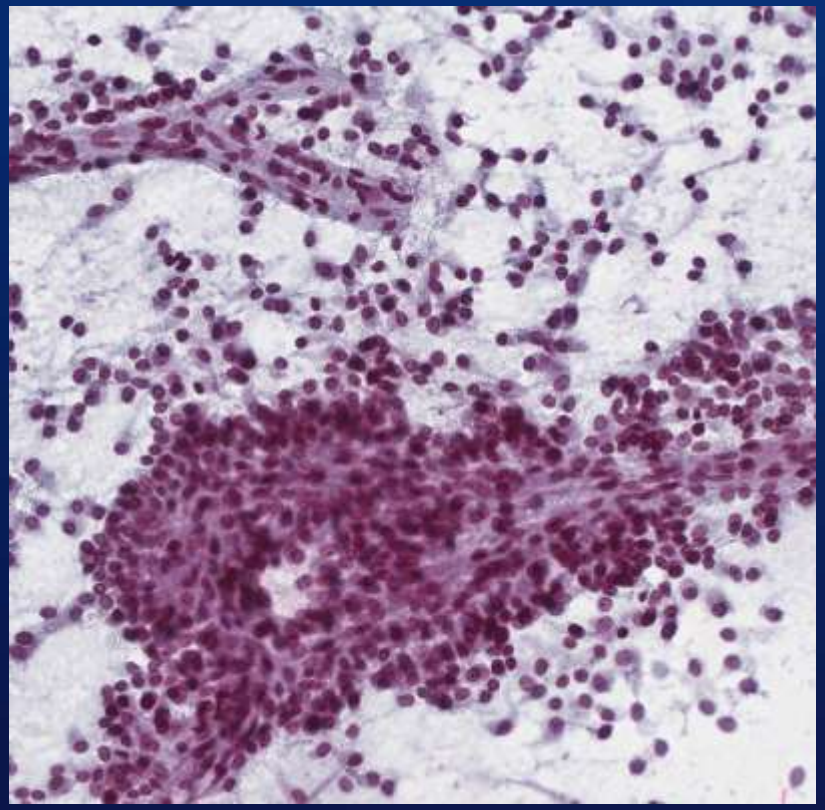
Neuroendocrine tumor*

Solid pseudopapillary tumor

Not definitive benign but warrants distinction from high grade malignancy

Case 1 Vs SPN





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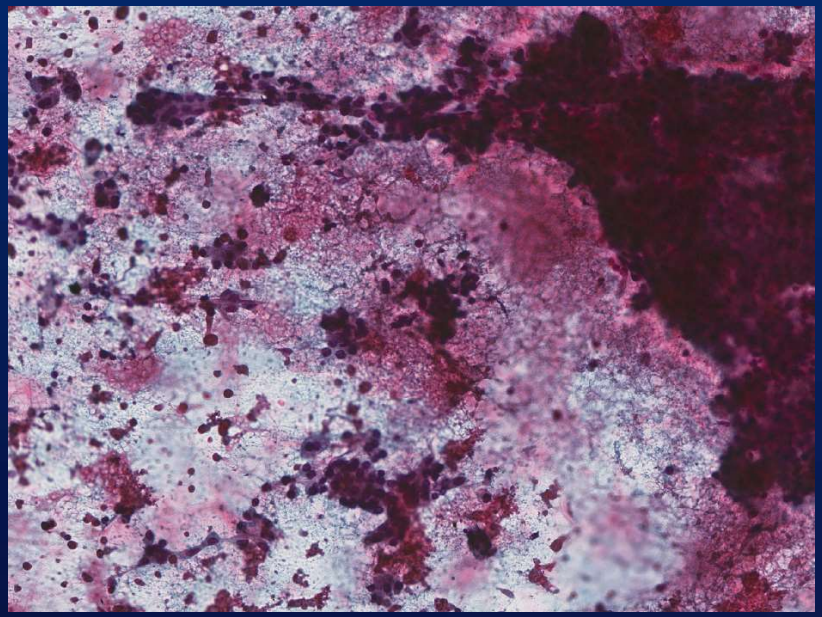

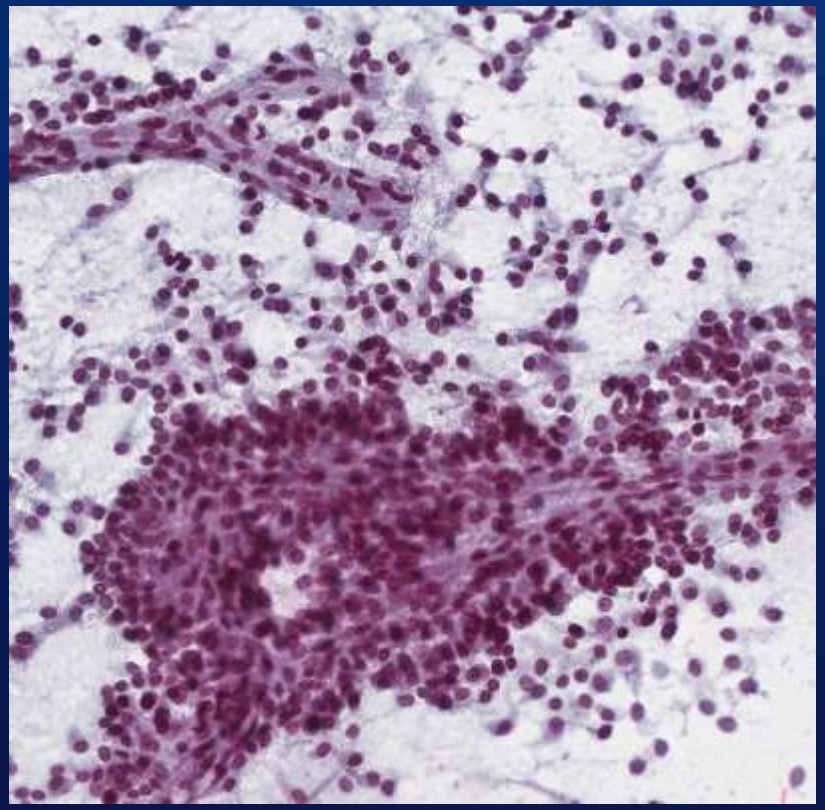

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SPN vs Case 1

- Mild nuclear enlargement (CHECK)
- Irregular nuclear contours
- Intranuclear grooves
- Cytoplasmic tails
- Extracellular PAS+ hyaline globules

- Nuclear (N) size = RBC
- Basally located N
- Round, smooth membranes
- Key: architecture “grape-like”, uniform cells adhesed to fibrovascular core

Thanks

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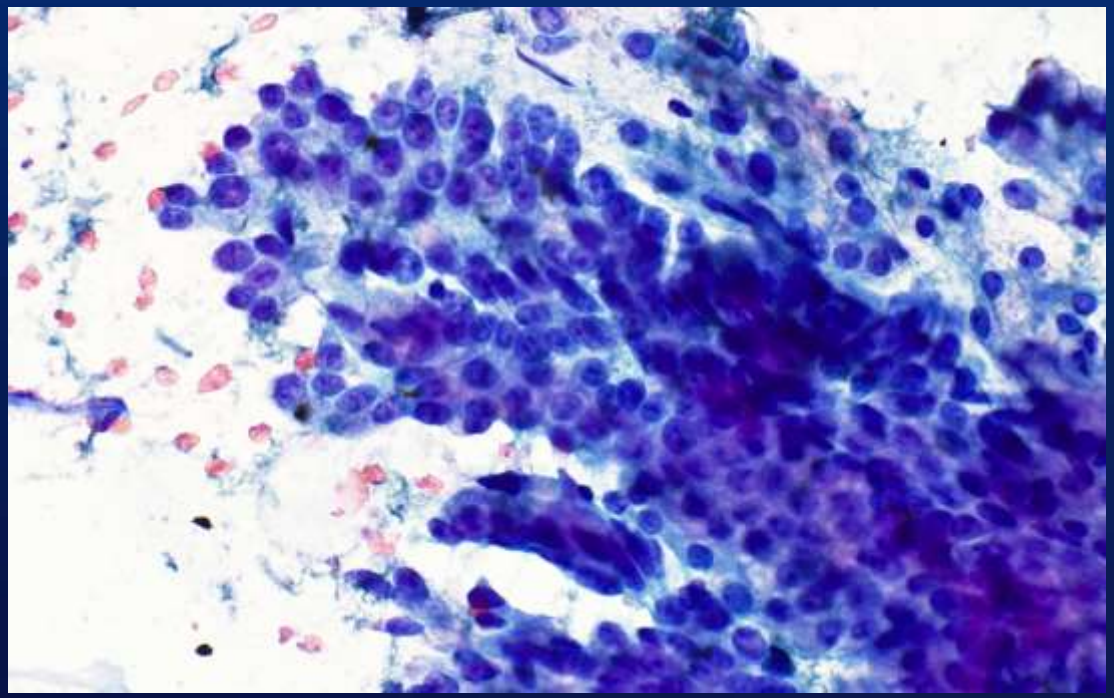
Case 1

Duodenal papilla Reactive



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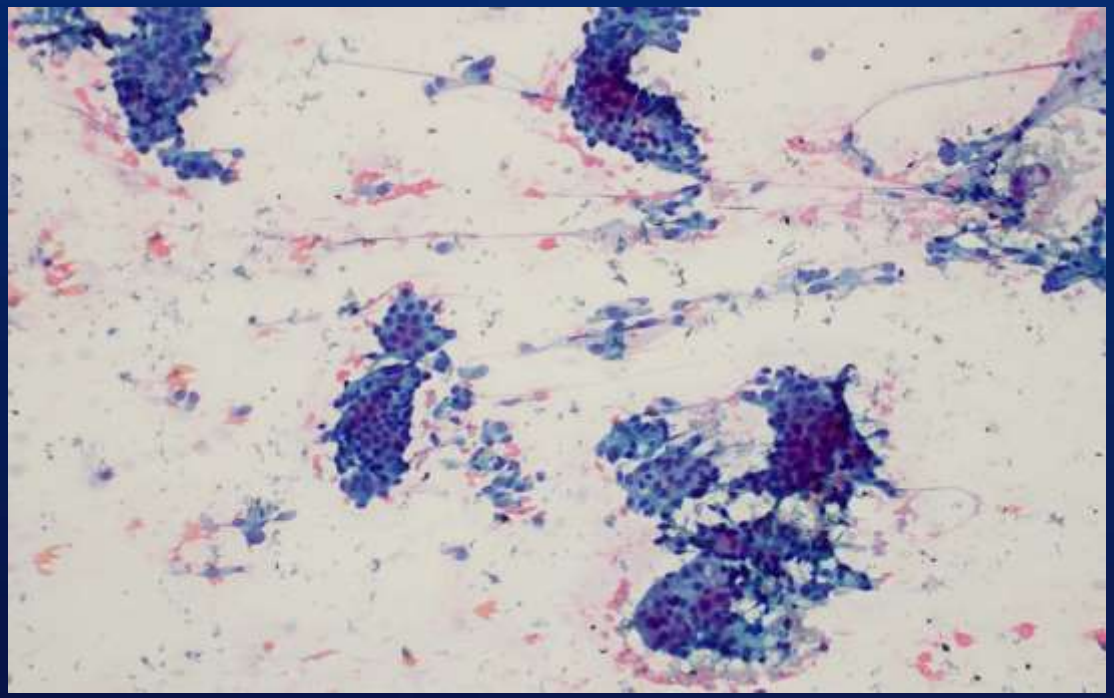
Duodenal papilla Reactive



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Cystic Neuroendocrine Neoplasms: Cytology

Patterns: Loosely cohesive tissue fragments with predominately dispersed single cells; Epithelial proliferations with fibrovascular stroma or cores within epithelial tissue fragments

Cellularity: varies

Perivascular/coronal pattern

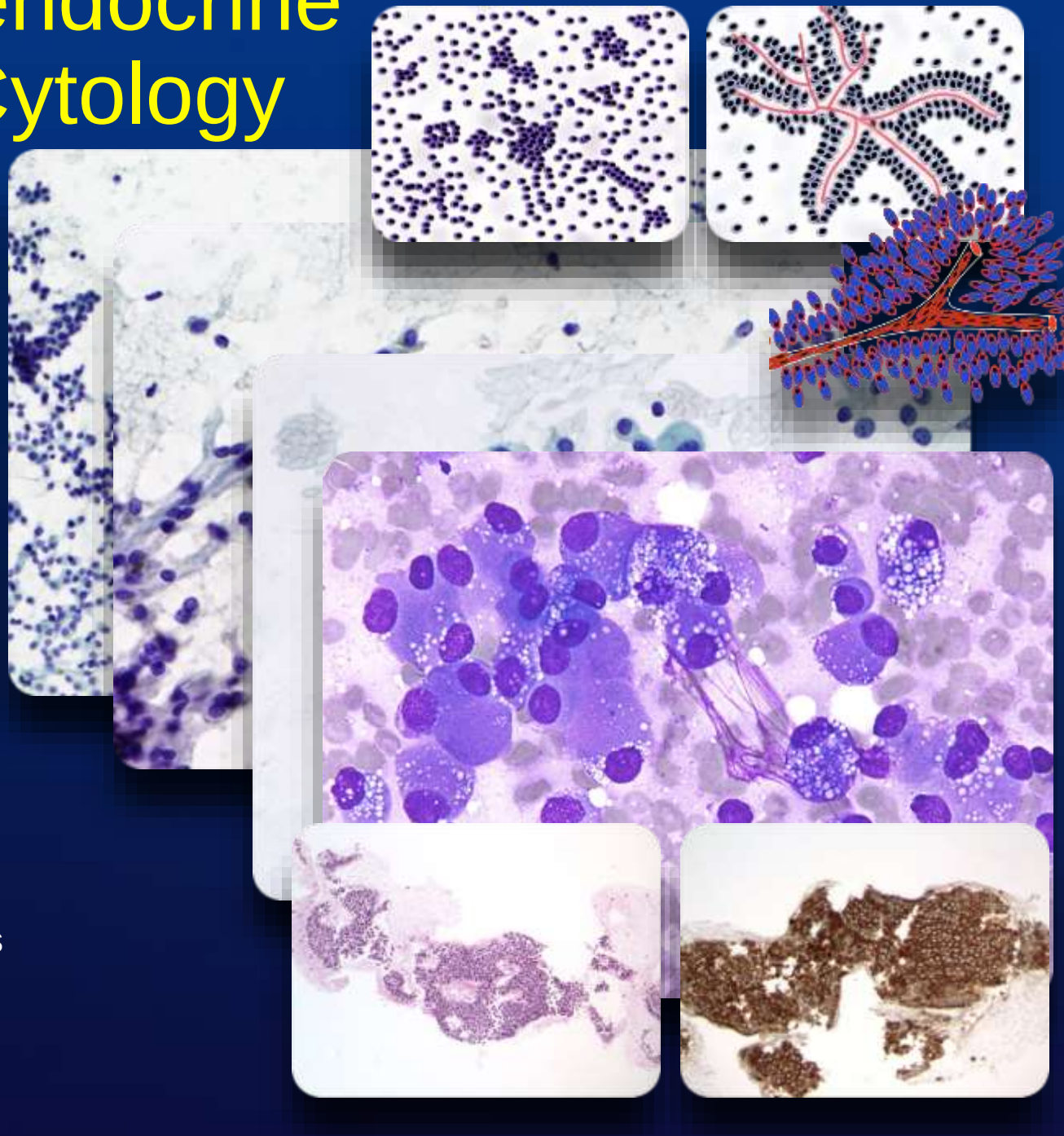
Monomorphic appearance; some cells out of proportion to others

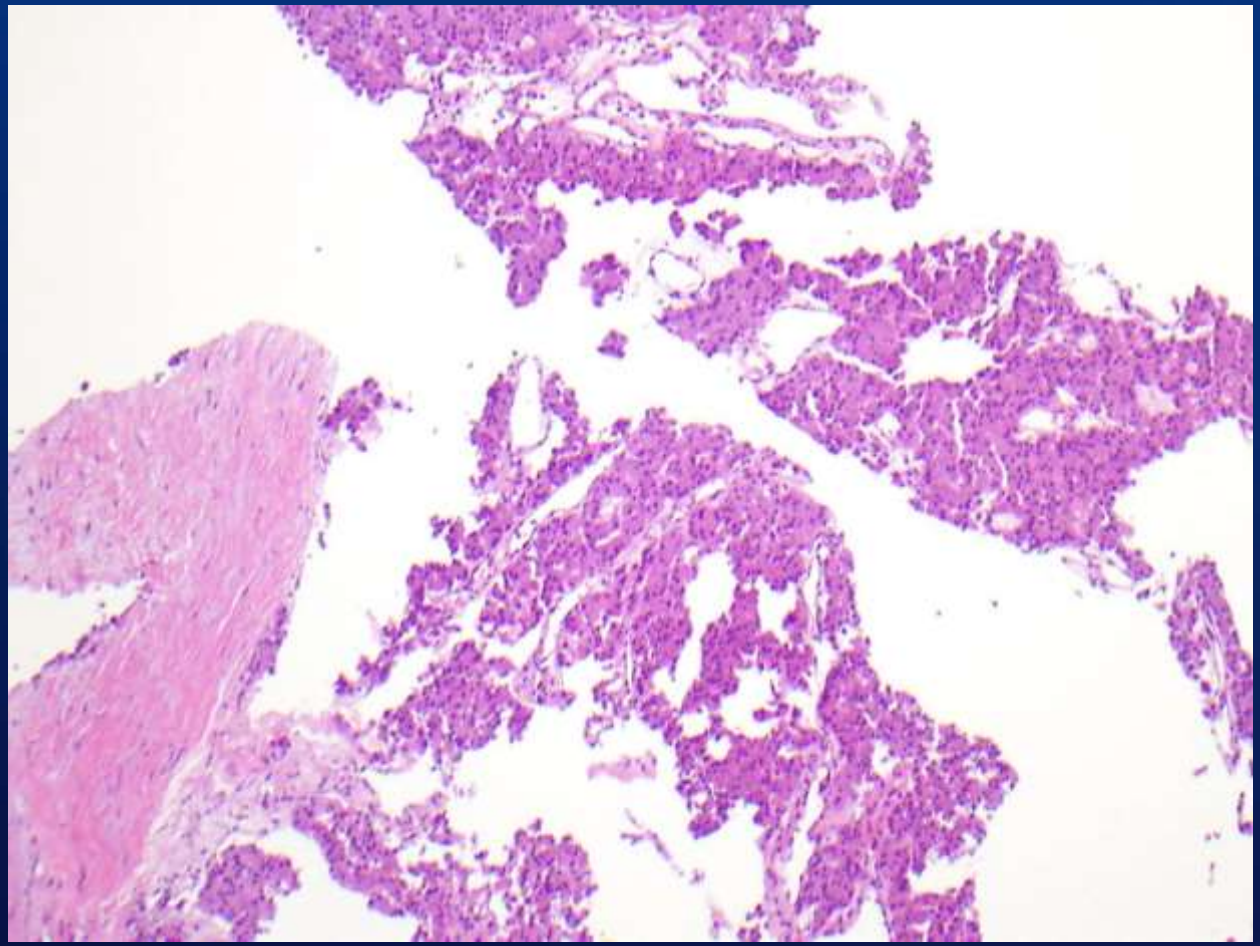
Plasmacytoid, bi-nucleate; stripped nuclei

Salt and pepper chromatin

Pink granules with air dry stains

Synaptophysin +; chromogranin+ patchy





Liver mass, needle biopsy

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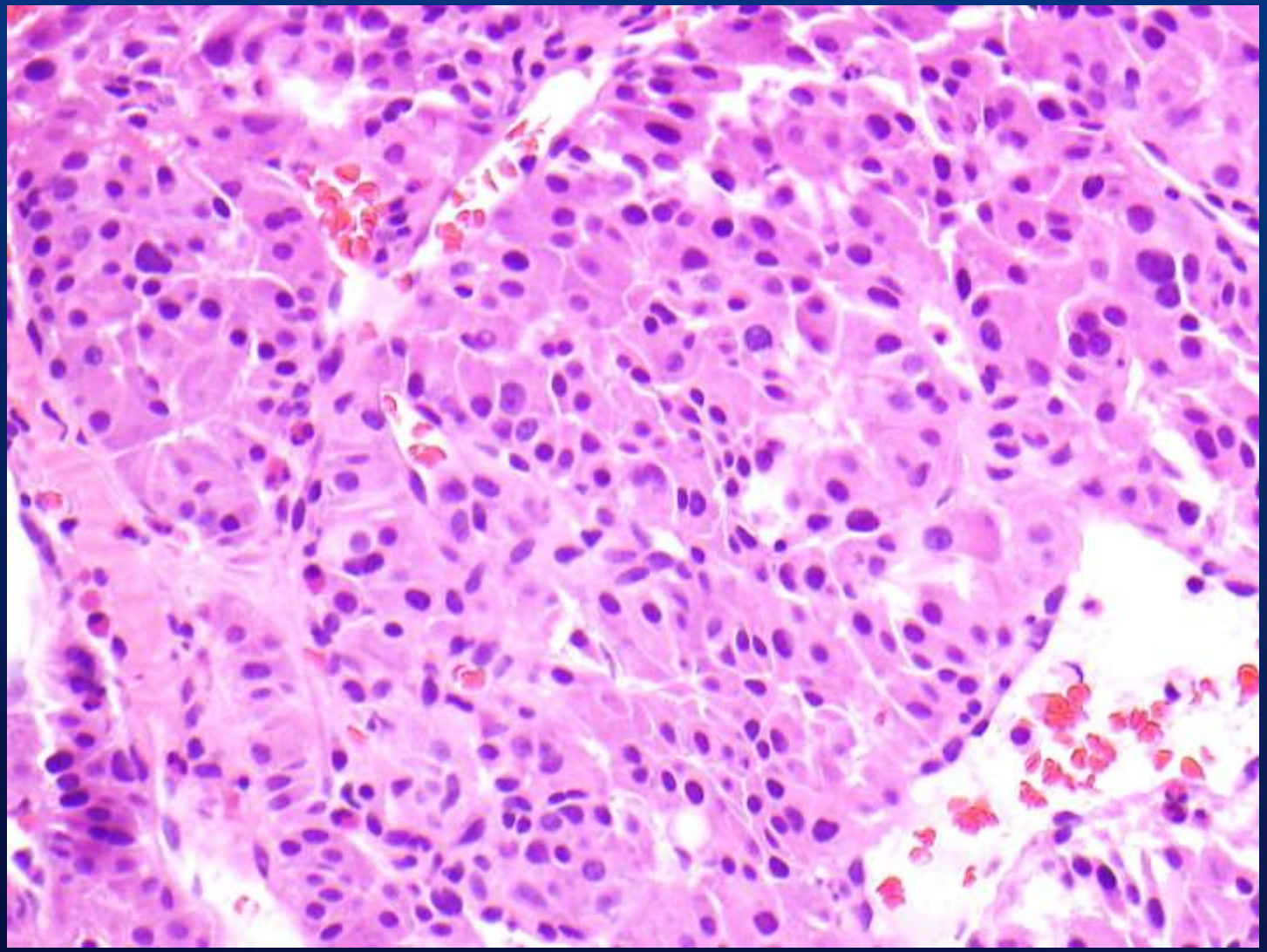

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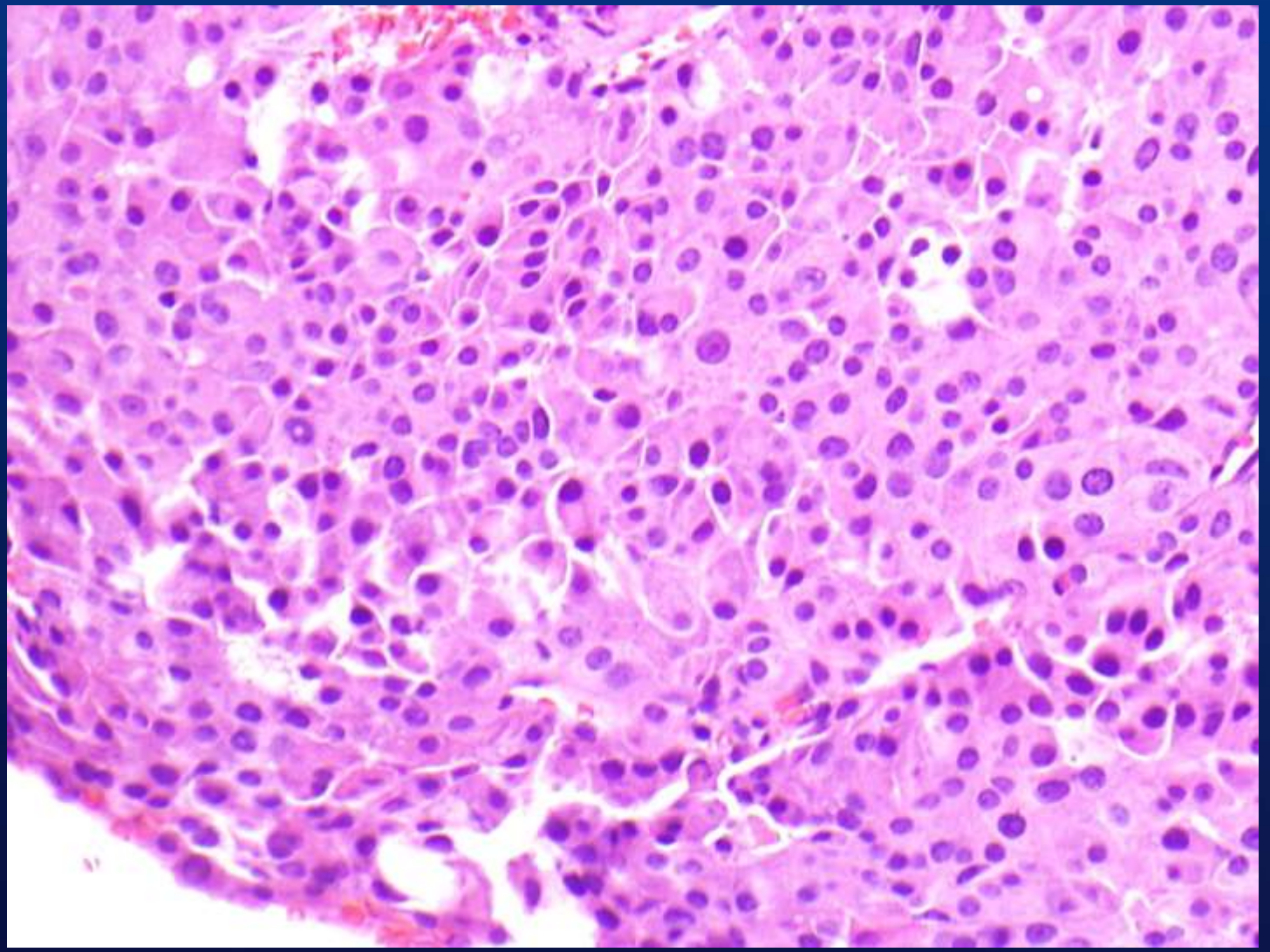

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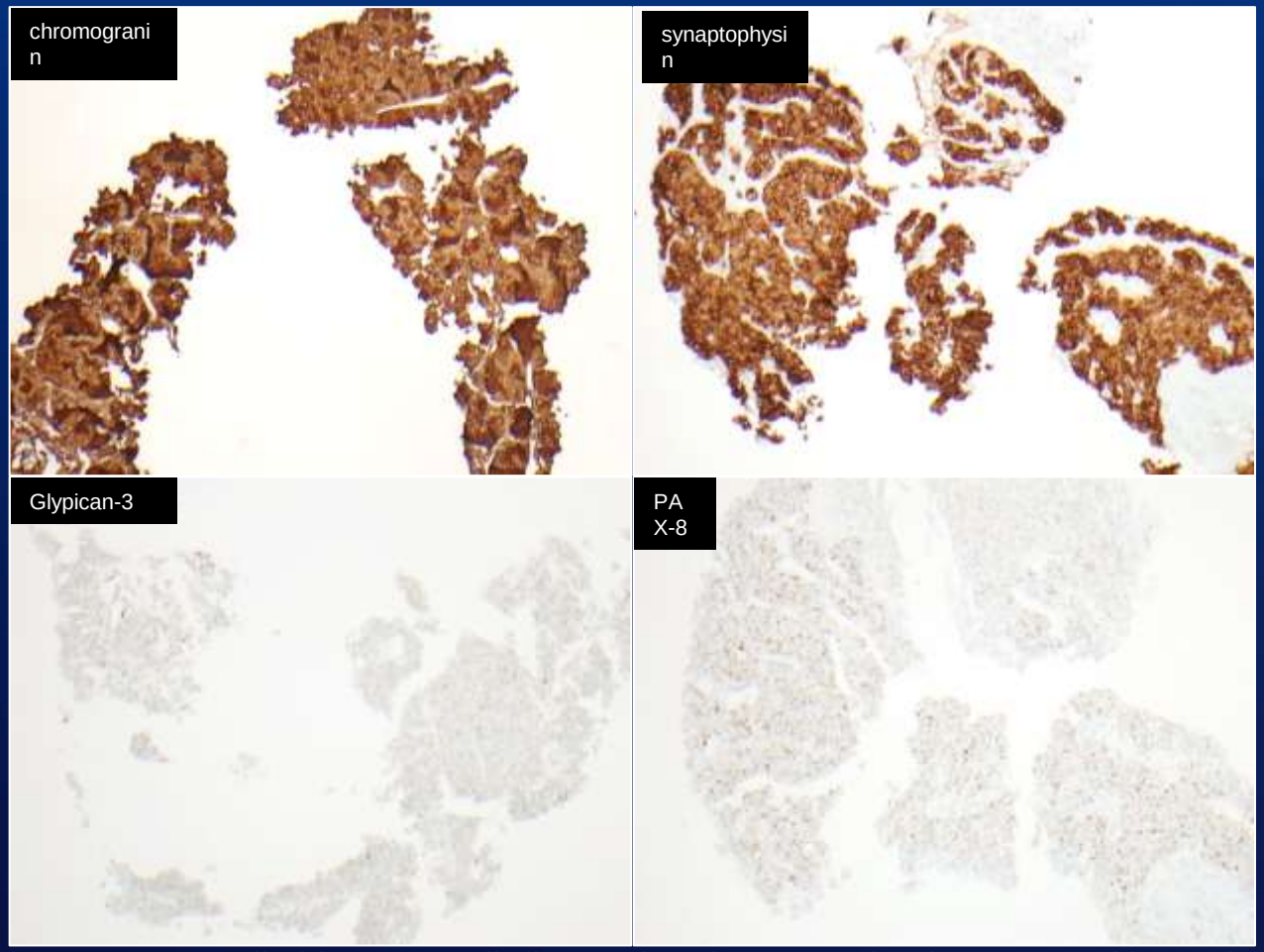

Liver mass, needle biopsy: Well-differentiated neuroendocrine tumor with focal hepatoid differention. Ki67 performed on the outside biopsy = WHO grade 2 of 3 (Ki-67 = 14.35%).

Recent Updates on Neuroendocrine Tumors From the Gastrointestinal and Pancreatobiliary Tracts

Joo Young Kim, MD, PhD; Seung-Mo Hong, MD, PhD

• *Context.*—Gastrointestinal (GI) and pancreatobiliary tracts contain a variety of neuroendocrine cells that constitute a diffuse endocrine system. Neuroendocrine tumors (NETs) from these organs are heterogeneous tumors with diverse clinical behaviors. Recent improvements in the understanding of NETs from the GI and pancreatobiliary tracts have led to more-refined definitions of the clinicopathologic characteristics of these tumors. Under the 2010 World Health Organization classification scheme, NETs are classified as grade (G) 1 NETs, G2 NETs, neuroendocrine carcinomas, and mixed adenoneuroendocrine carcinomas. Histologic grades are dependent on mitotic counts and the Ki-67 labeling index. Several new issues arose after implementation of the 2010 World Health Organization classification scheme, such as issues with well-differentiated NETs with G3 Ki-67 labeling index and the evaluation of mitotic counts and Ki-67 labeling. Hereditary syndromes, including multiple endocrine neoplasia type 1 syndrome, von Hippel-Lindau syndrome, neurofibromatosis 1, and tuberous sclerosis, are related to NETs of the GI and pancreatobiliary tracts. Several prognostic markers of GI and pancreatobiliary tract NETs have been introduced, but many of them require further validation.

Objective.—To understand clinicopathologic characteristics of NETs from the GI and pancreatobiliary tracts.

Data Sources.—PubMed (US National Library of Medicine) reports were reviewed.

Conclusions.—In this review, we briefly summarize recent developments and issues related to NETs of the GI and pancreatobiliary tracts.

(*Arch Pathol Lab Med.* 2016;140:437–448; doi: 10.5858/arpa.2015-0314-RA)

clinical symptoms.[85] In addition to the typical features of NETs, some pancreatic NETs show morphologic variations, including clear cell, oncocytic, and pleomorphic types. Clear cell NETs will be discussed in the section on von Hippel-Lindau syndrome (Figure 3, A). Oncocytic pancreatic NETs contain large polygonal cells with eosinophilic granular cytoplasm and prominent nucleoli (Figure 3, B). Some studies reported that oncocytic tumors have a malignant clinical behavior.[86,87] In the setting of liver metastasis of oncocytic pancreatic NETs, immunohistochemical staining

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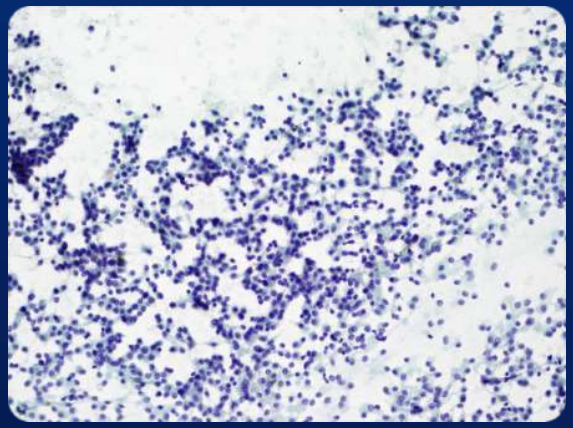
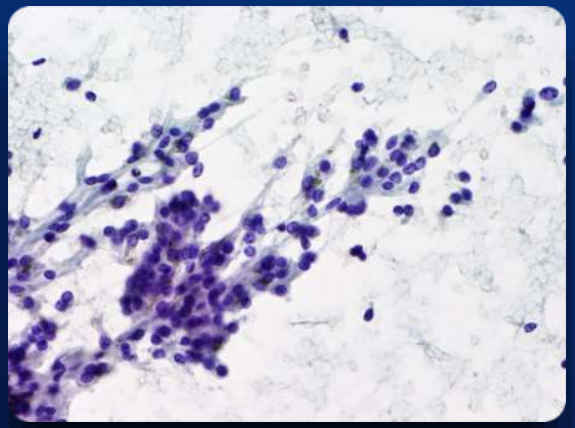
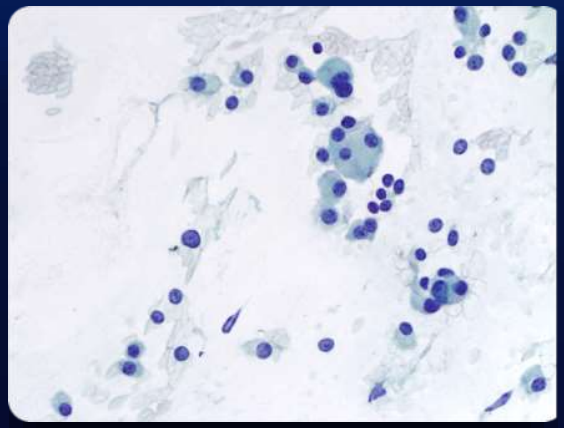
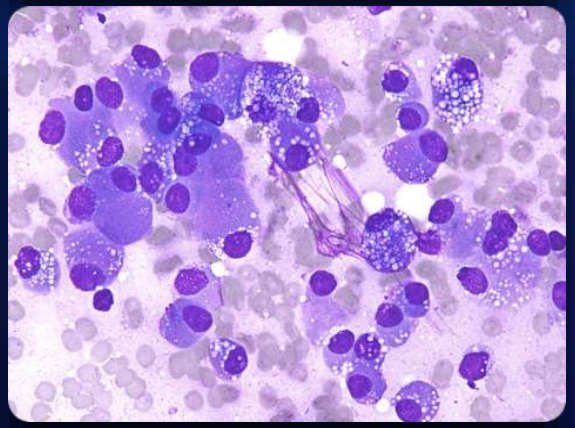
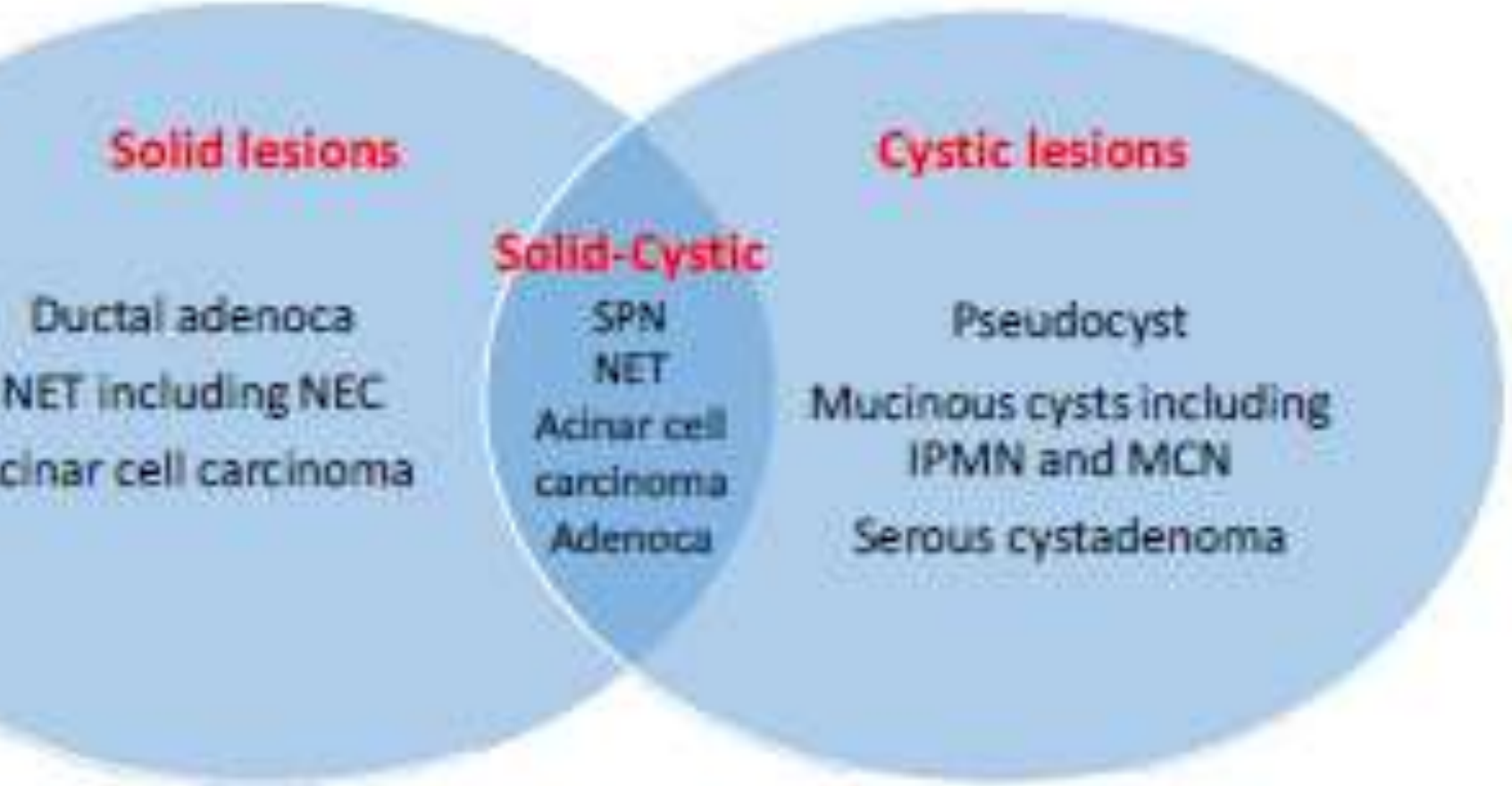
Neuroendocrine Tumors











Adenoca: Ade
NET: Neuroen
NEC: Neuroen
carcinoma
SPN: Solid ps
neoplasm
IPMN: Intradu
mucinous neo
MCN: Mucino
neoplasm

PSC Categories

- I: Non- diagnostic
- II: Benign
- III: Atypical
- IVb: Neoplastic, other
- IV: Suspicious

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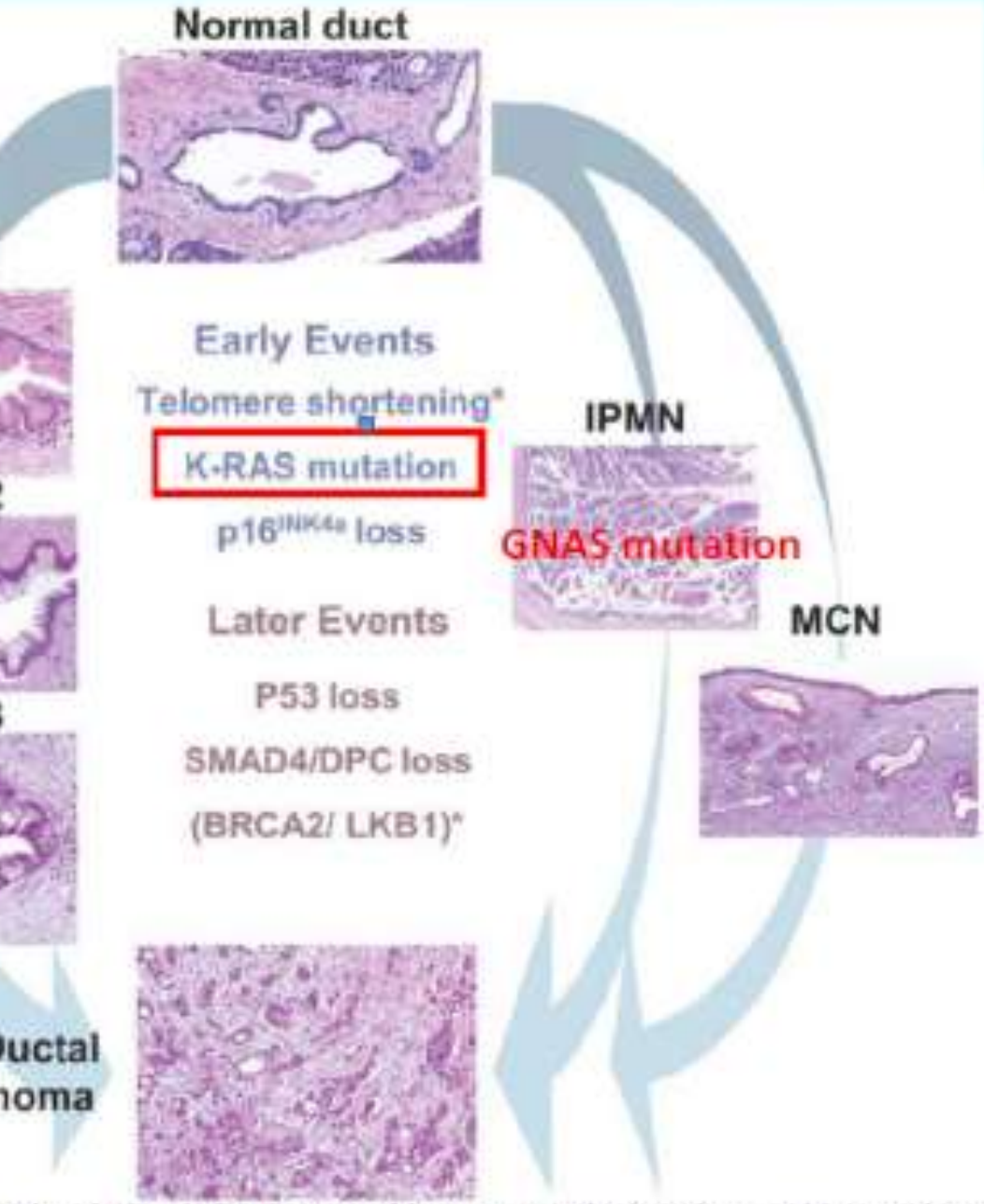
Cysts of the pancreas

- Non-neoplastic
  - Pseudocyst
  - Retention cyst
  - Congenital cyst
  - Foregut cyst
  - Endometriotic cyst
- Cystic nonepithelial neoplasms
  - Lymphangioma
  - Hemangioma

Adsay NV. ModPathol (2007): 20:S71-S93



- KRAS seen in about 61 % of IPMN and 21% of MCN
- GNAS mutation almost exclusivel found in IPMN but has been four SCA
- KRAS and GNAS seen together suggests IPMN
- KRAS or GNAS has no prognostic indication, can be seen in both lo and high grade dysplasia

Kishore & Chen, QJ. (2016). Cancer of the Pancreas: Molecular Pathways and Current Advancement in Treatment. Journal of Cancer. 7. 1497-1514.

ucinous cystic neoplasm: tology

Pattern: Mucinous background

- Thick mucous, if present, extremely helpful
- Low cellularity
- Flat sheet or single mucous cells
- Ovarian-type stroma often absent
- Cytologic atypia depends on degree of differentiation
  - Cytology often underestimates the final histologic grade

Pitman et al. Cancer Cytopathol. 2010:1181-13

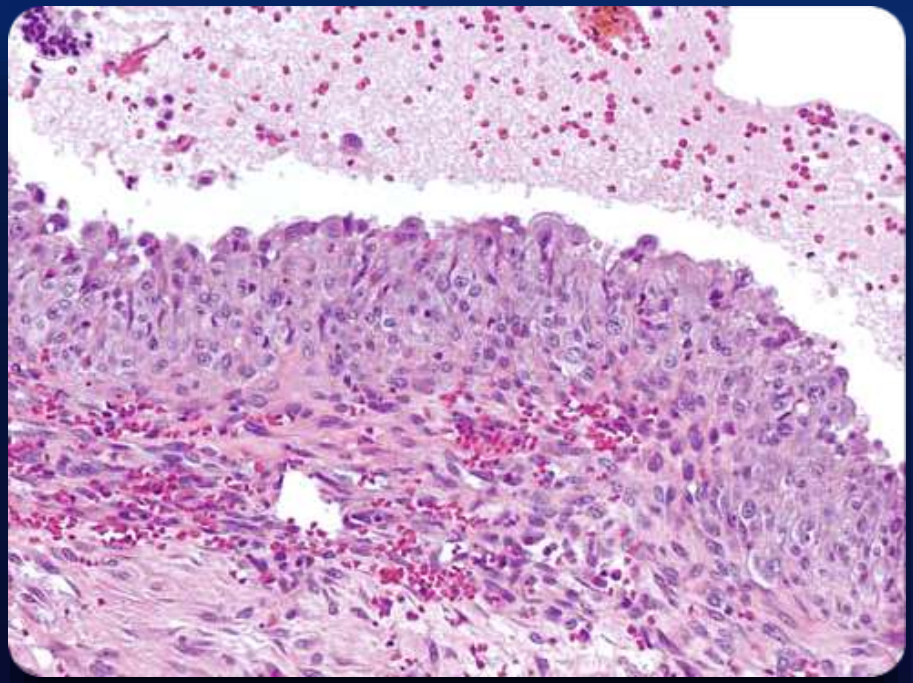
Is this a mucinous cyst?

Neoplastic mucin or GI mucin?

If there is abundant “gut” epithelium, be careful!

Pancreatic pseudocyst

- Clinical
  - Age: All ages (pancreatitis – older)
  - Males>Females
  - Tail more common
  - 2-30 cm
- Gross: fibrous, necrotic wall
- Chemistry: high amylase (usually in the 1000s U/l) and lipase, low CEA



Adsay NV. ModPathol (2007): 20:S71-S93

ncreatic pseudocyst tology

Patterns: **Inflammatory cells predominating without epithelial tissue fragments; Stromal fragments without epthithelial tissue fragments**

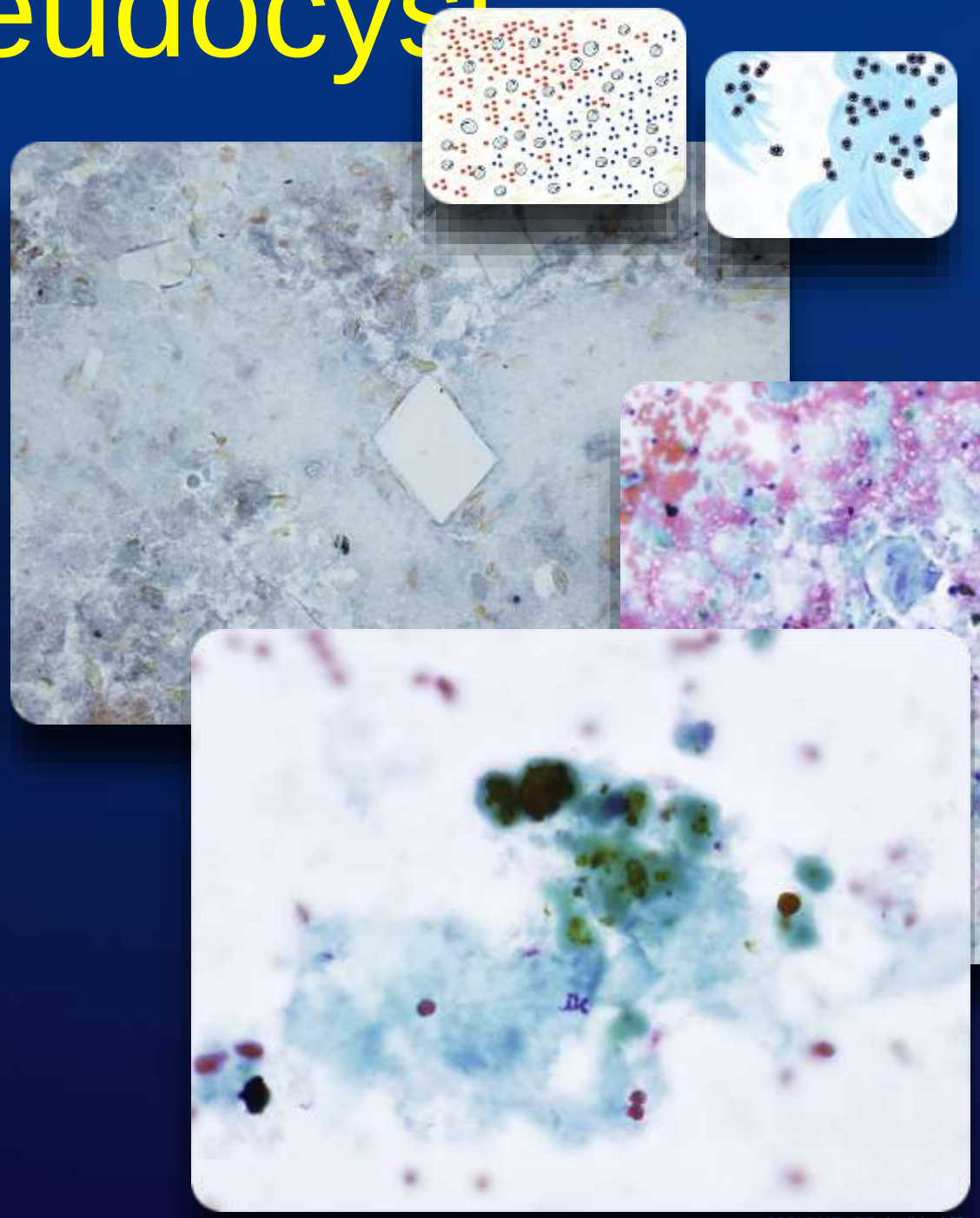
Hypocellular and lack epithelial cells; no serous or mucinous or lining epithelium

- GI contaminant common

Nonspecific cystic contents

Necrosis, protein debris, mixed inflammatory cells, mostly lymphocytes and histiocytes, including hemosiderin laden macrophages,cholesterol crystals

- granulation tissue uncommon

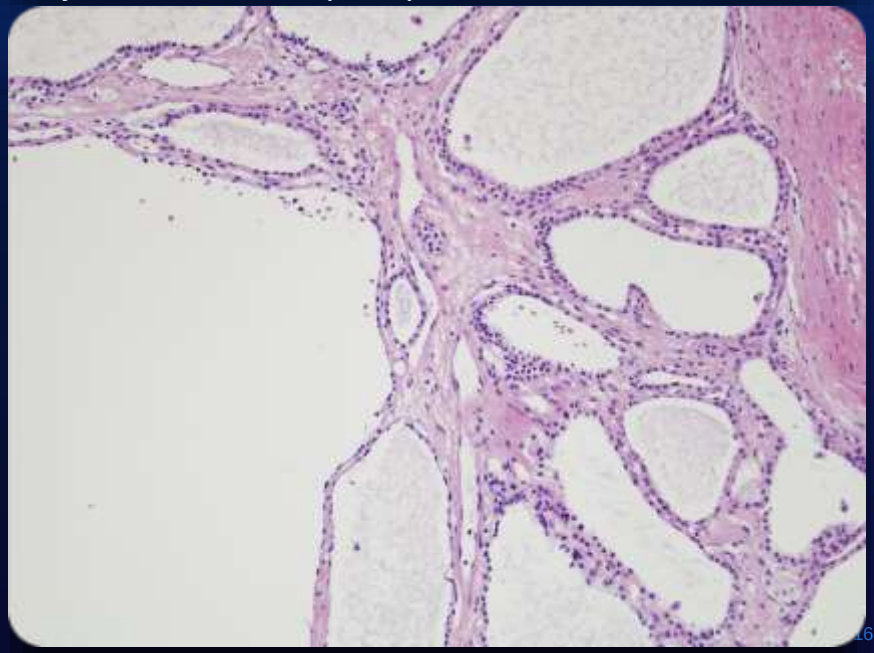


Serous cystadenoma

- Gender: more common in women than men (7:3)
- Older (average 61-68)
- Location: anywhere, ? predilection in the head
- Symptoms: abdominal pain and weight loss
- Prognosis: vast majority benign

- Gross: Numerous tightly packed small cyst and stellate scar; sponge-like
- Chemistry: low amylase (< 250 ng/ml and CEA (< 5ng/ml)

Adsay NV. ModPathol (2007): 20:S71-S93



rous Cystadenoma: tology

Patttern: Predominately discohesive epithelial cells with single cells.

Usual scant cellularity

Bloody aspirate; possible strands of fibrous, vascularized tissue. histiocytes and histiocytes with hemosiderin common

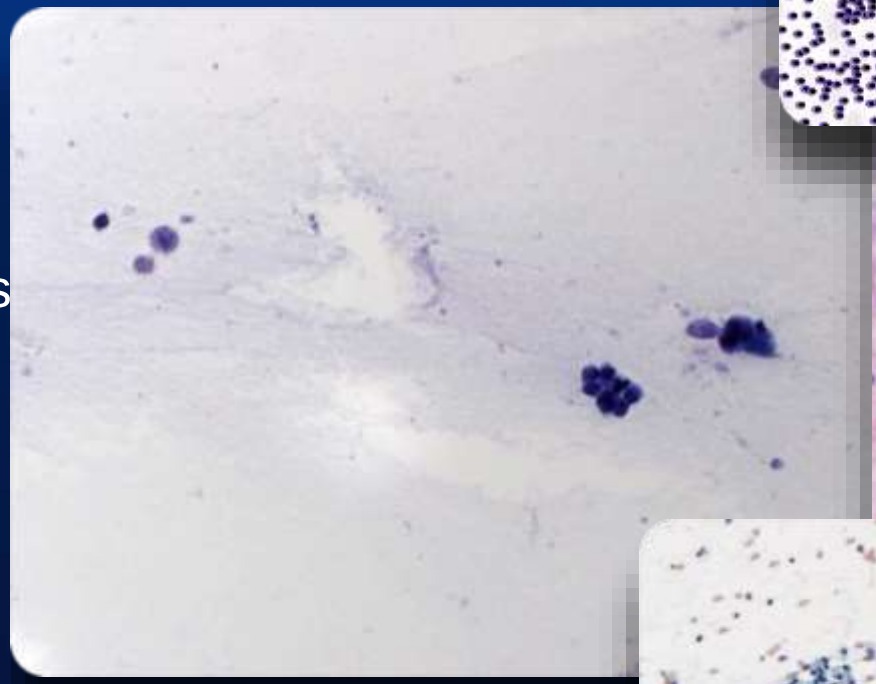
- usually absent in mucinous cysts

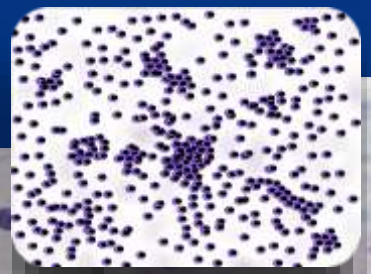
Delicate flat sheet of cuboidal, bland, serous-type epithelium

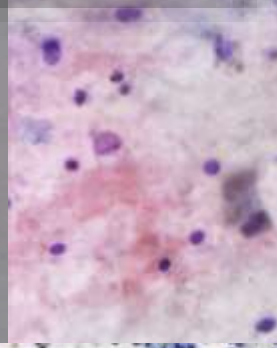
- often not present
- liquid based preps may preserve lining cells better

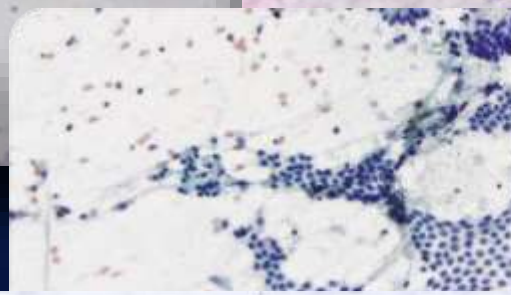
Lining cells with bland, centrally located nuclei, and may have nuclear grooves

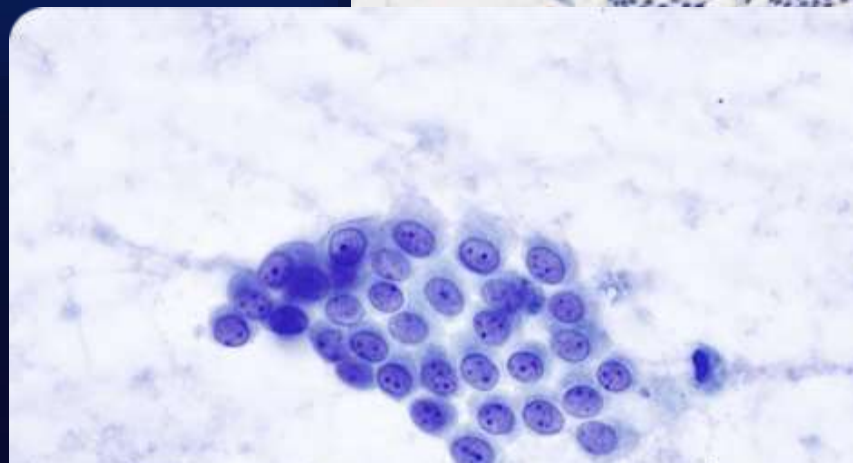
- mimic benign mesothelial cells





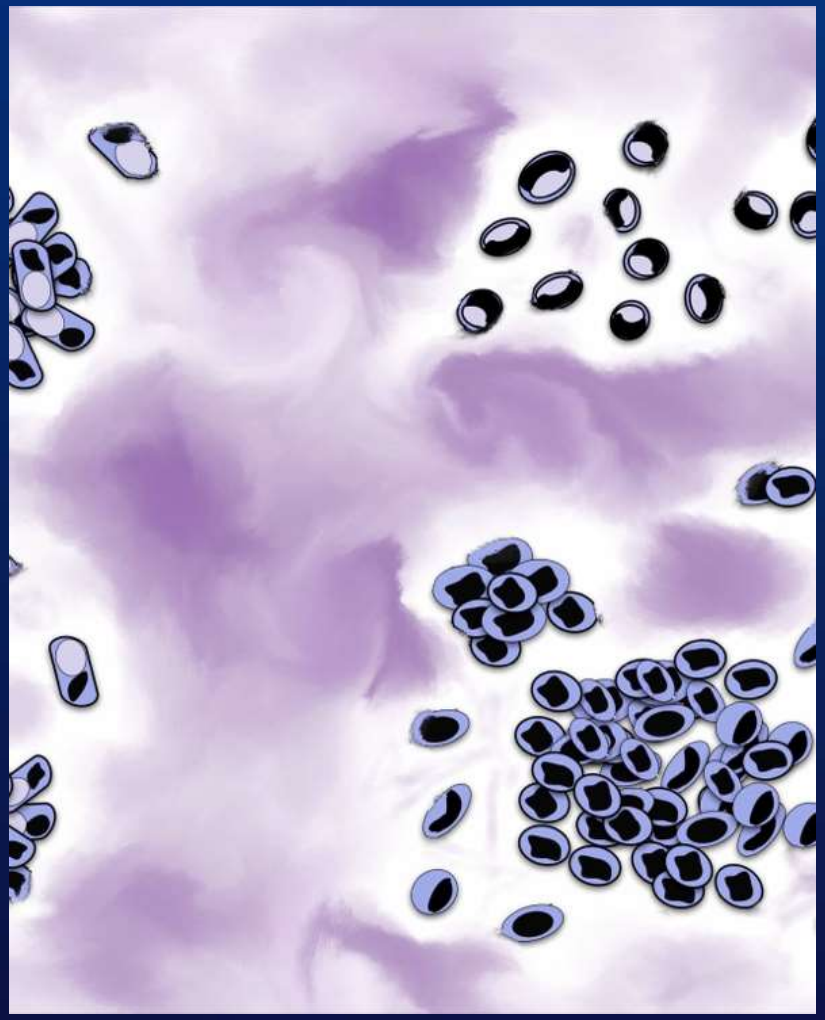






Mucinous Background

- **Benign**
  - Gastric epithelium
  - Duodenal epithelium
  - Squamoid cyst of pacnreatic ducts
- **Neoplastic**
  - Mucinous cystic neoplasm
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm
- **Malignant**
  - Mucinous non-cystic adenocarcinoma
  - Signet ring carcinoma



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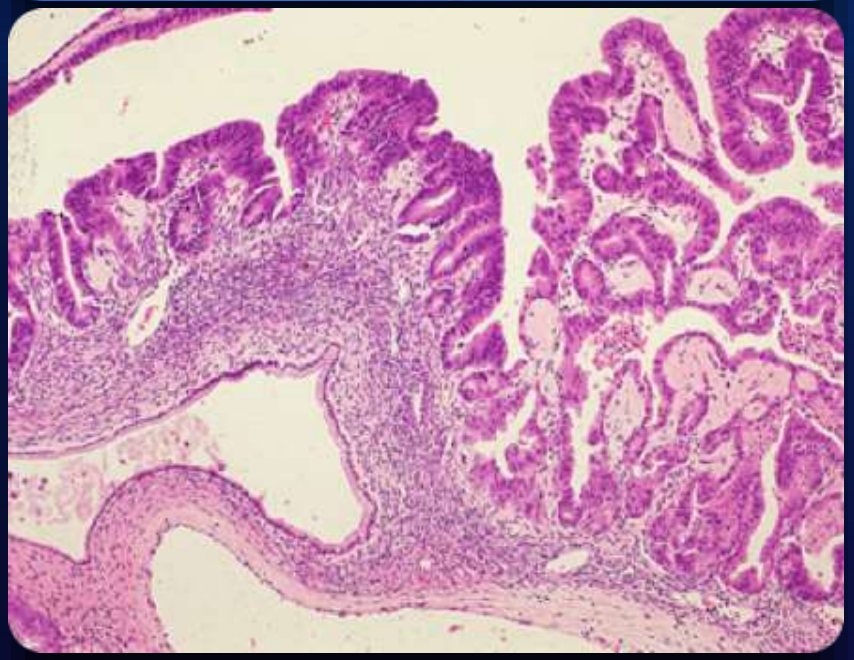
Mucinous Cystic Neoplasm

- Clinical
  - Gender: much more common in women than men
  - Age: mean age at diagnosis 50
  - Location: Tail > head
- Gross: Thick fibrous wall, multicystic; usually larger than 2cm
- Lined by glandular cells and ovarian stroma; septae; may show calcifications
- Chemistry: low amylase, high CEA



Adsay NV. ModPathol (2007): 20:S71-S93

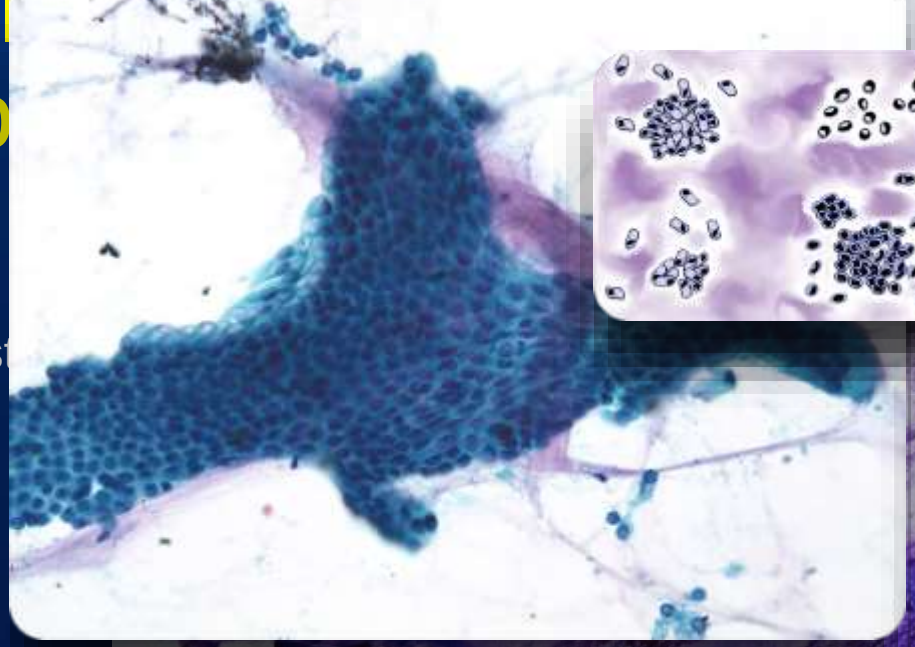
Intraductal Papillary Mucinous Neoplasm (IPMN)

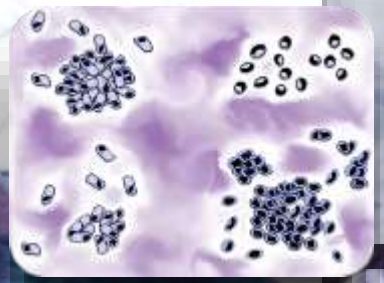
- Clinical
  - Male >> Female
  - Mean age 68
  - Location: Head (89%)
- Gross: Localized, multicentric, important to document relation with pancreatic ductal system
  - Cystically dilated ducts containing mucin with various degrees of atypia
- Chemistry: High amylase, high CEA (>192 ng/ml)
- Imaging: communicate with pancreatic duct system
  - – mucin oozing from the ampulla of Vater

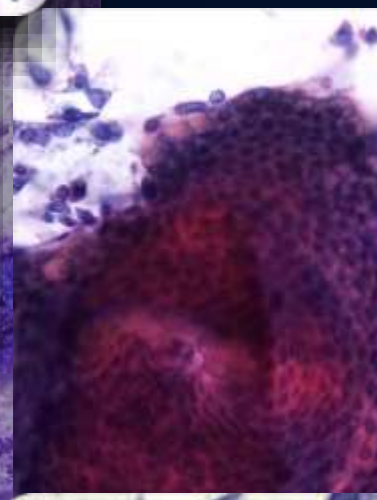
ntraductal Papi
Neoplasm: Cyto

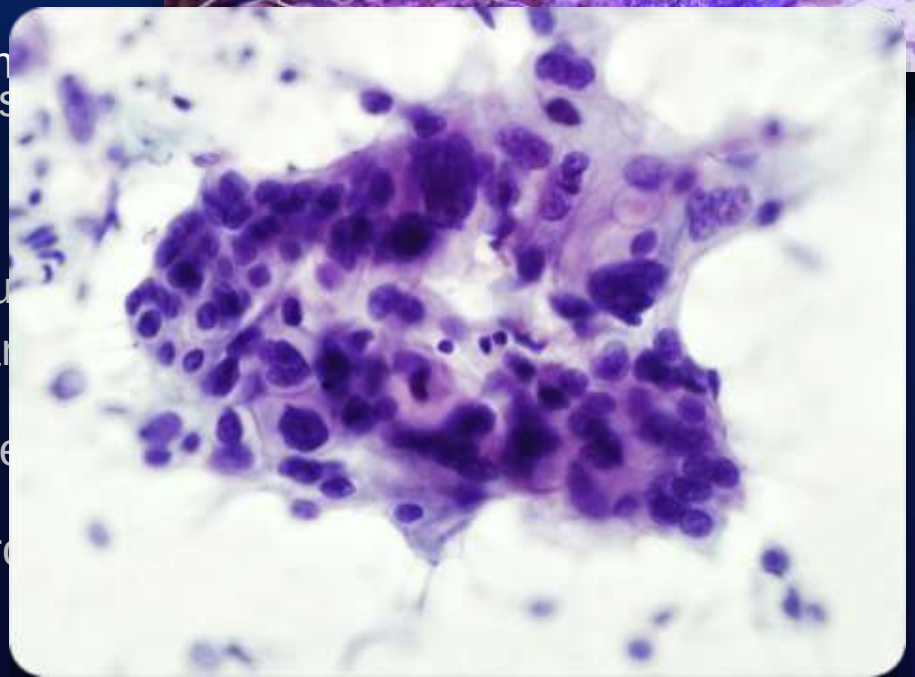
attern: Mucinous background

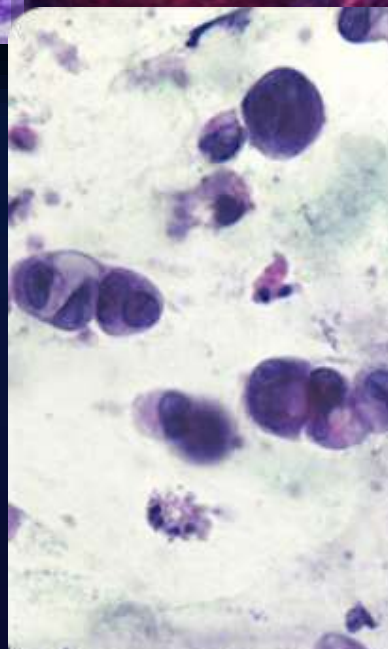
- hick mucus; foamy histiocytes
- ngle cells, flat sheets, small clust
- w vs high cellularity
- oblet cells
- ypia
- Low grade (low-intermediate dysplasia)
- High grade (high grade dysplasia)
  - 3D architecture
  - Variable amount of cytoplasm w/o visible mucin or vacuoles
  - 2-4 tight buds of cells
  - High N/C ratio
  - Mild-moderate nuclear irregu
  - Hypo or hyperchromasia, var nucleoli
  - Scant to moderate cellular ne
  - Small single cells (< 12 micron duodenal entero





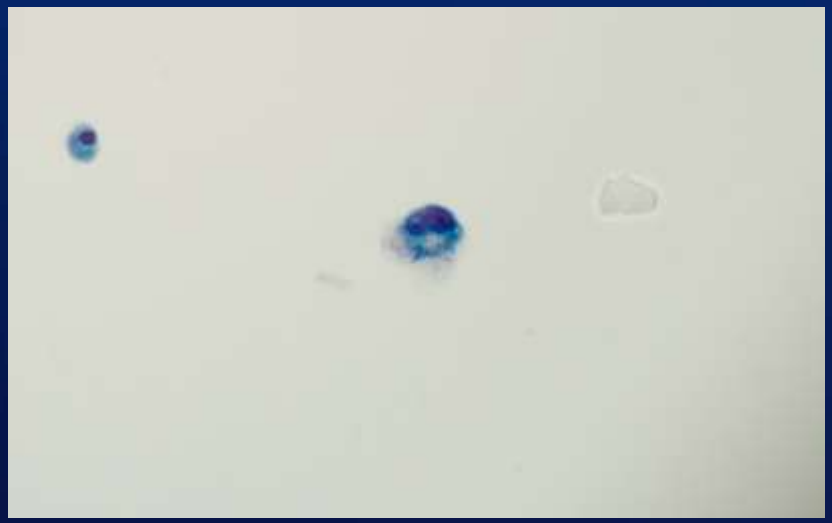






Case …

63 yo male with UC
Multiple cystic pancreatic lesions since 2018
2019 Pancreas FNA



MAYO CLINIC

Atypical cells present

Atypical mucinous epithelium, cannot exclude high grade dysplasia

Follow up MRI

- Stable pancreatic tail cystic lesions communicating with pancreatic duct measuring up to 1.4 cm
- No pancreatic ductal dilatation, no atrophy.
- Clinical impression “IPMN indeterminate for atypia”
- Distal pancreatectomy recommended, but patient decided on conservative management.
- Patient still alive 2022
- No worrisome imaging findings
- Follow-up MRI/MRCP in 1 year

MAYO CLINIC

- Invasive ductal adenocarcinoma, moderately differentiated arising in a background of high grade pancreatic intraepithelial neoplasia (PanIN- 3)

MAYO CLINIC

Standardized Terminology and Nomenclature for Pancreato- Biliary Cytology

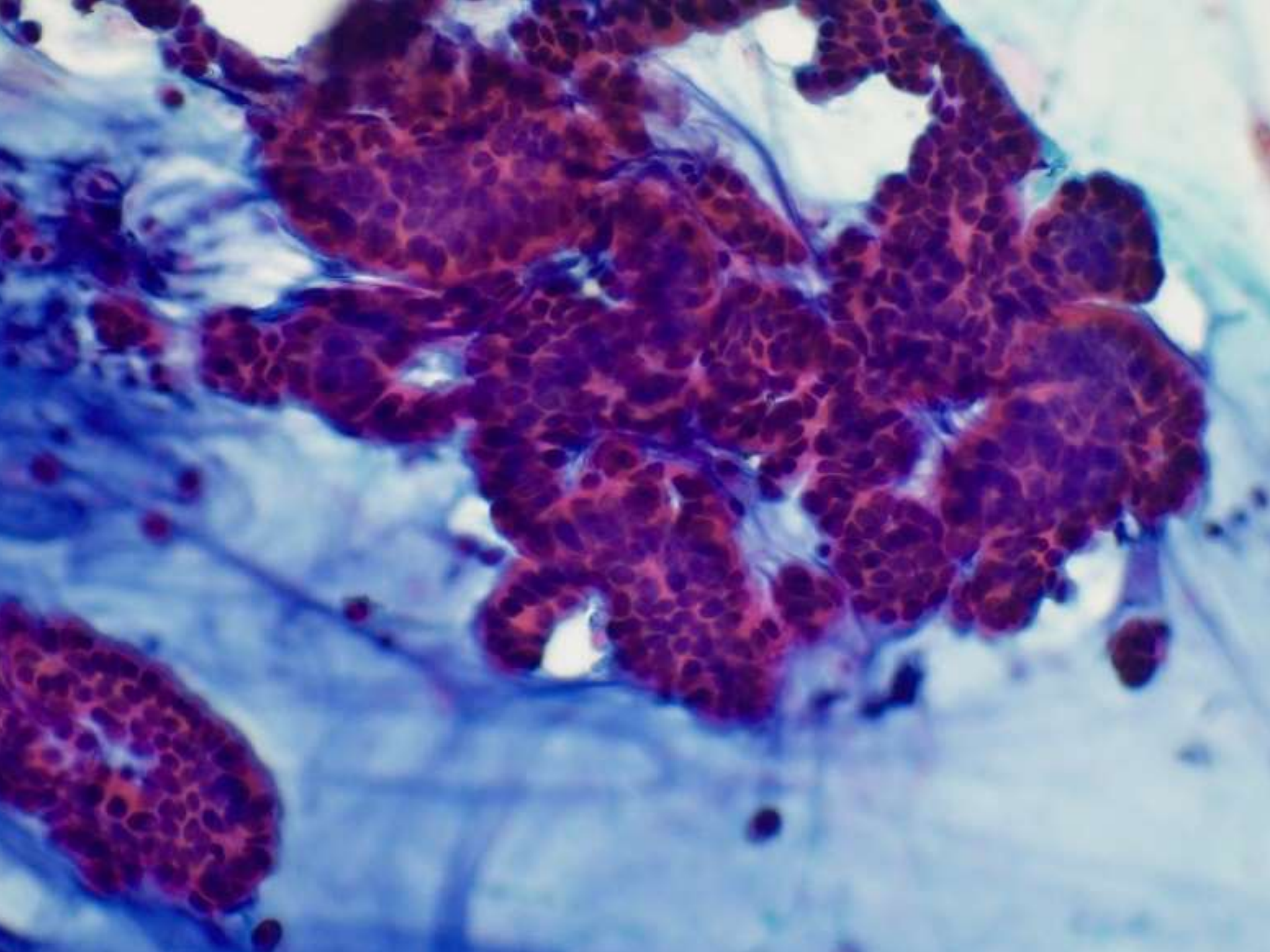
- I. Non- Diagnostic
- II. Negative for malignancy
- III. Atypical
- IV. Neoplastic:
  - Benign (serous cystadenoma)
  - Other:
    - Mucinous cysts (low- and high- grade dysplasia)
    - Well- differentiated neuroendocrine tumors
    - Solid- pseudopapillary neoplasm
- V. Suspicious for malignancy
- VI. Positive for malignancy

MAYO CLINIC

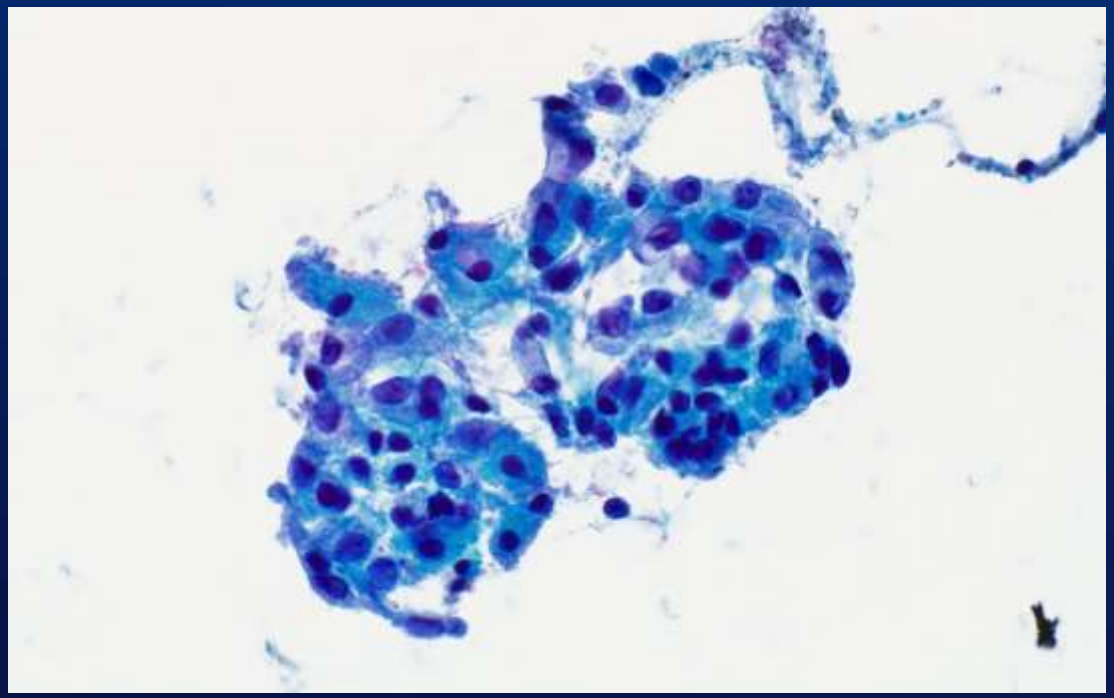
LG IPMN

- Flat sheets, papillary groups
- Bland nuclei or mild atypia
- Abundant colloid like thick mucin in the background
- Radiology:
- Cystic lesions with communication with the main duct, or main duct IPMN
- Chemistry/ molecular analysis:
- High CEA (196ng/mL), amylase is variable
- KRAS mutation common in mucinous

MAYO CLINIC

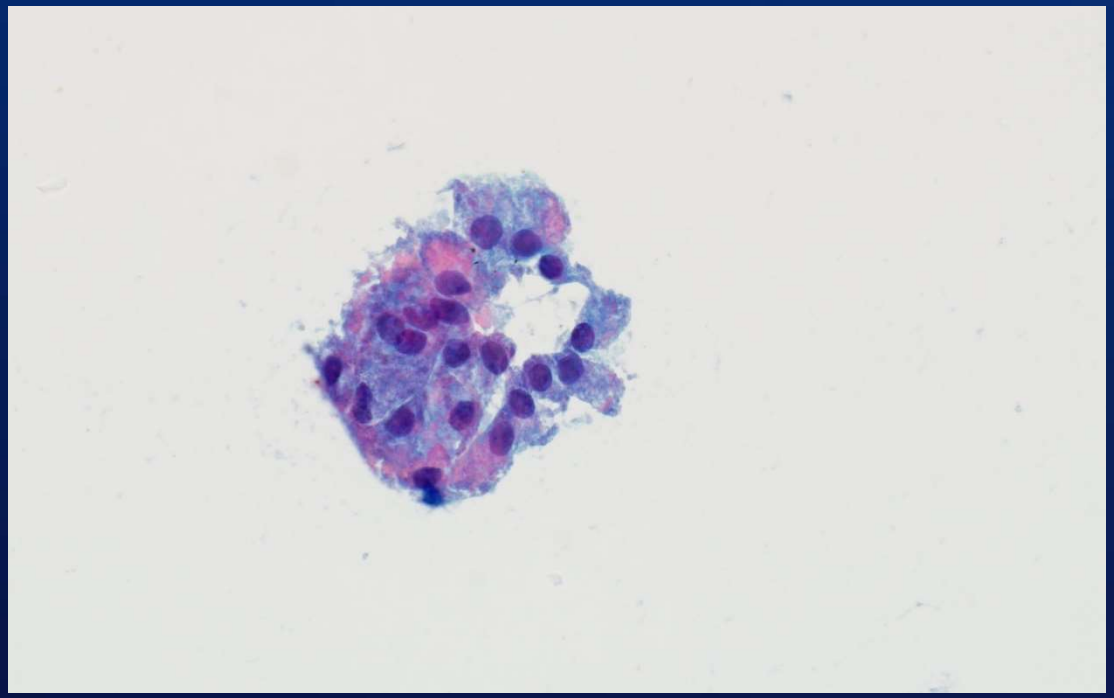


Another IPMN



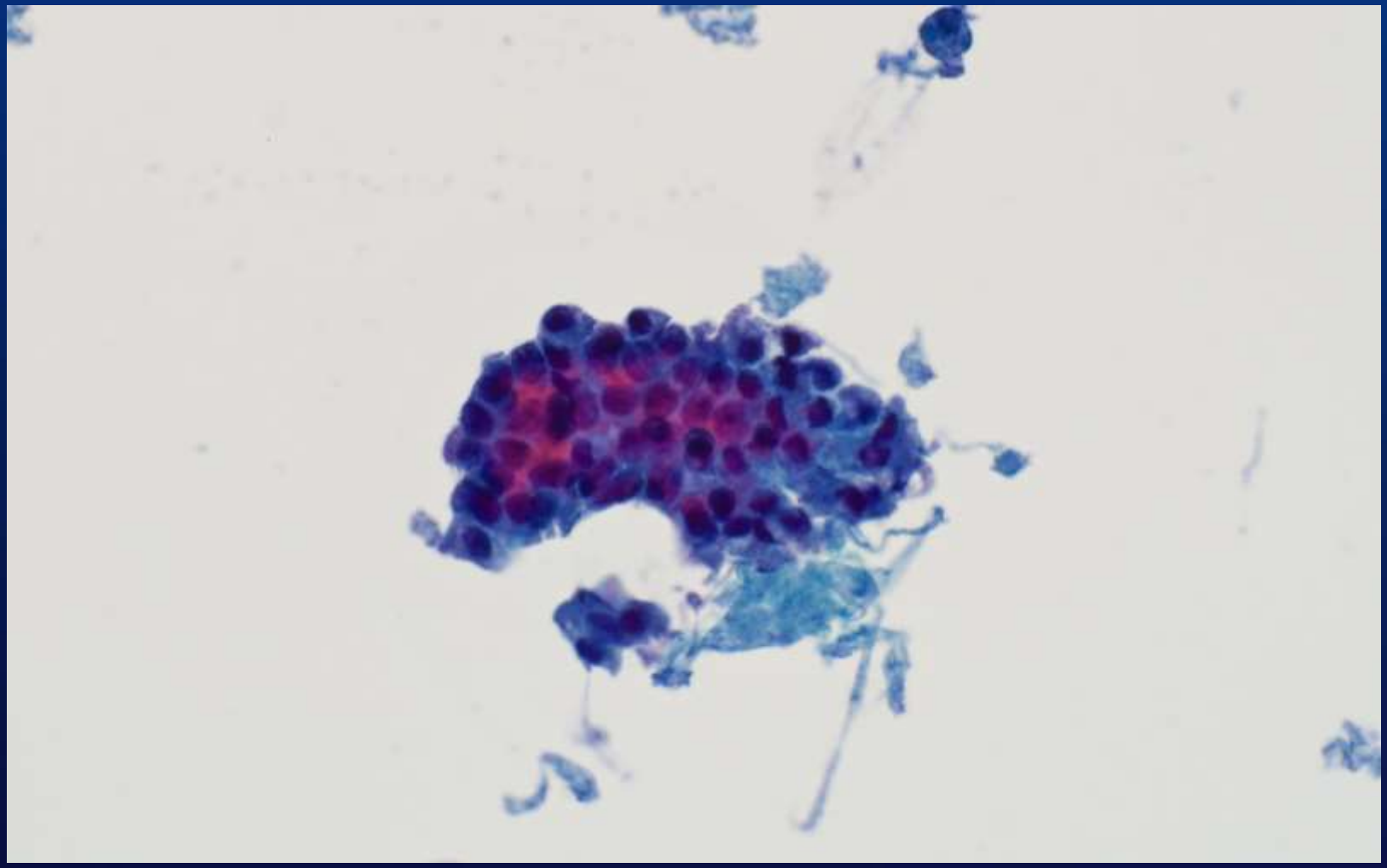
MAYO CLINIC

Another case (same as prior)

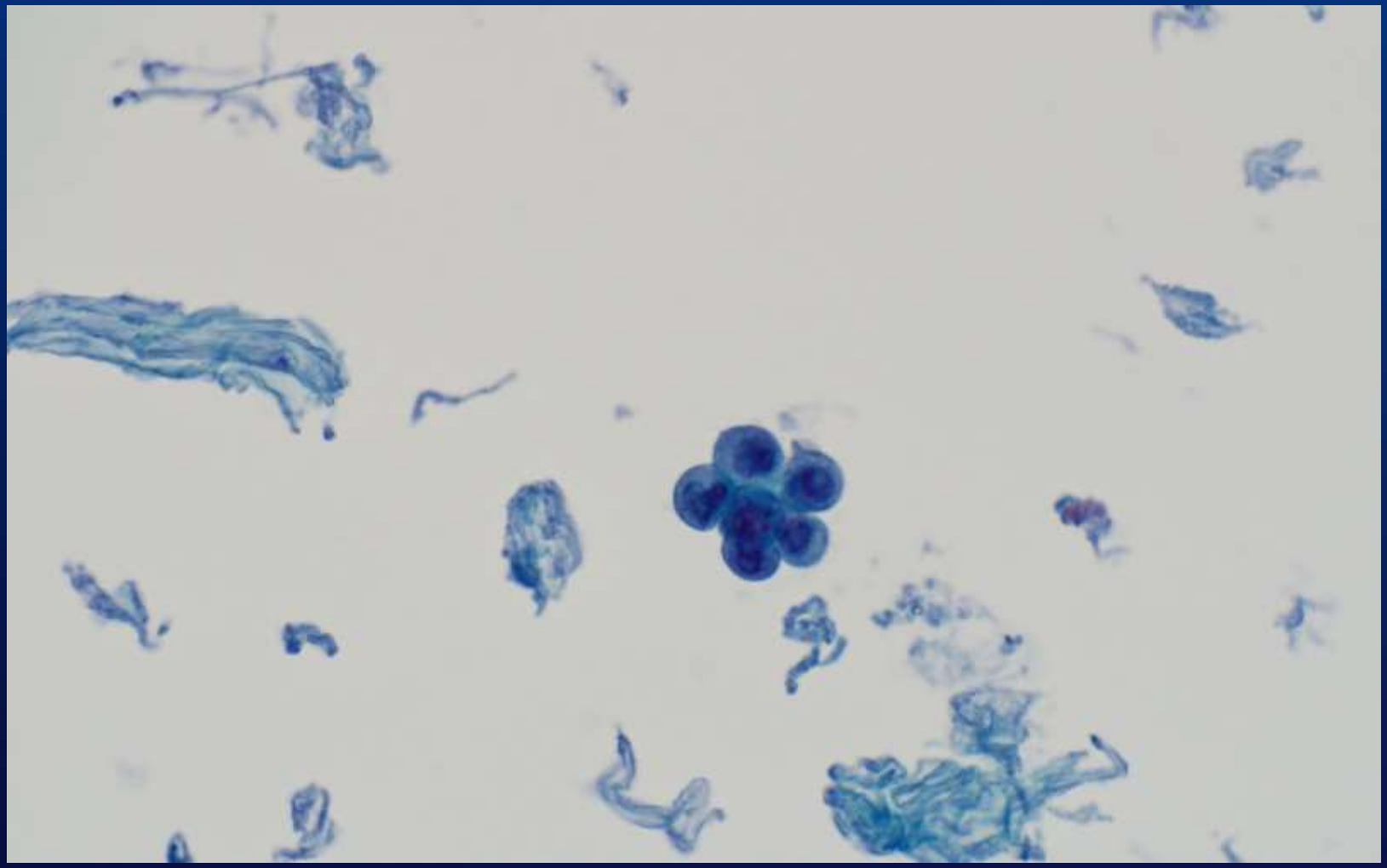


MAYO CLINIC

Another case ipmn w hgd



MAYO CLINIC



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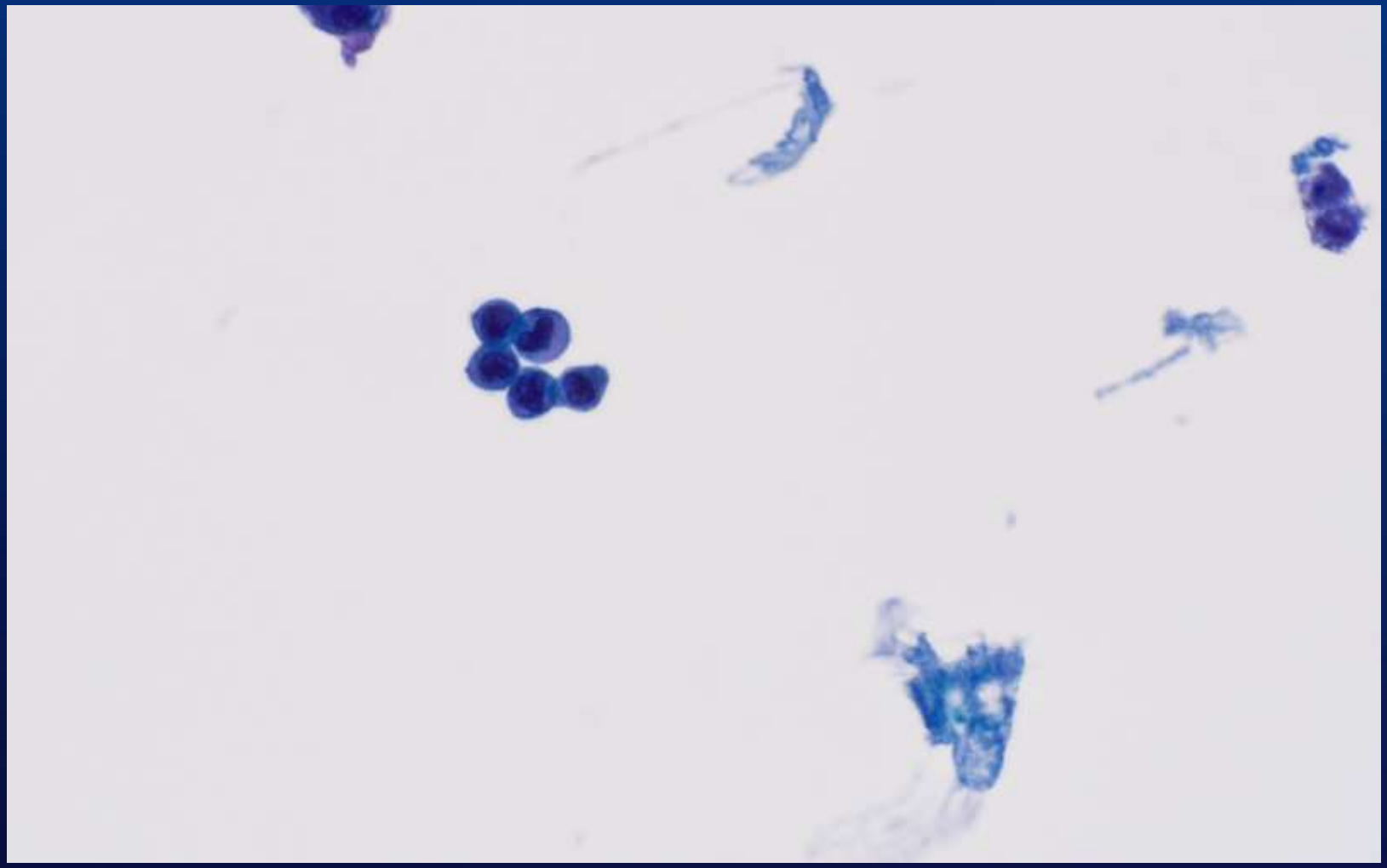

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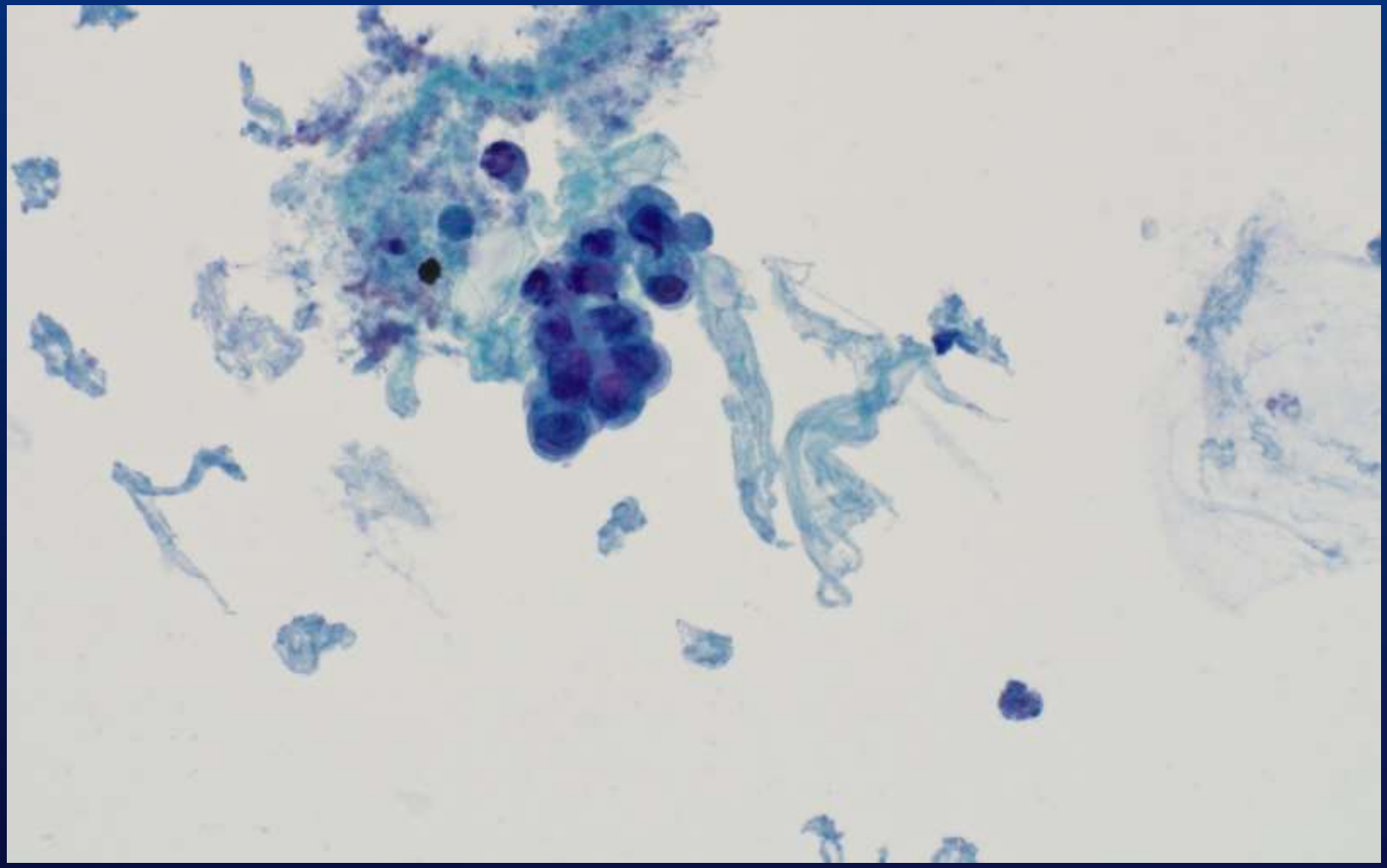

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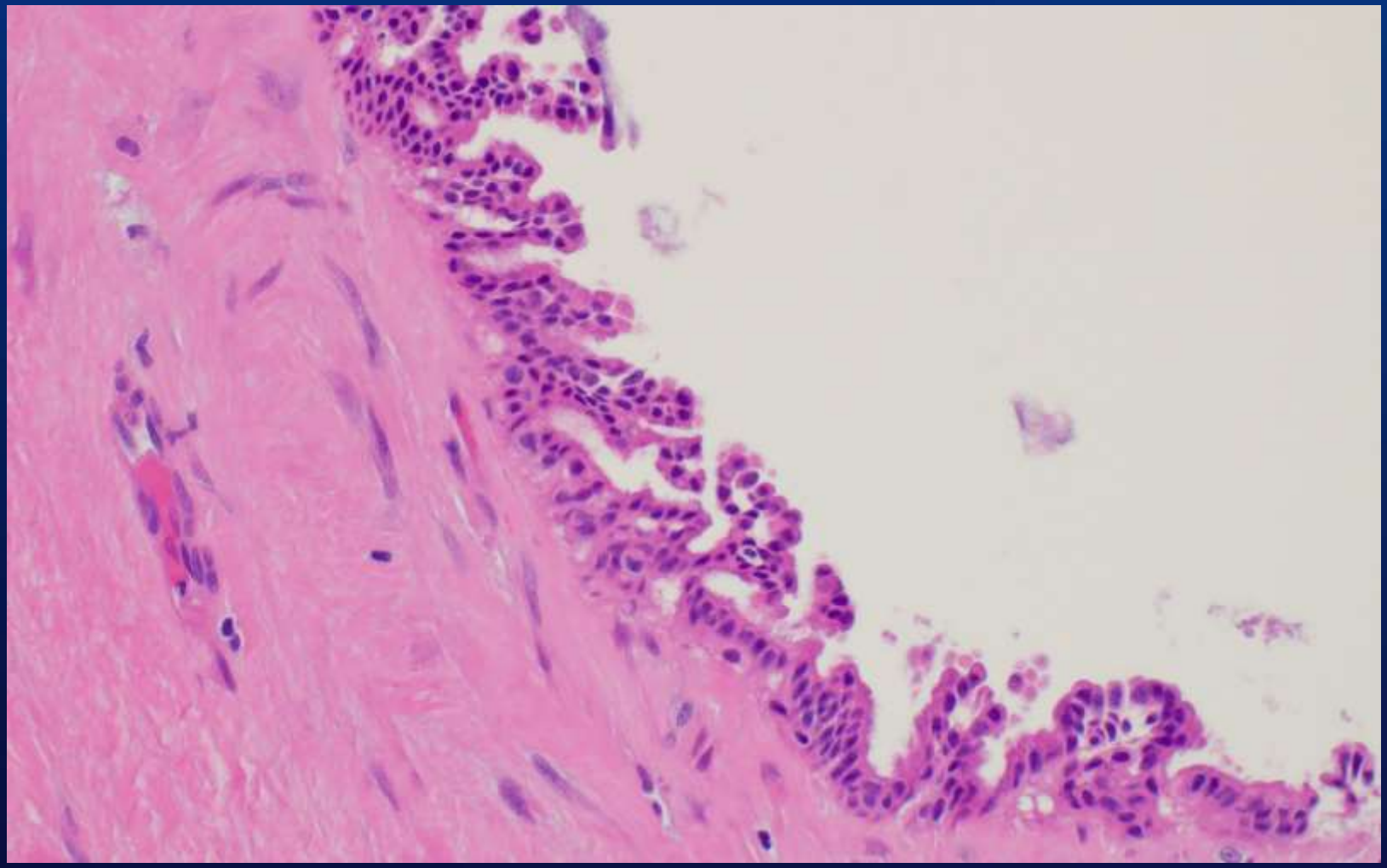

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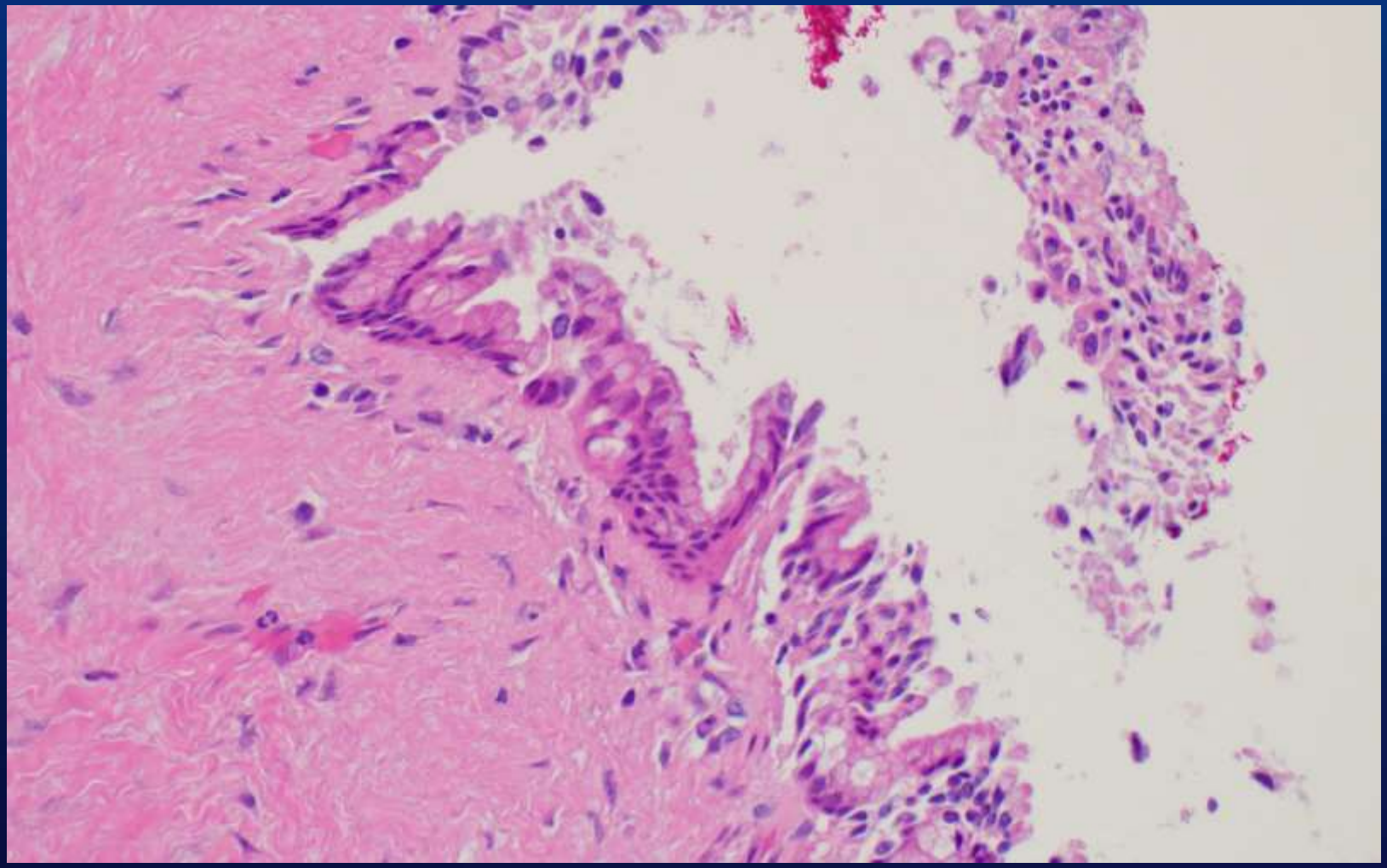

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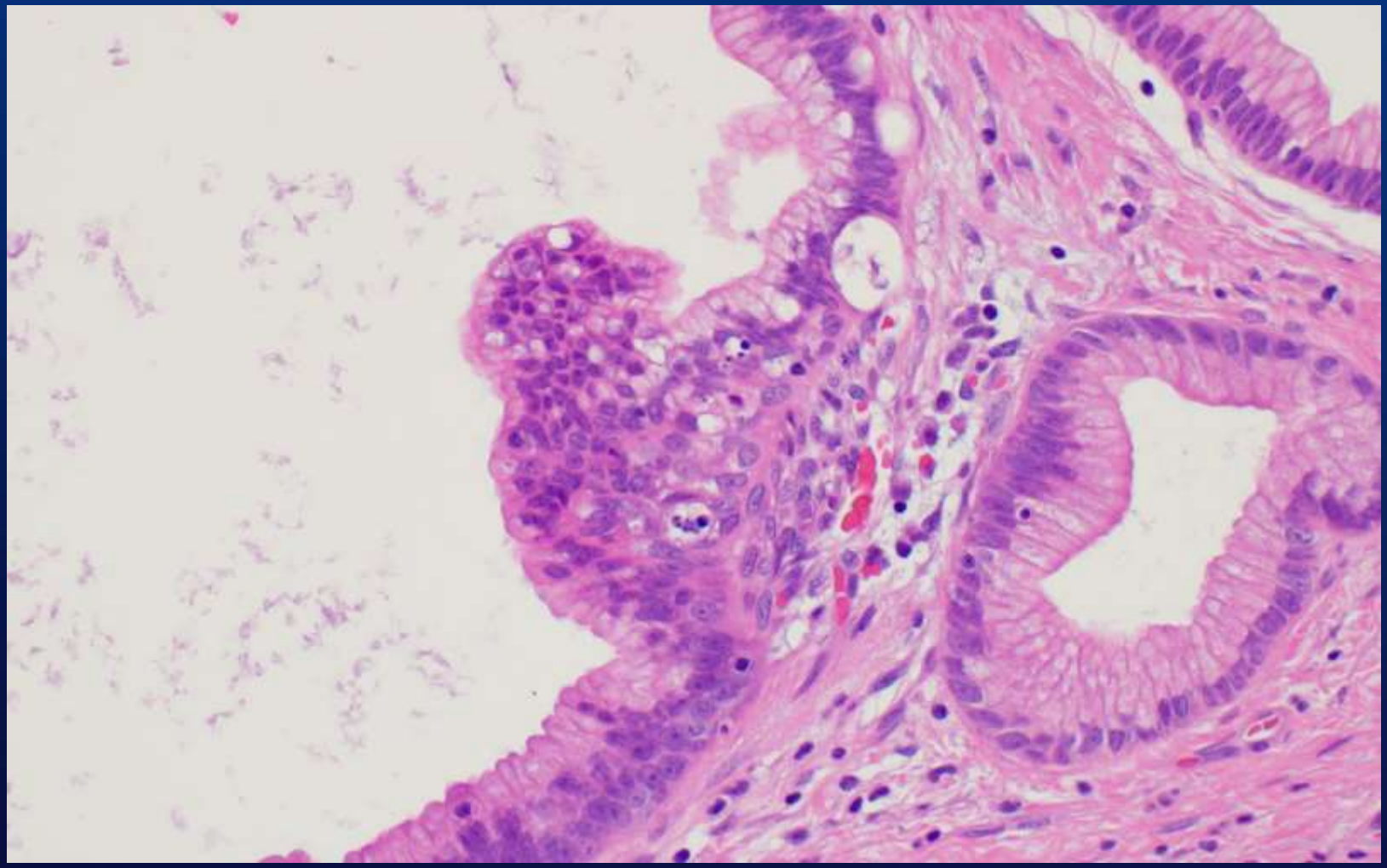
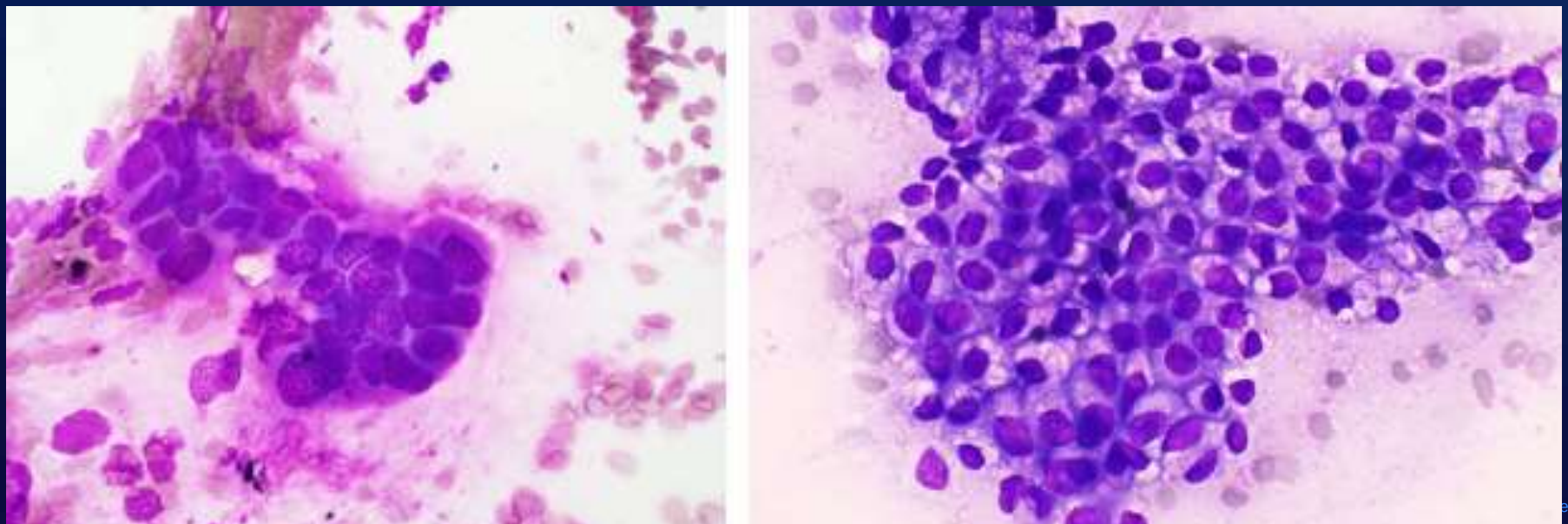


MAYO CLINIC

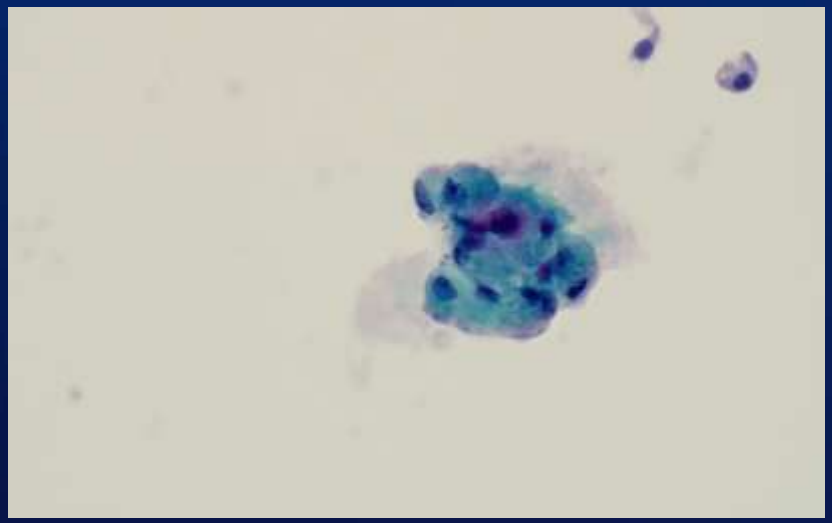
IPMN HG vs LG Dysplasia

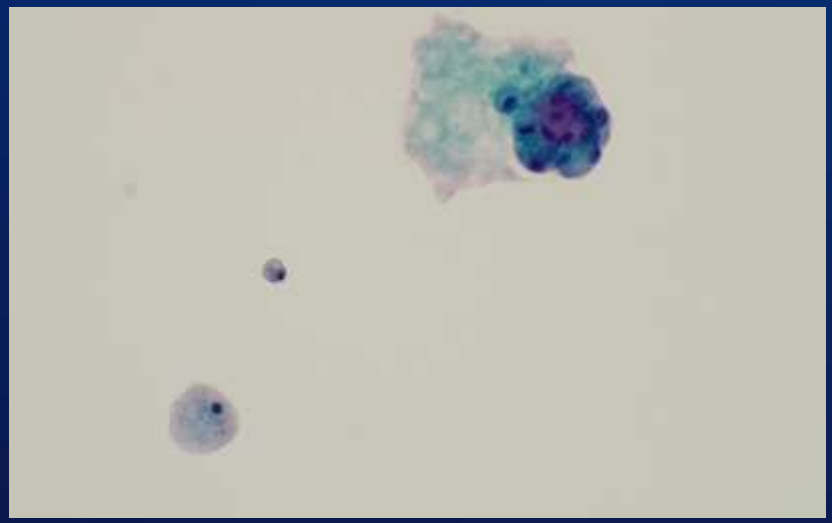
- High N/C ratio, “small”cells, variable cytoplasm
- Nuclear atypia (irregularity, hyper or hypochromasia)
- Loss of nuclear polarity
- Single cells or complex architecture (3D, 2-4 tight buds of cells)
- Less/ scant background mucin, -/+ necrosis

- Uniform cells
- Bland or mild nuclear atypia
- No architectural complexity
- Intracytoplasmic mucin
- Abundant extracellular mucinous material



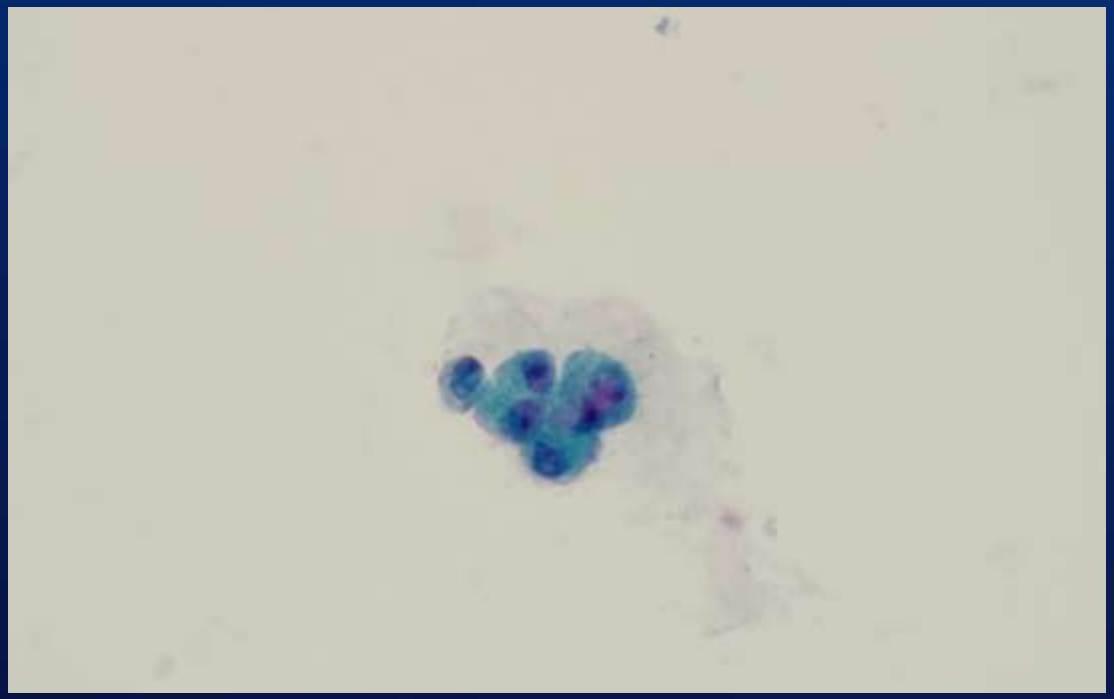
Another case highly atyp cells susp colloid ca CEA 11500 cw IPMN clinically





MAYO CLINIC

Same case



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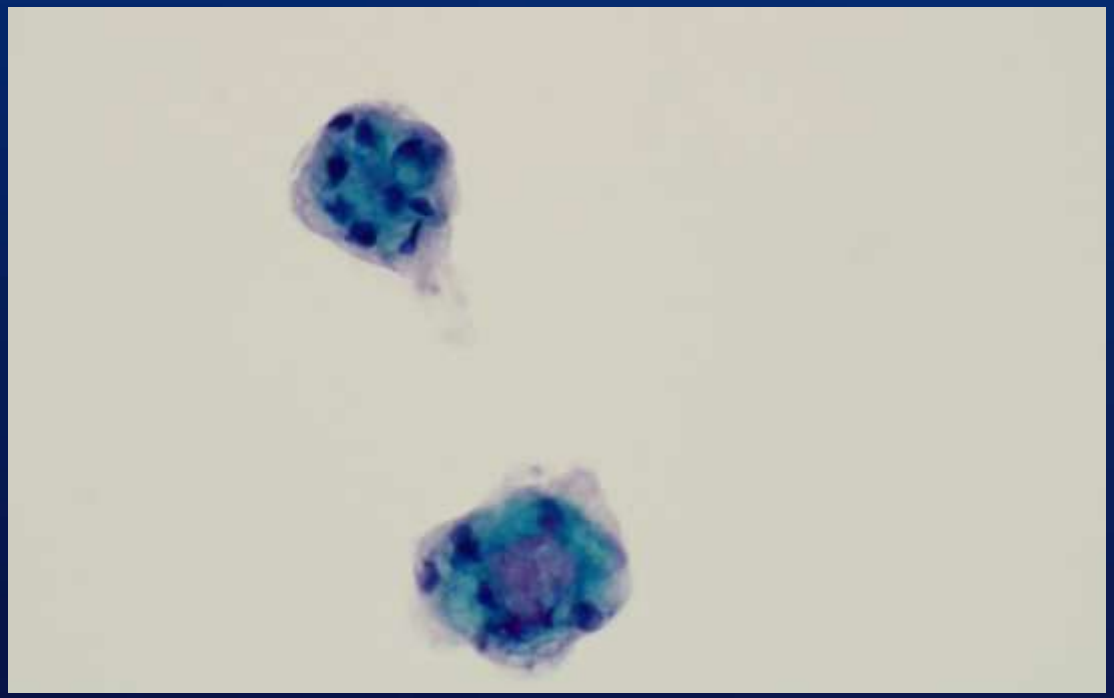
Same

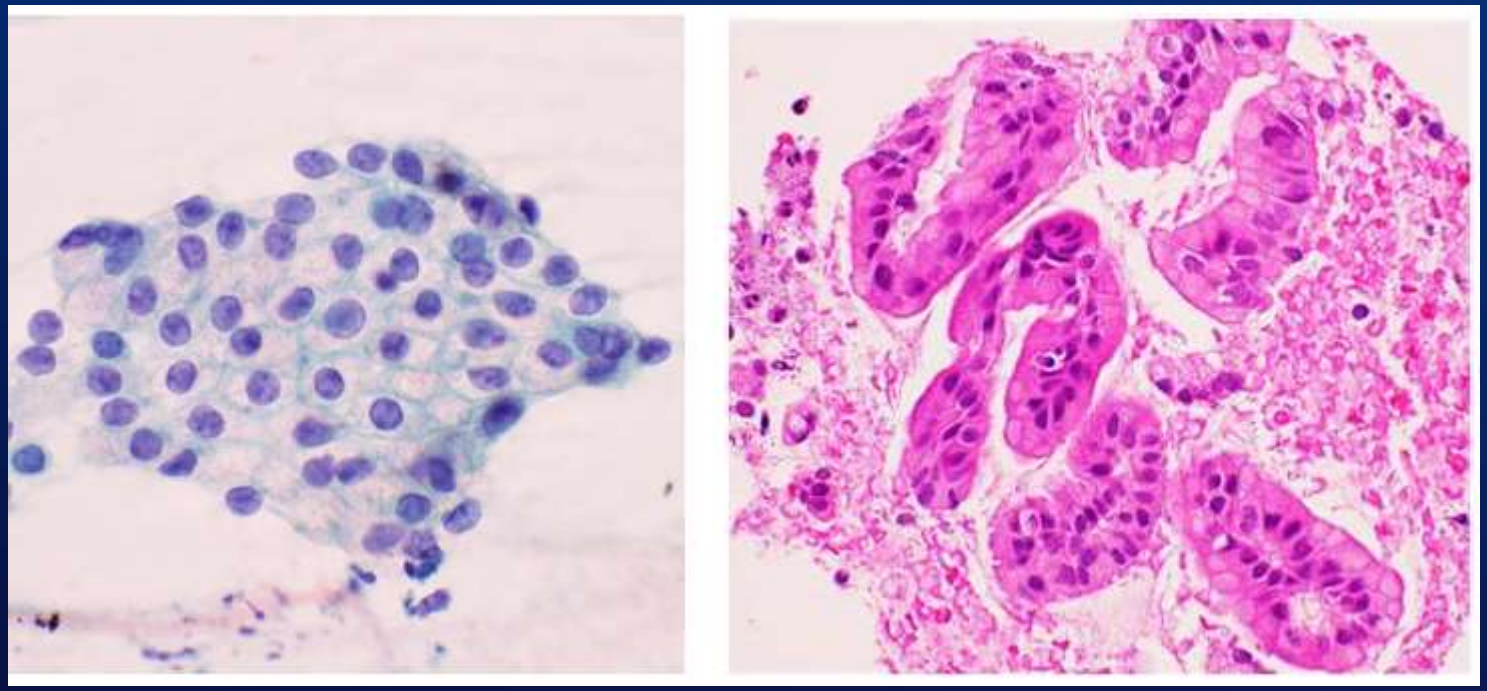


MAYO CLINIC

Same

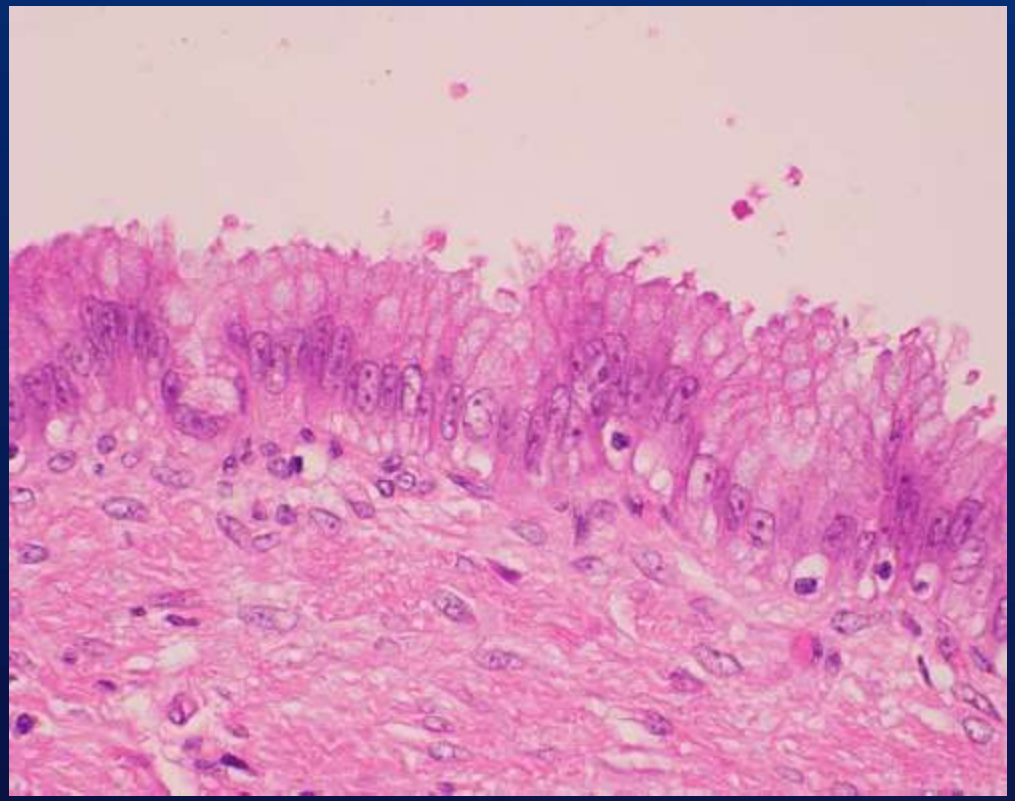
MAYO CLINIC

DO NOT DELETE MCN (ASC Meeting)



MAYO CLINIC

DO NOT DELETE EP slimier to CB of case w atyp cannot r/o adeno, but this MCN ASC Meeting more organizezed, no loss of polarity

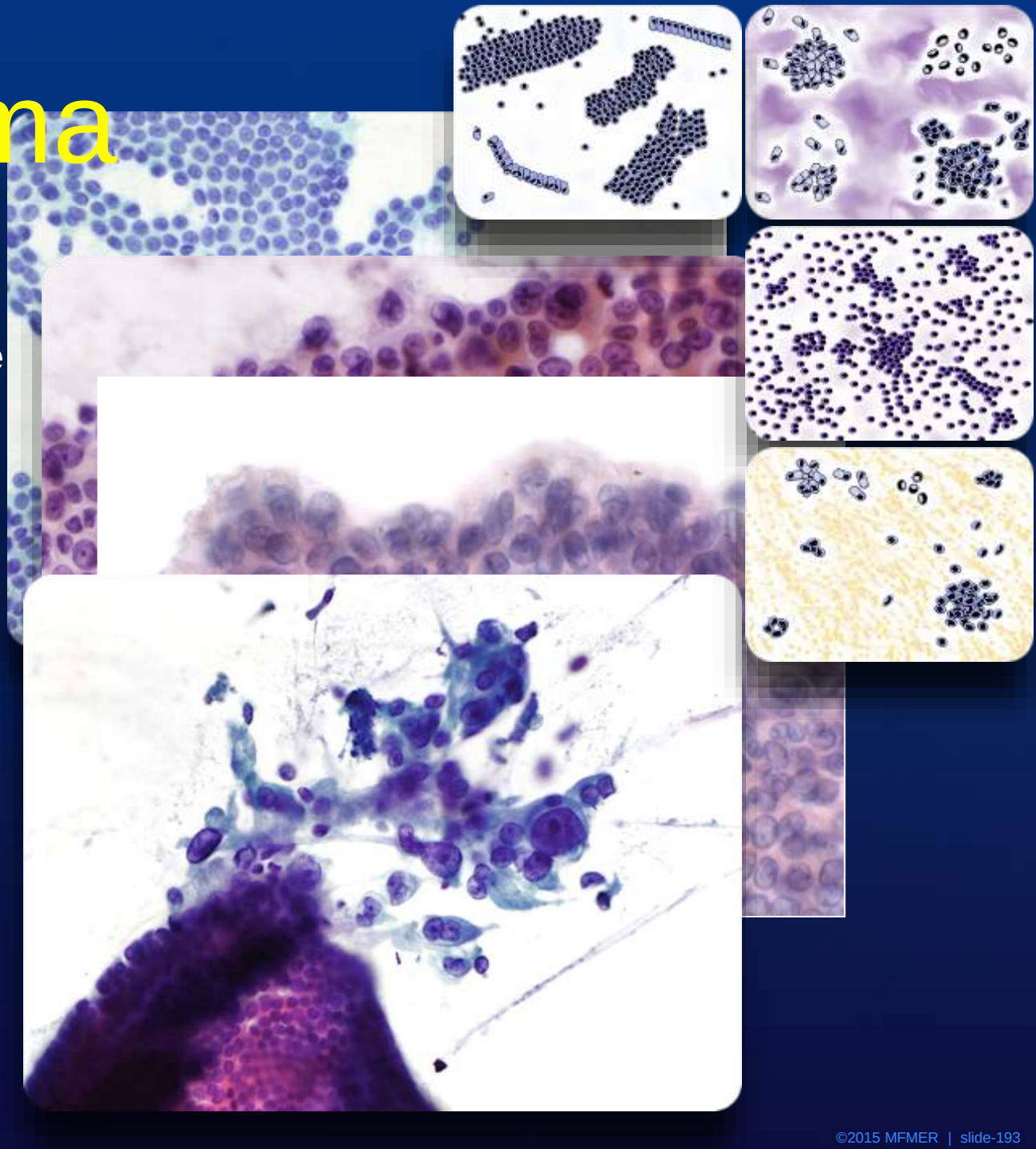


MAYO CLINIC

nocarcinoma

Patterns: Predominately cohesive epithelial or ductal-type tissue fragments; Mucinous background; Predominantly discohesive epithelial cells with single cells; Dirty or Necrotic Background

- Major criteria
  - Nuclear overlap and crowding
  - Nuclear contour irregularity
  - Chromatin clearing or clumping
- Minor criteria
  - Single epithelial cells
  - Necrosis, mitosis
  - Nuclear enlargment



Acta Cytol, 1995; 39:1-10

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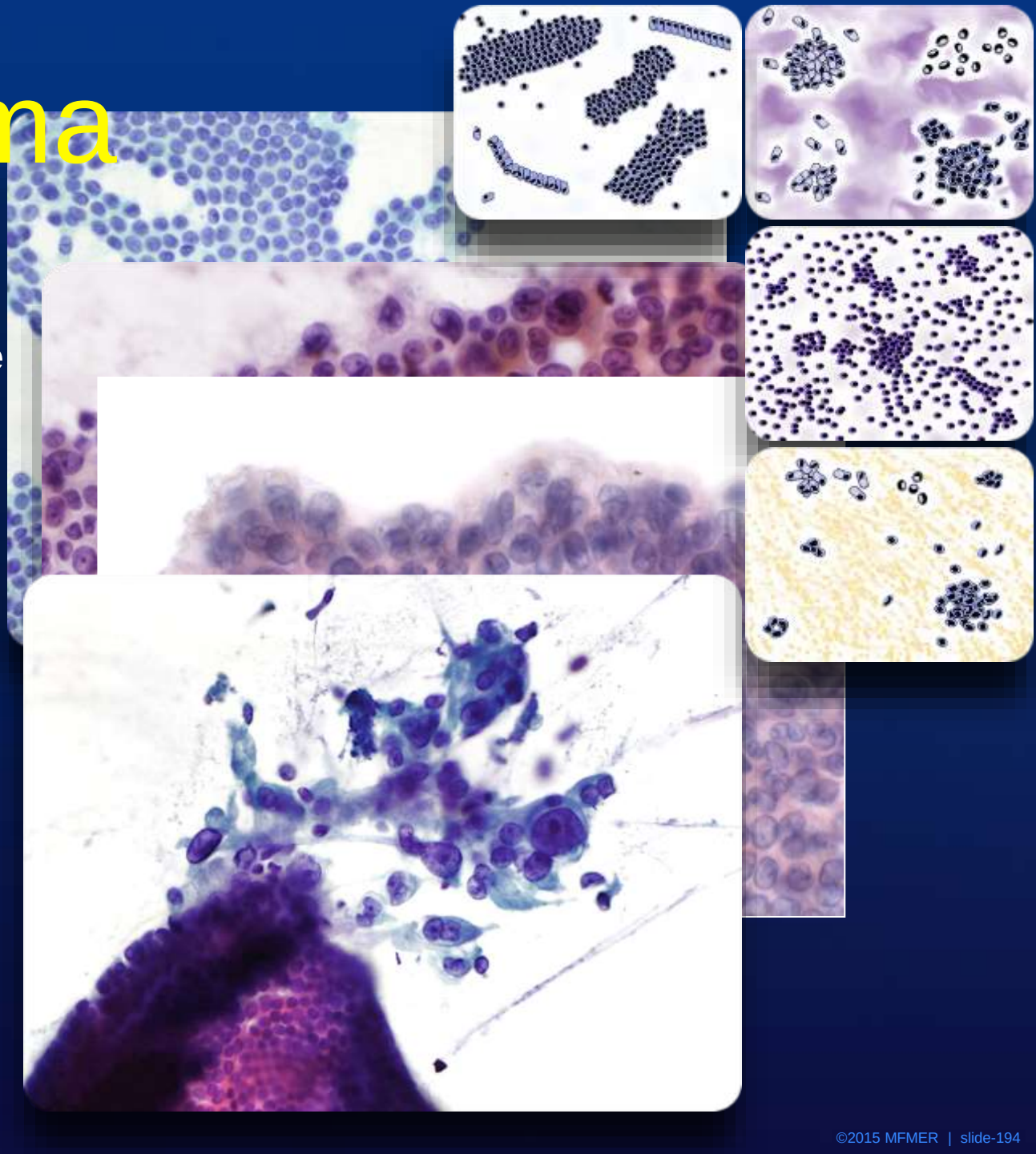
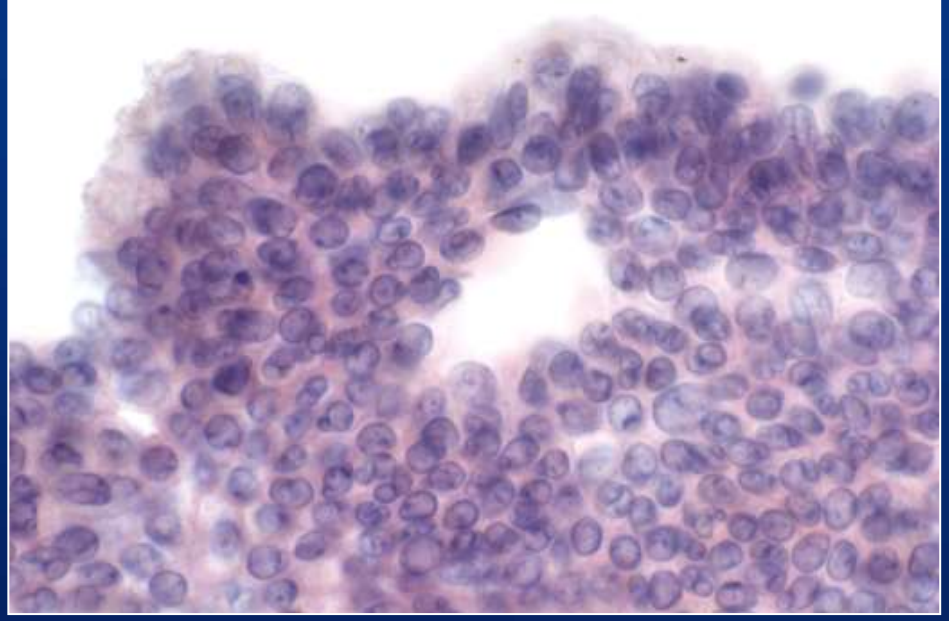
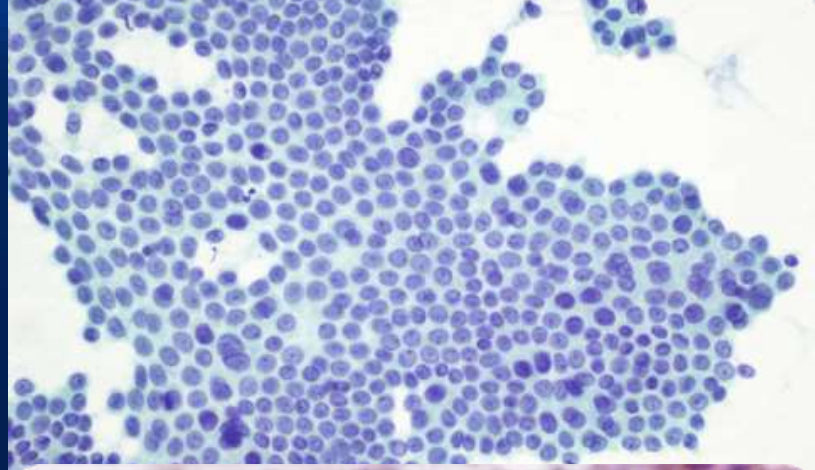
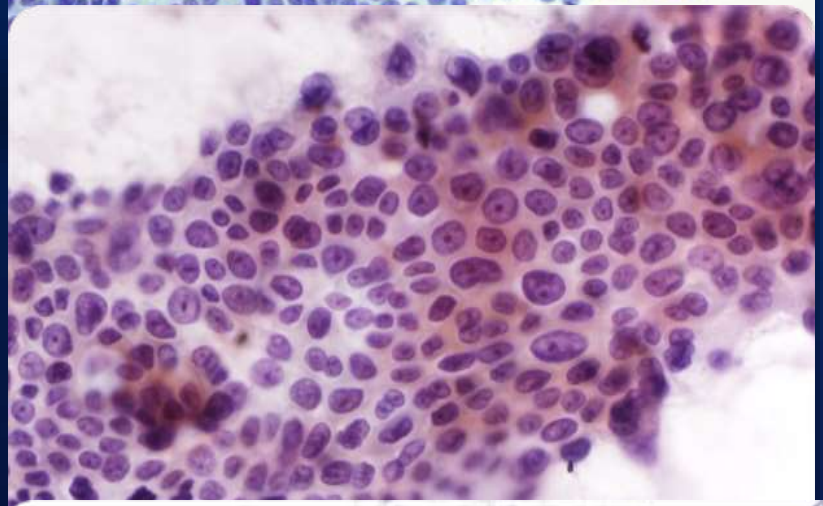
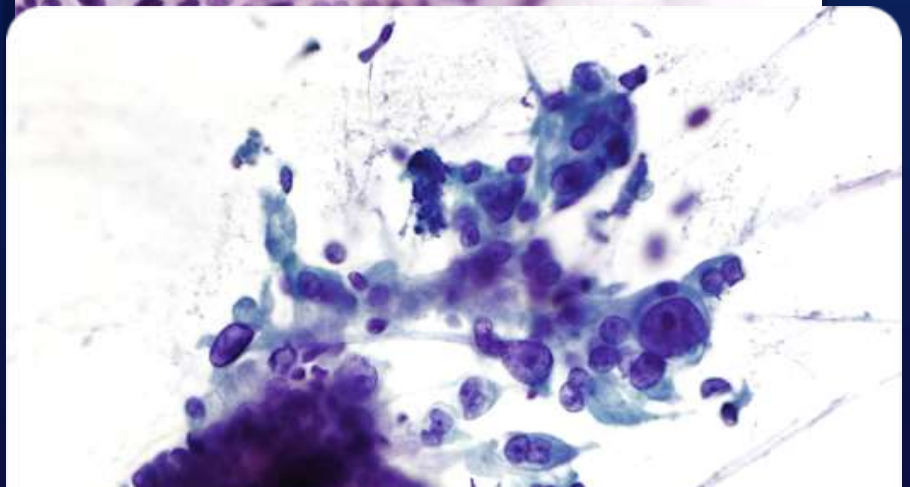


Acta Cytol, 1995; 39:1-10









Crowding/ overlapping/ 3D, single cells, drunken honeycomb

Nuclear features:

- Enlargement, anisonucleosis (4:1), membrane irregularity, clearing/ hyperchromasia, macronucoli

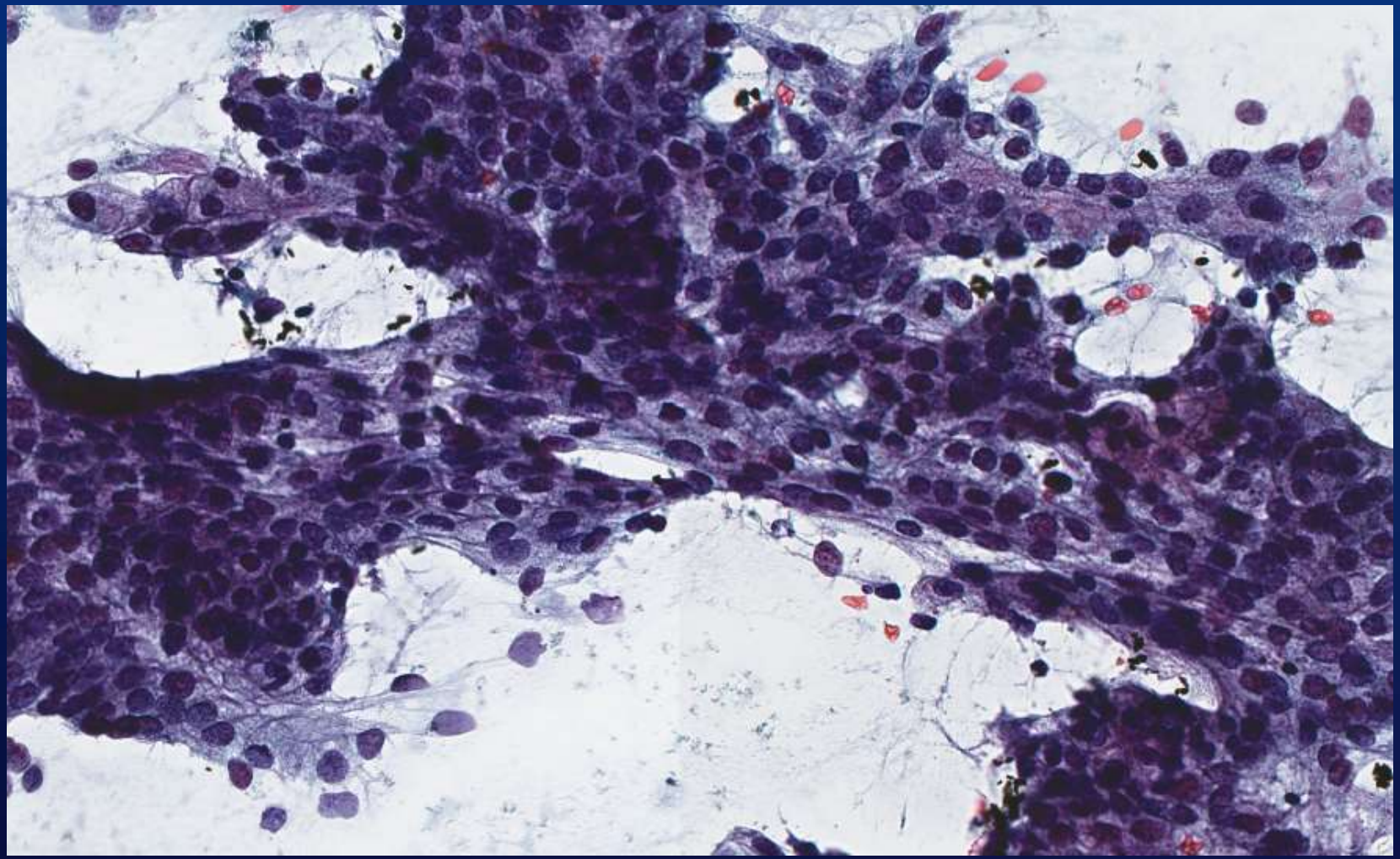
Cytoplasm:

- Scant or abundant- mucinous

Necrosis, mitosis, single cells

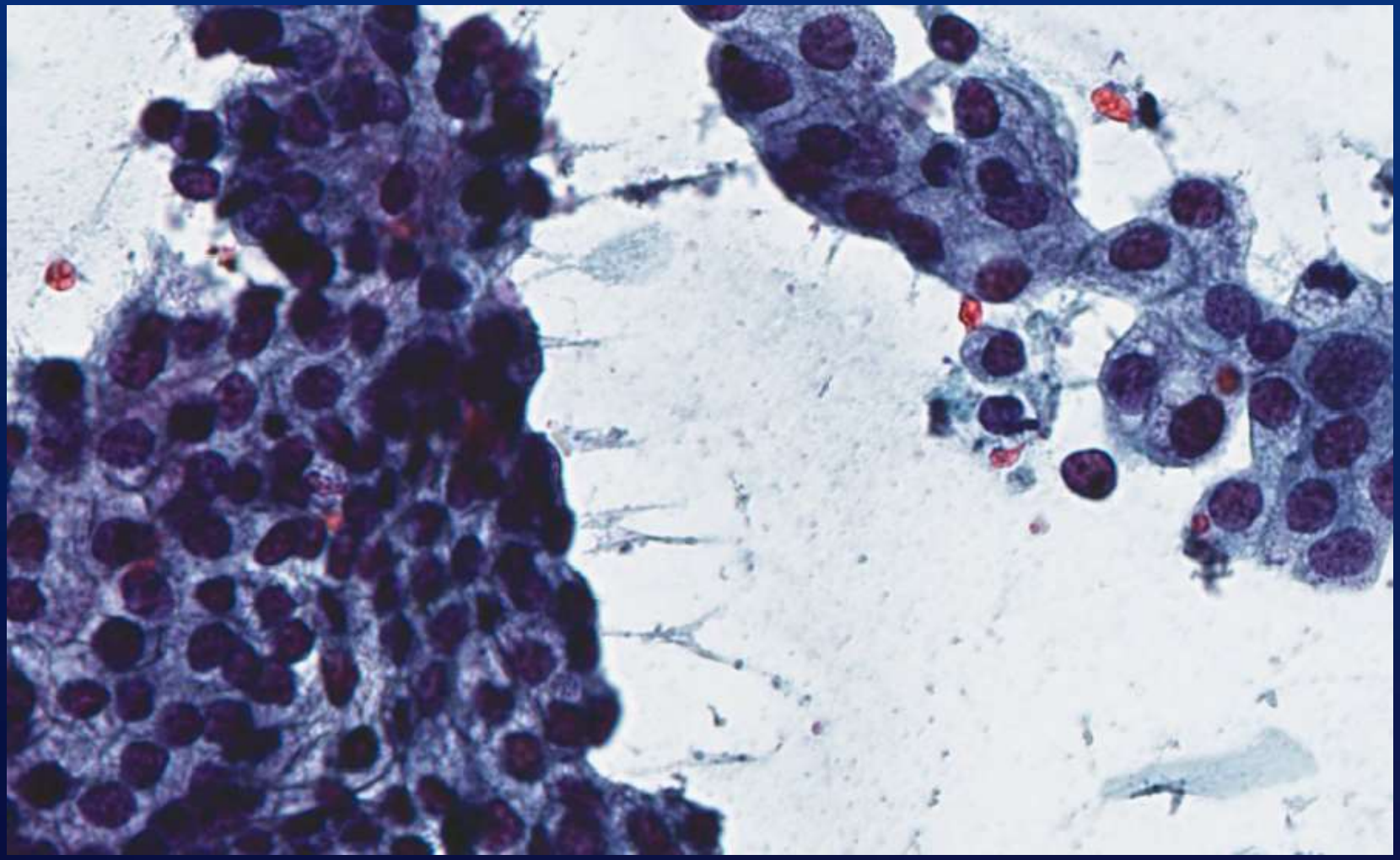
MAYO CLINIC

Adenoca



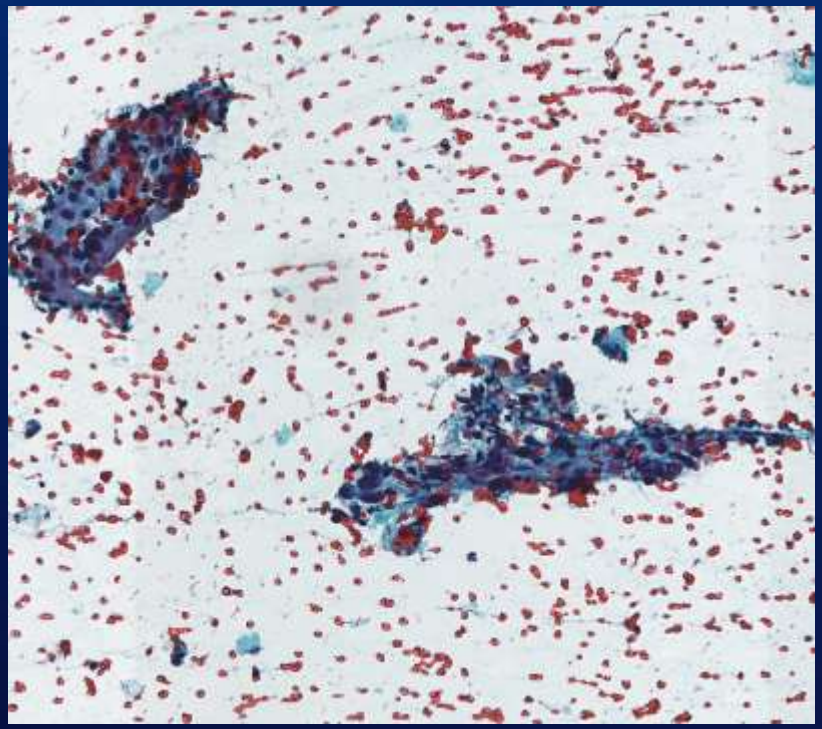
MAYO CLINIC

Adenoca



MAYO CLINIC

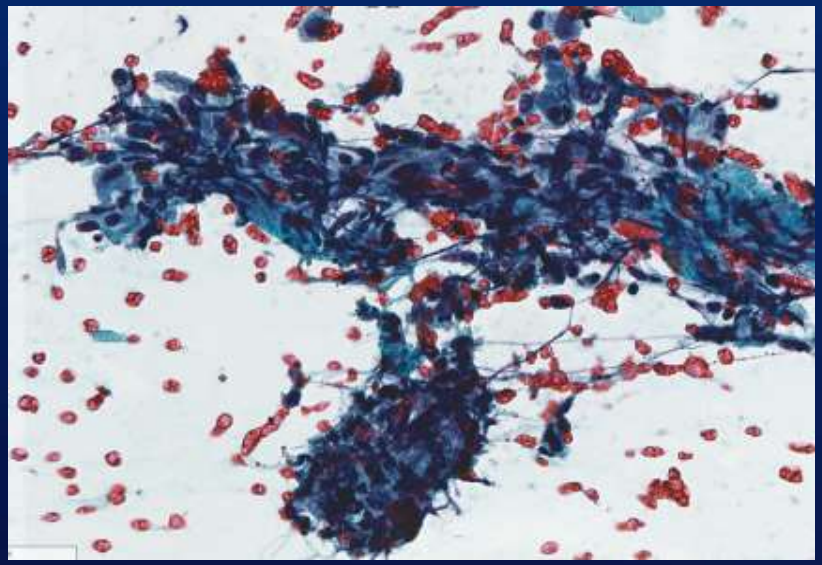
AIP Cytology



- Decreased ductal- type groups, abundant acinar epithelium
- Atypia
- Cellular stromal fragments rich in lymphocytes or lymphoid tangles
- Variable background inflammation: nil to moderate

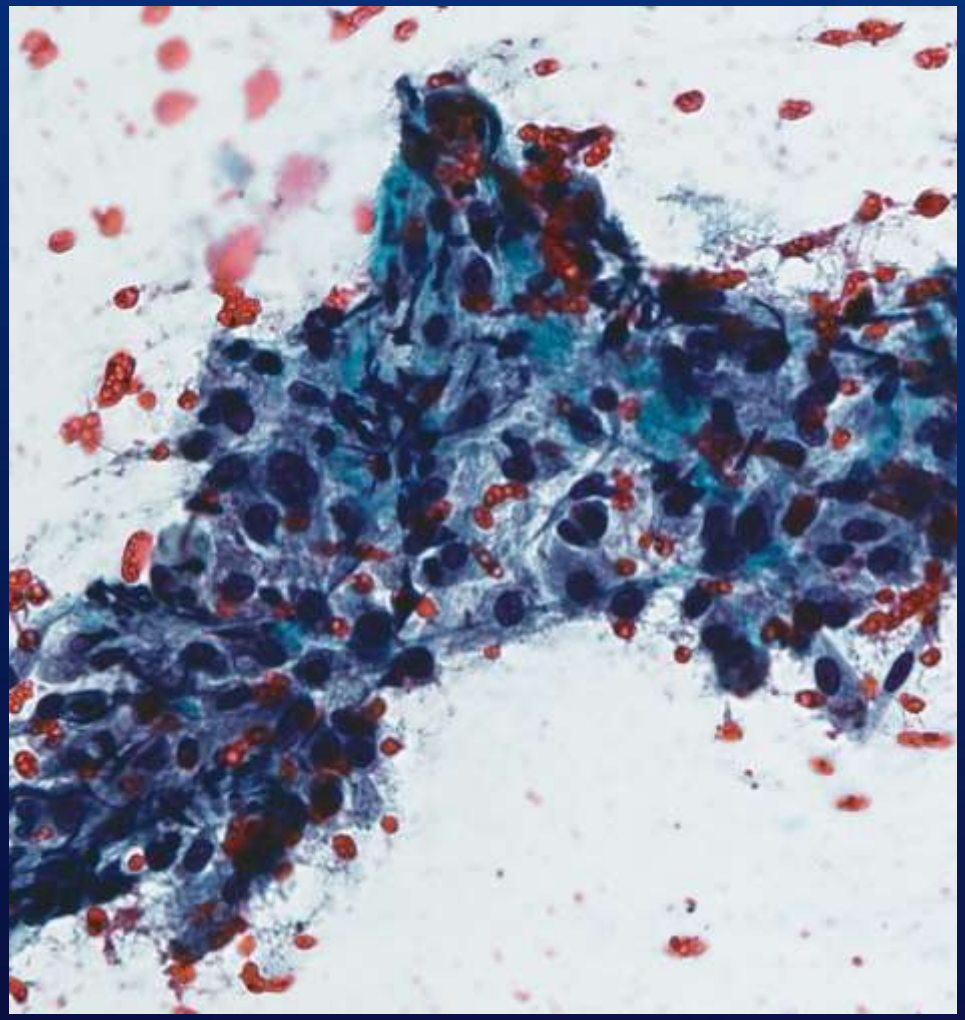
MAYO CLINIC

AIP



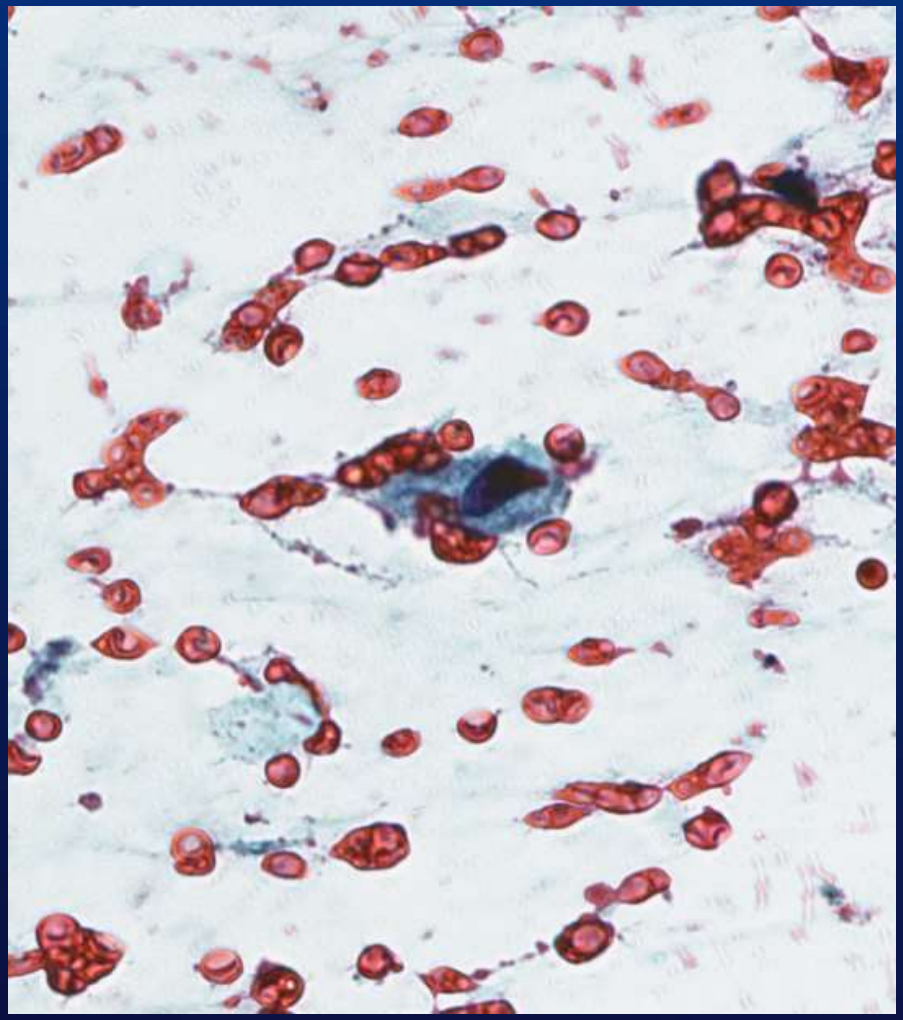
MAYO CLINIC

AIP



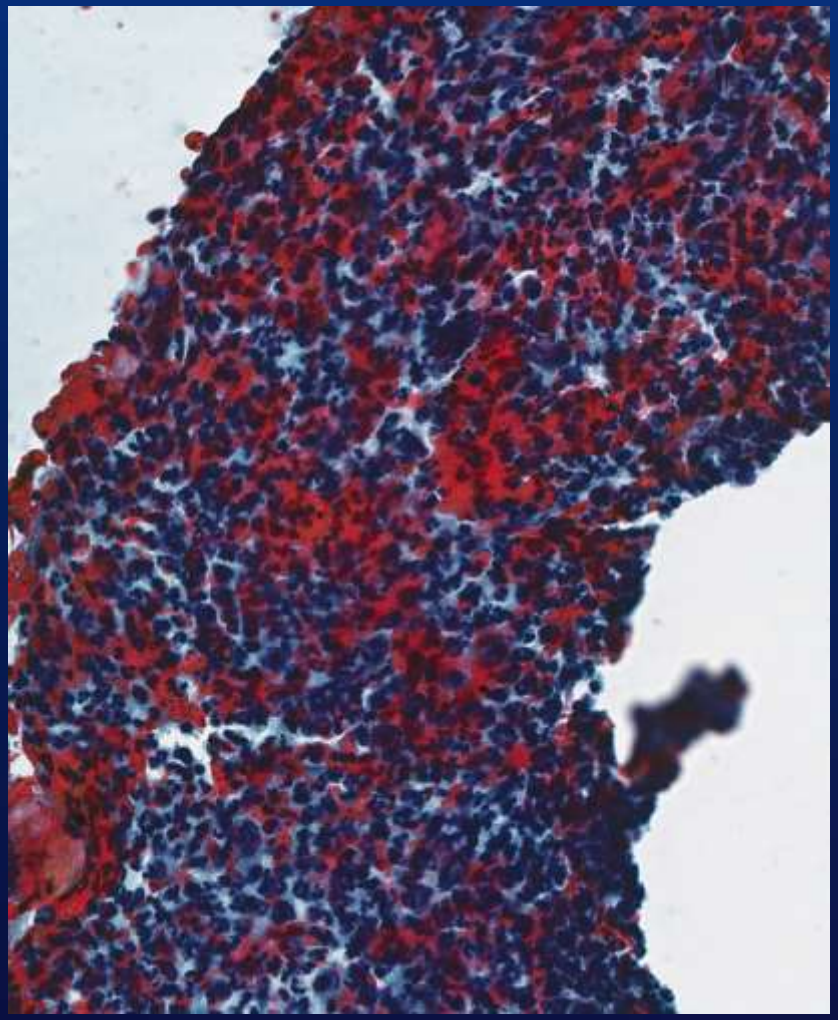
MAYO CLINIC

AIP



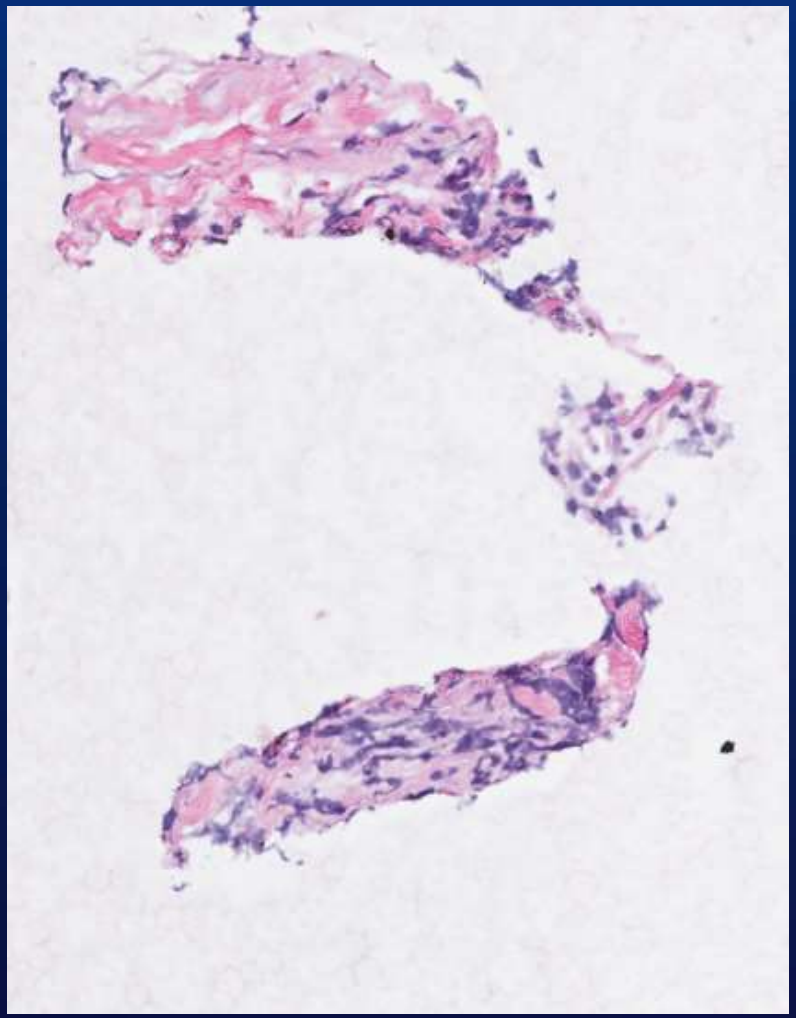
MAYO CLINIC

AIP



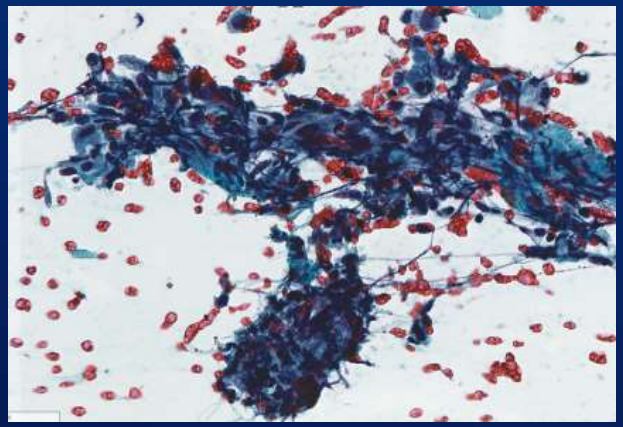
MAYO CLINIC

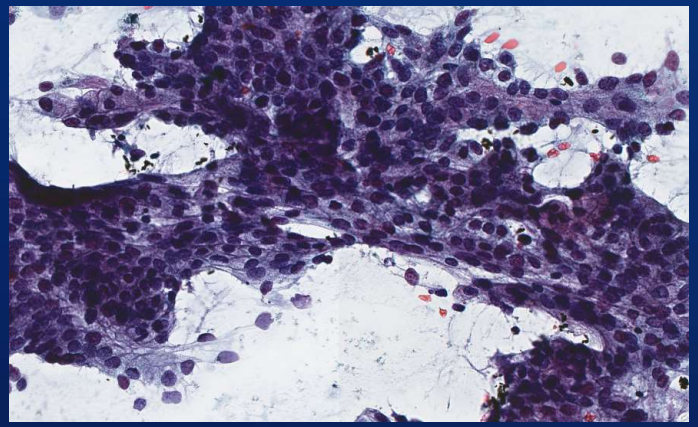
AIP CB

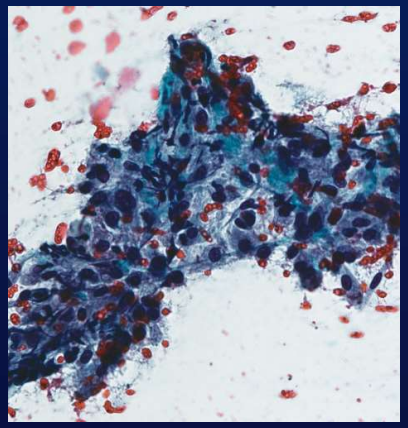


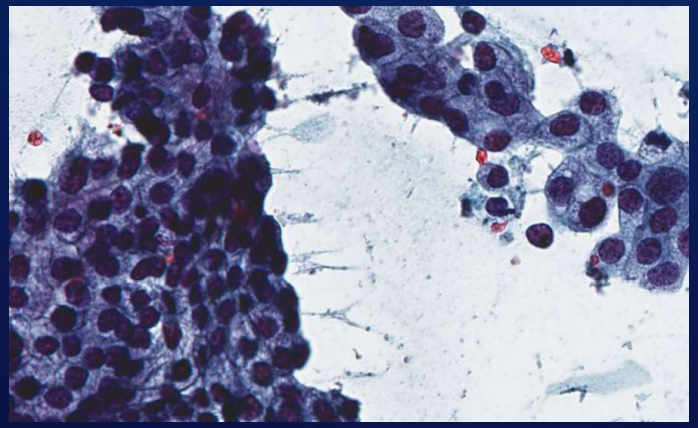
MAYO CLINIC

AIP vs Adenocarcinoma

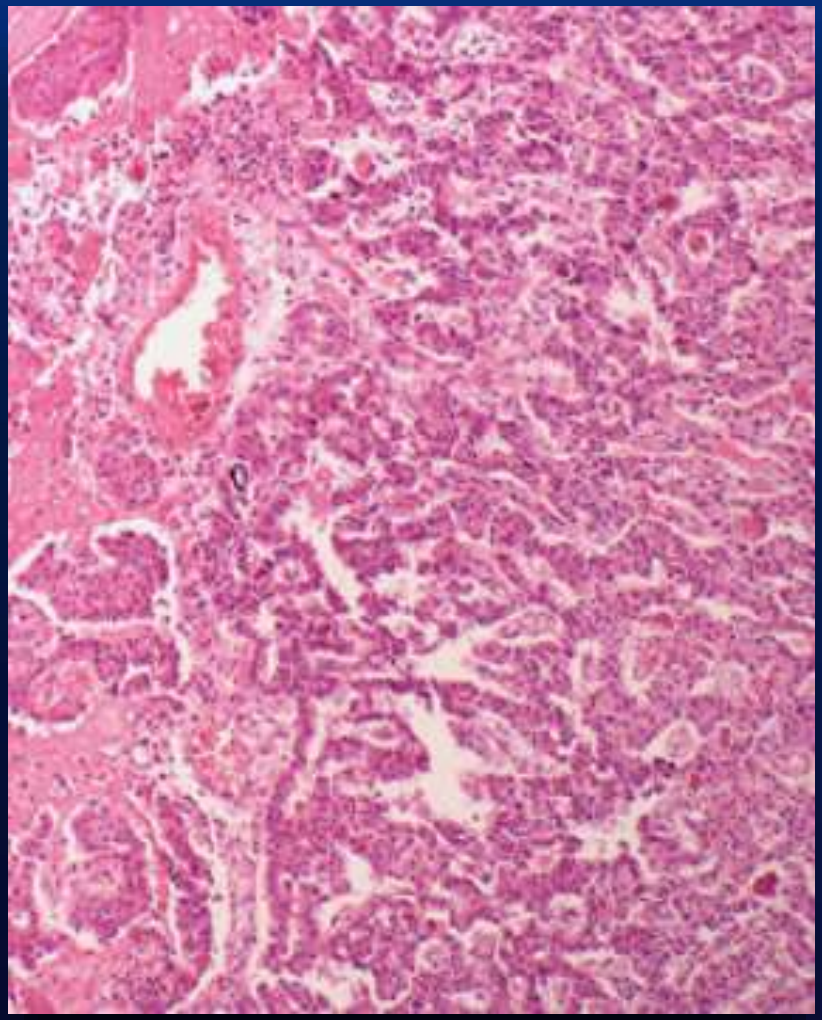








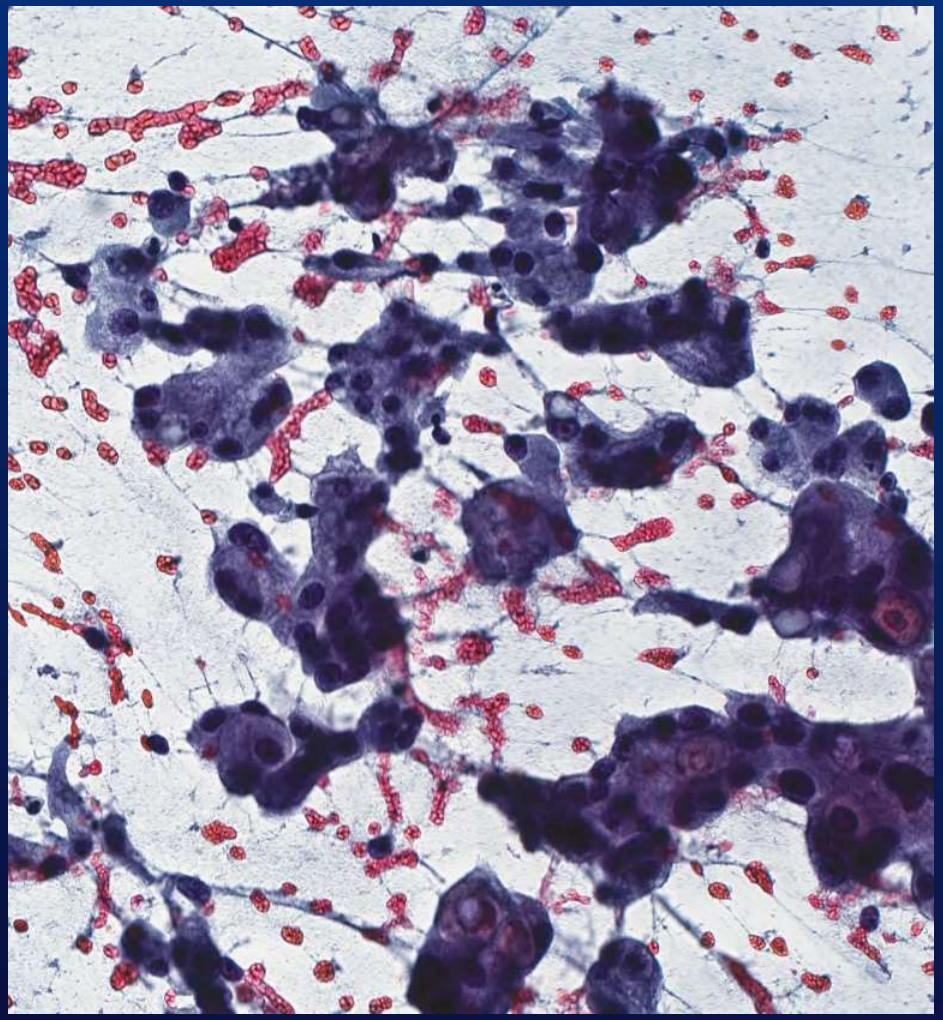
Cystic Pancreatic Neuroendocrine Tumors (PanNET)



- Rare; 5-10% of pancreatic neoplasms
- Cyst formation not due to necrosis in contrast to cystic adenocarcinoma
- Usually unilocular; up to 25 cm

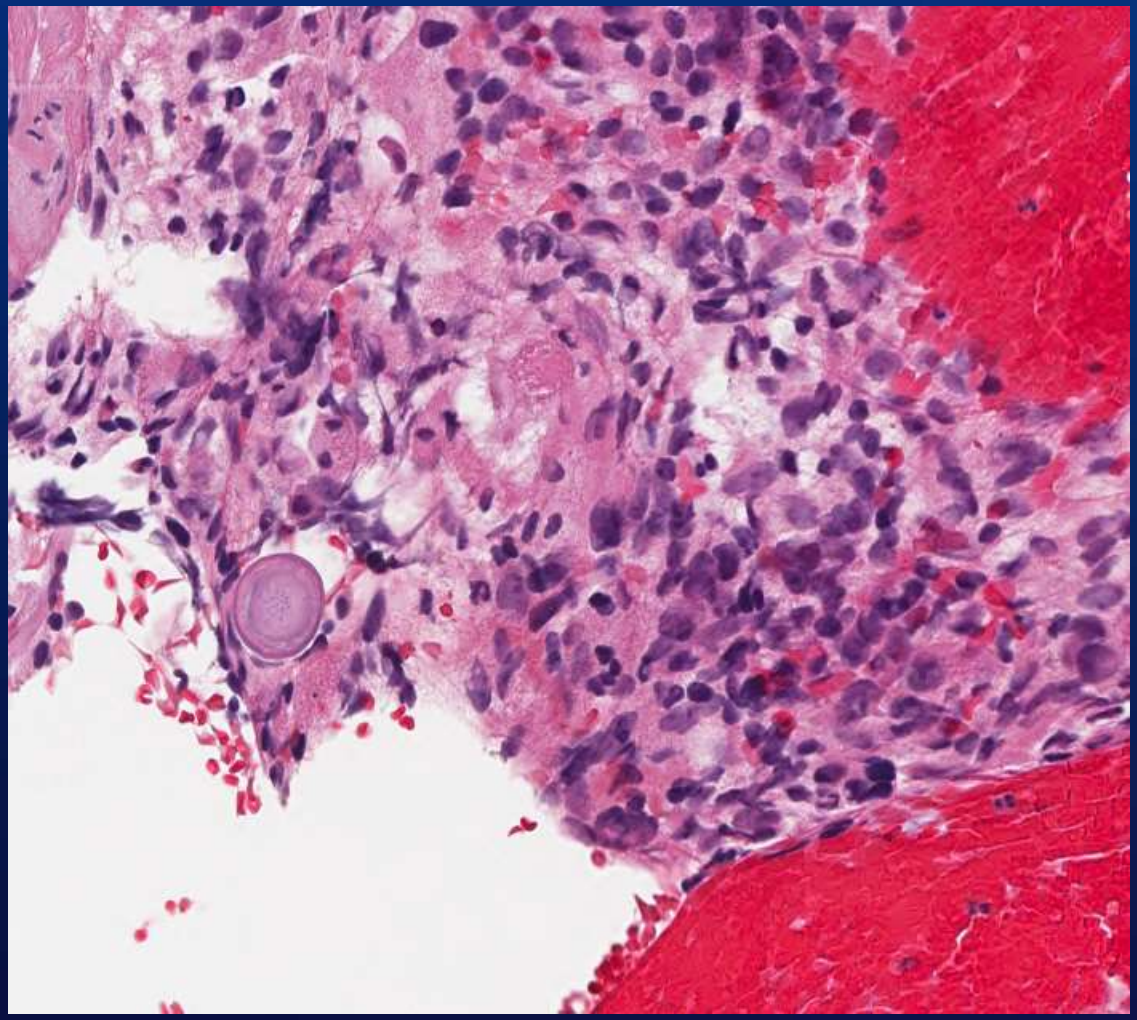
MAYO CLINIC

Somastatinoma



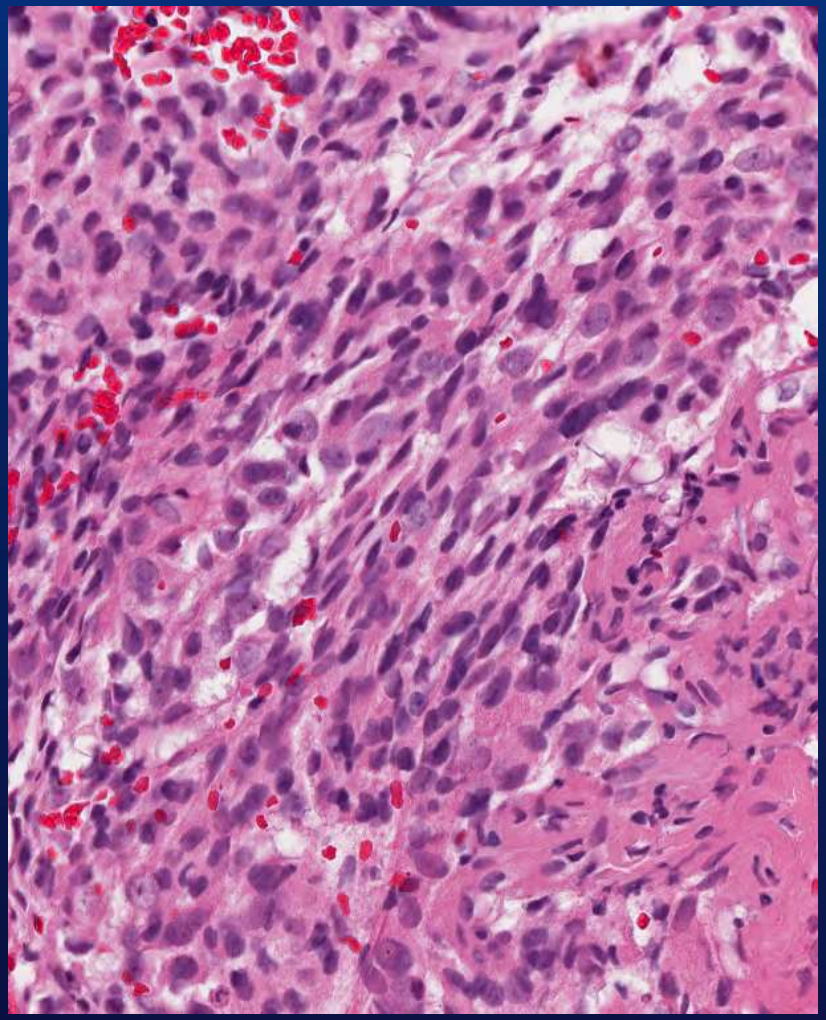
MAYO CLINIC

Somastatinoma CB



MAYO CLINIC

Somastatinoma CB



MAYO CLINIC

Summary- Pancreas FNA Pitfalls

- Normal Pancreas
- May mimic neoplasms
- Preserved acinar architecture
- Cystic lesions:
- Low cellularity
- Correlation with imaging, CEA, Amylase
- Adenocarcinoma:
- Low N/C ratio
- Look for ….

MAYO CLINIC

Summary- Pancreas FNA Pitfalls

- Normal Pancreas vs Neoplasm
  - Preserved acinar/ lobulated architecture
- Cystic lesions
- Challenges:
  - Low cellularity
  - GI contamination
- Helpful:
  - Correlation with imaging, fluid chemistry (CEA, Amylase), molecular analysis very he
  - Thick colloid like extracellular mucin favors mucinous cystic neoplasm
  - Cell block, IHC
- Adenocarcinoma:
  - May have low N/C ratio
  - Chronic pancreatitis, AIP: false positive
  - Look for fibrotic fragments with lymphoid tangles

MAYO CLINIC

NOTES IF ENOUGH TIME ADD

- Slide w solid pseudopap neopl (SSP) before sldie w IHC
- Slide w descriptive comparison ssp vs normal
- TABLEs W KI-67 AND NET (ASC pg 59)
- Table PNT vs acinar pg60 (for keeping)
- Slide w NET vs adeno text and pictures comparison

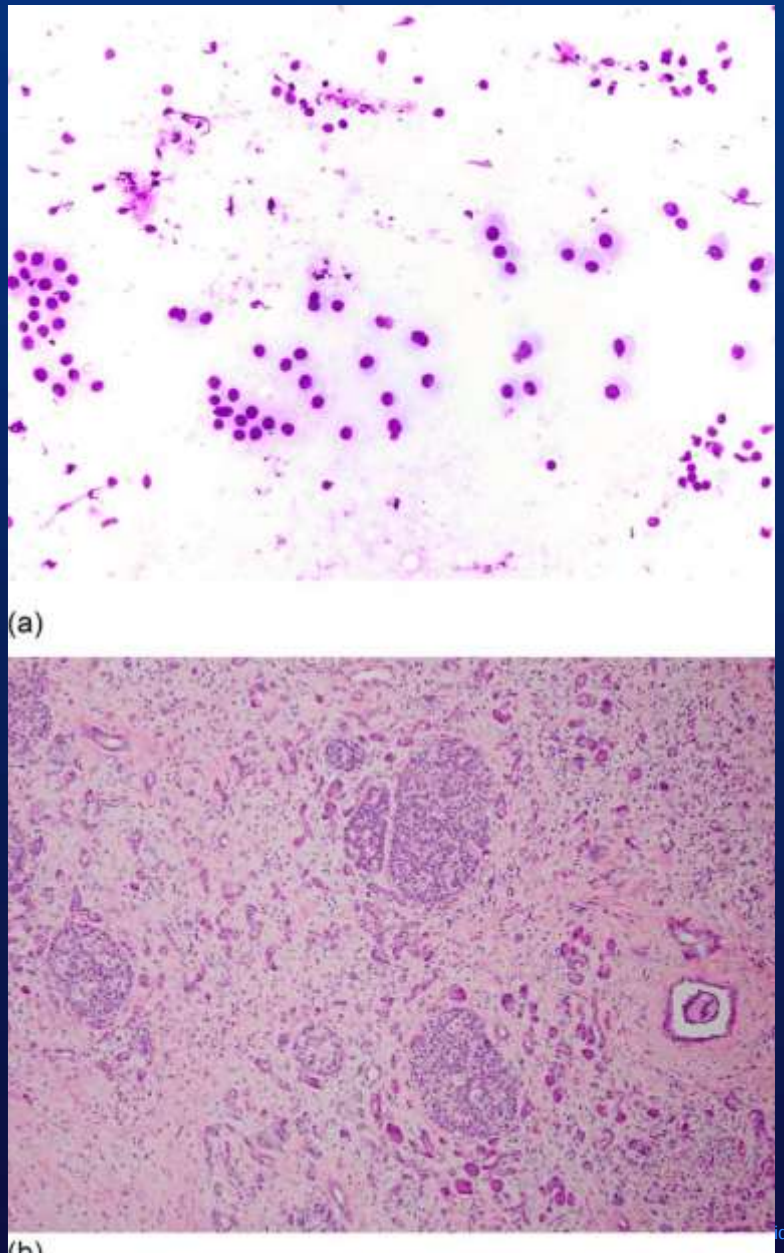
MAYO CLINIC

SSP Cytology

MAYO CLINIC

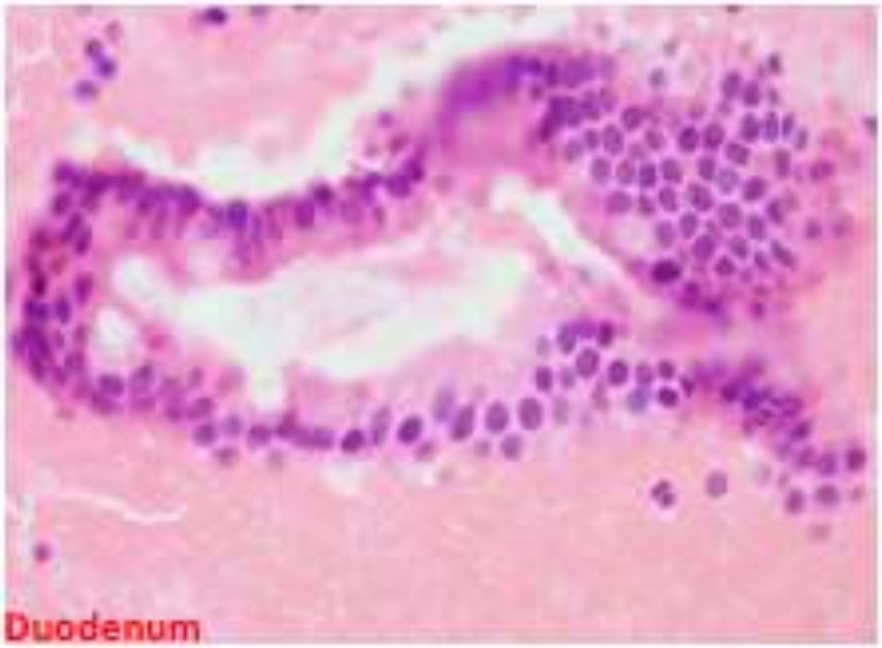
CP Misdiagnosed as PanNET on FNA

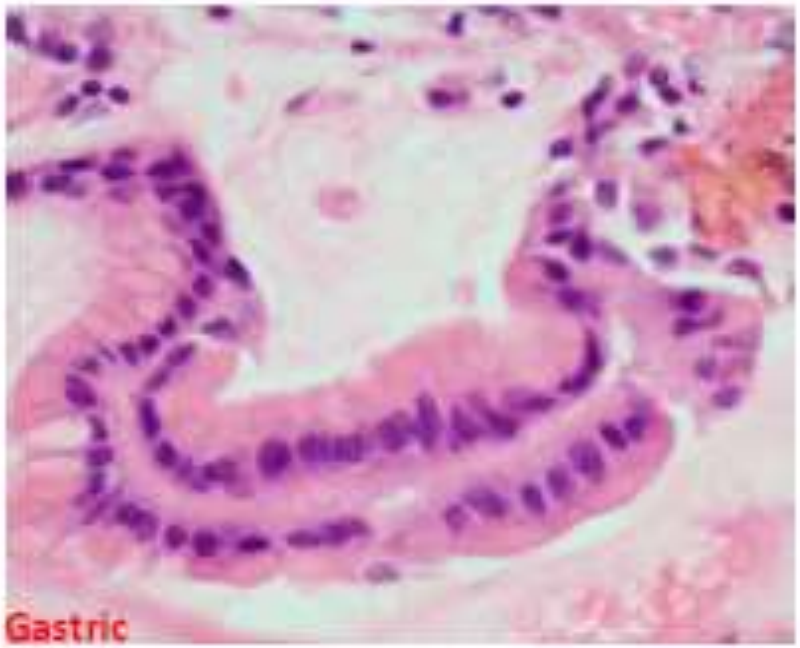
- Isolated and loosely cohesive cells with eccentrically located bland appearing nuclei
- Background of lymphocytes
- Resection:
  - Predominance of islet cells



Begeron JP et al. Endoscopic Ultrasound- Guided Pancreatic Fine-Needle Aspiration: Potential Pitfalls in One Institution's Experience of 1212 Procedures. Cancer Cytopathology 2015; 98-107.

MAYO CLINIC

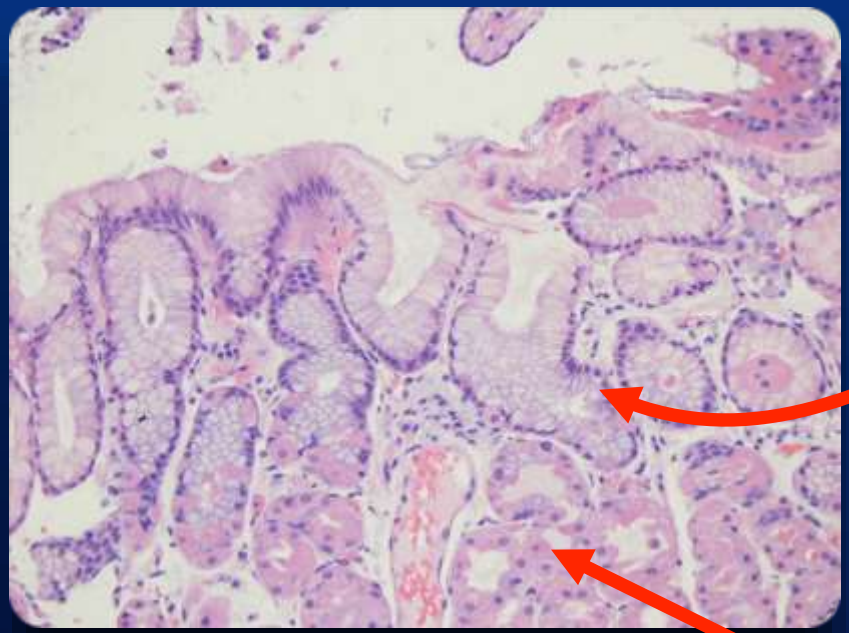


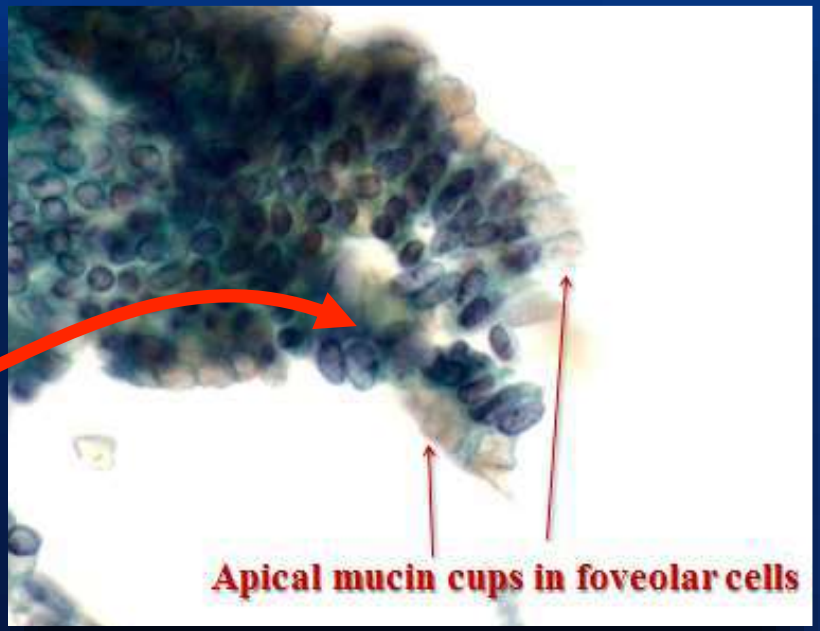


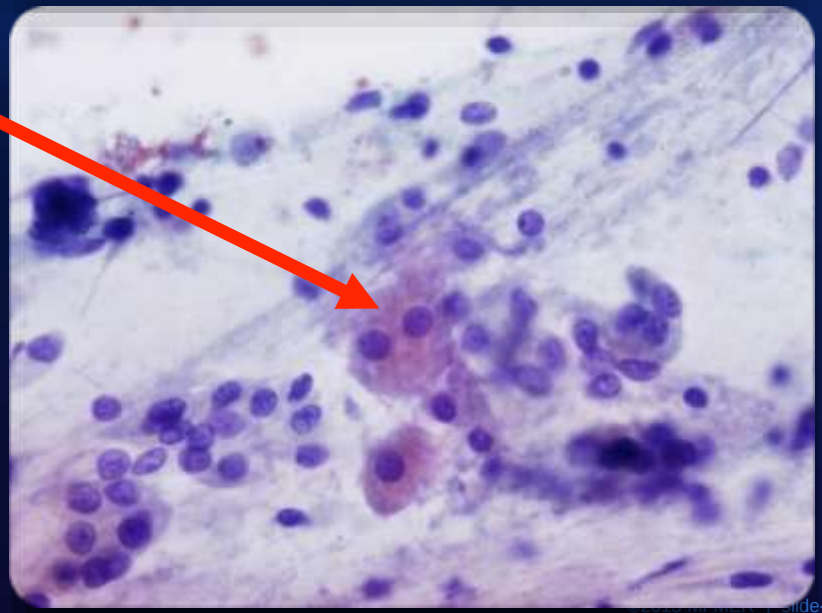
Duodenal and gastric epithelium contaminant in EUS-FNA of pancreas
Cell block section

MAYO CLINIC

Stomach







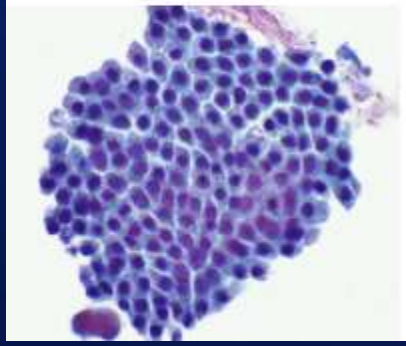
- Thin, watery mucin
- Small /intermediate/large clusters
- Apical mucin cups
- Grooved naked nuclei within mucin
- Cell types:
- Mucinous, parietal, chief cells

Slide by Dr. Matthew Zarka

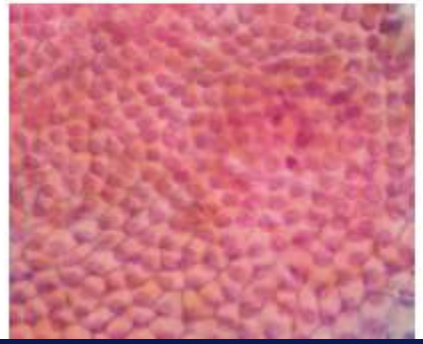
Which of the following is IPMN?

MAYO CLINIC

IPMN, LOW GRADE



GASTRIC FOVEOLAR CELLS



BENIGN PANCREATIC DUCTAL CELLS

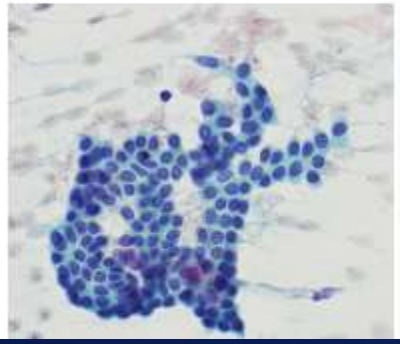


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Foto de ratoeira ou tap

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