Pancreatic Ductal Carcinoma

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Outline

- Background – Pancreatic Cancer
- Normal pancreatic elements
- Conventional pancreatic ductal adenocarcinoma (PDAC)
  - Differential diagnosis
  - Challenging scenarios
  - Immunohistochemistry
- PDAC variants

Pancreatic Cancer – United States

10th most common cancer in the U.S.

3rd leading cause of cancer-related deaths in the U.S.

Estimated New Cases in 2024	66,440
% of All New Cancer Cases	3.3%

- Lung: 26.7%
- Colorectal: 65.0%
- Breast: 91.2%
- Thyroid: 98.4%

SEER Cancer Stat Facts: Pancreatic Cancer. National Cancer Institute. Bethesda, MD

Pancreatic Ductal Adenocarcinoma (PDAC)

- >90% of all pancreatic neoplasms
- Highest incidence in ages 60-80, M>F
- Mutational profile
  - 4 main mutations: *KRAS*, *CDKN2A/p16*, *p53*, *SMAD4*: no targeted therapy
  - ~2.5% *BRCA1/2* mutations: PARP inhibitors (olaparib FDA-approved 12/2019)
  - ~1% MSI-high/MMR-deficient: pembrolizumab
- Only cure is early detection and complete surgical resection
  - 50-55% of patients present with metastatic disease
  - 25-30% present with locally advanced/unresectable tumors (neoadjuvant therapy)

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)

Know the path of the needle:
- Often transduodenal for pancreatic head/uncinate lesions
- Often transgastric for pancreatic body/tail lesions

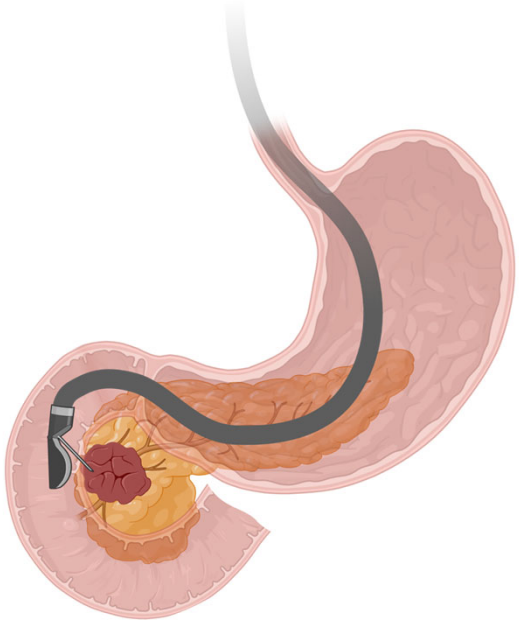

Figure created with BioRender.com

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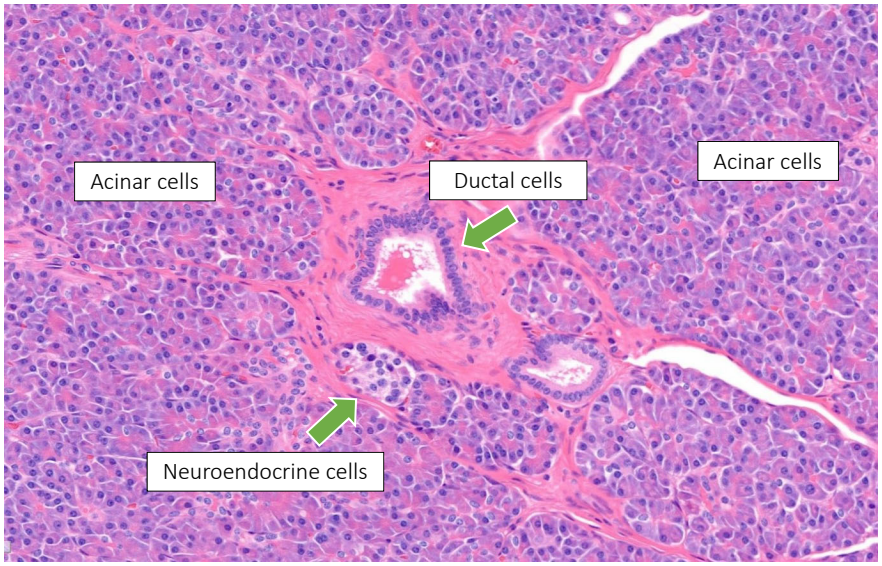
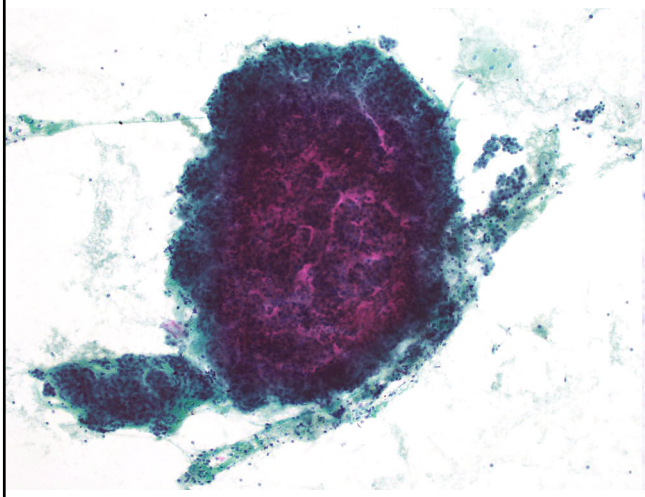
Normal pancreas

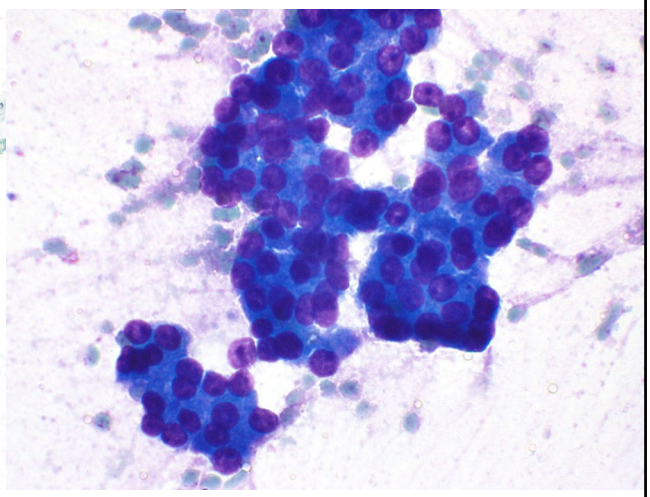


Acinar cells

Pap stain, low power



Diff-Quik stain, high power



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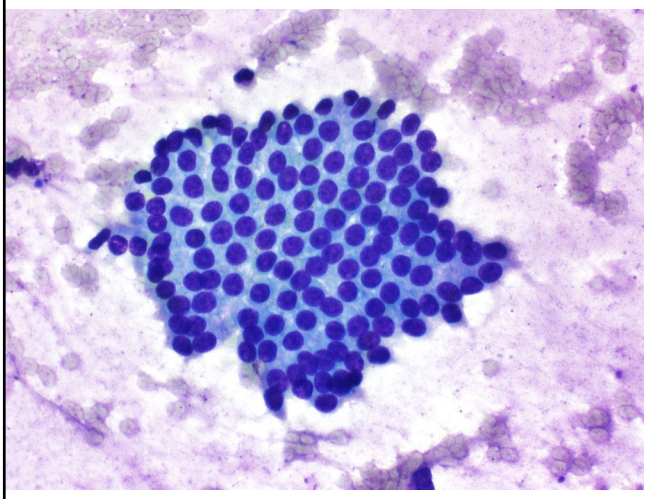
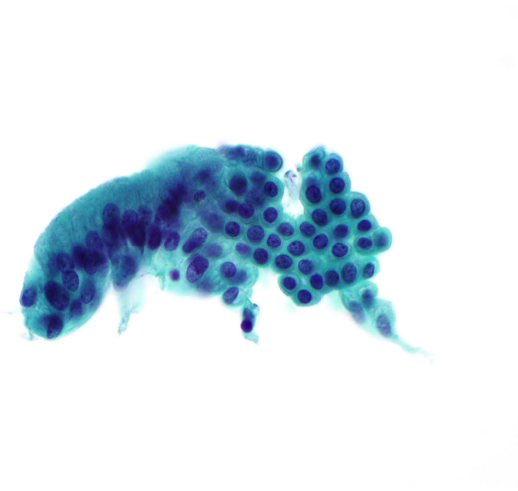
Ductal cells

Diff-Quik stain



Pap stain



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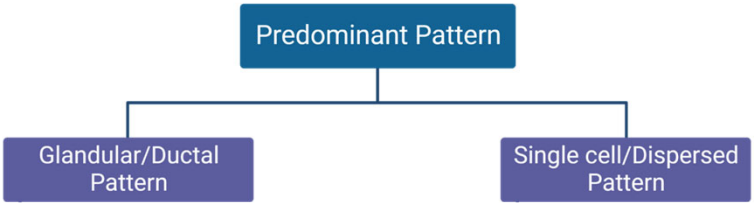
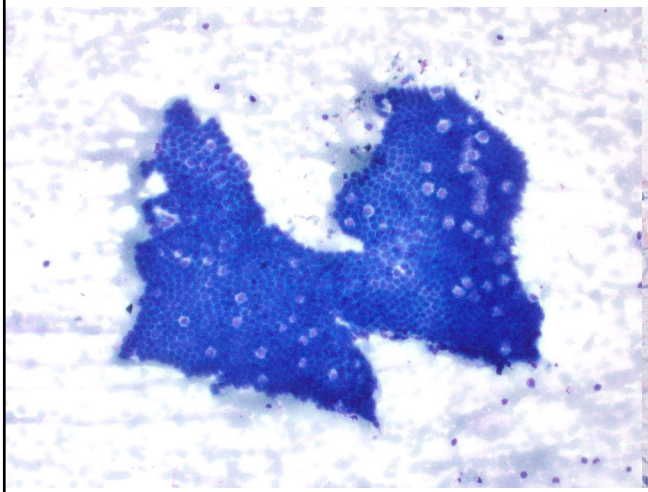
Differential Diagnosis of Solid Lesions

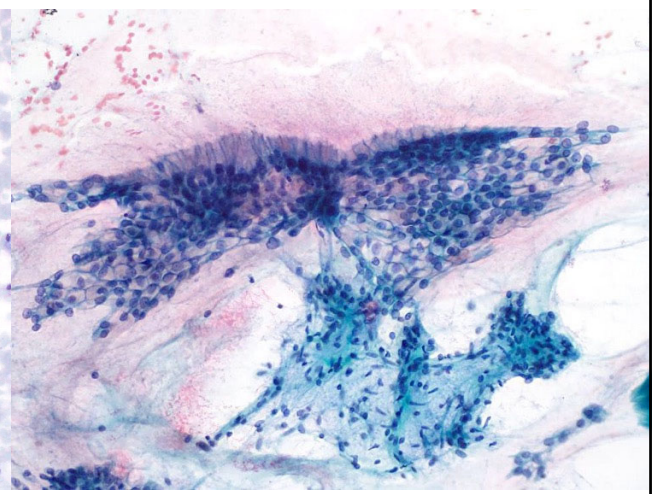


GI Contamination

Duodenal contamination



Gastric contamination



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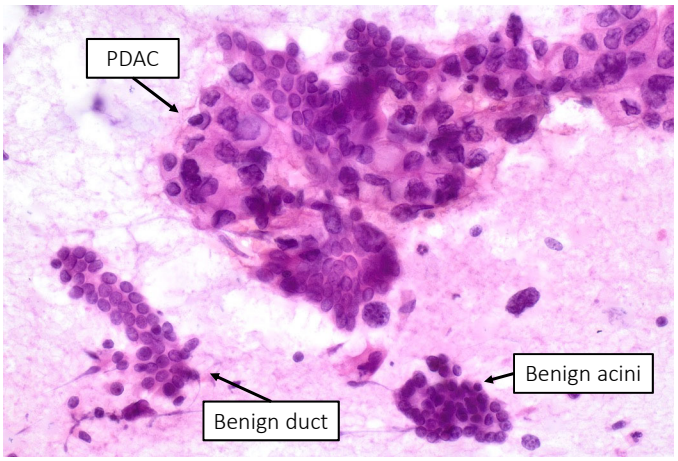
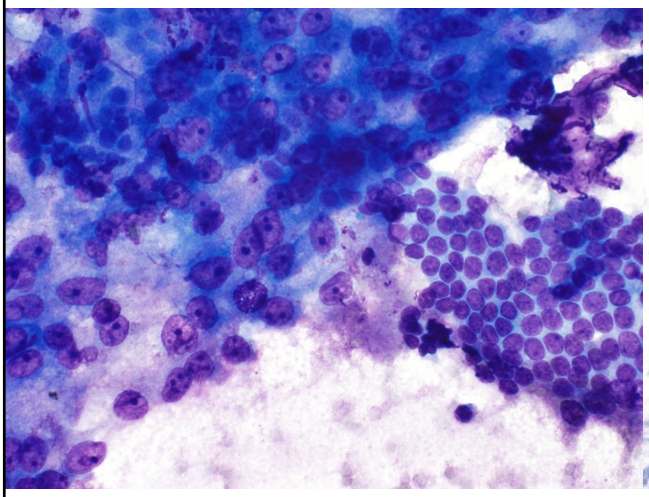
Pancreatic ductal adenocarcinoma (PDAC)

- Architecture
  - "Drunken honeycomb"
  - (Single atypical cells)
  - (Background necrosis)
- Cytomorphology
  - Anisonucleosis >4:1
  - Nuclear membrane irregularities
  - Nuclear hypo or hyperchromasia
  - Variably prominent nucleoli
  - Variably mucinous cytoplasm



Pancreatic Ductal Adenocarcinoma (PDAC)



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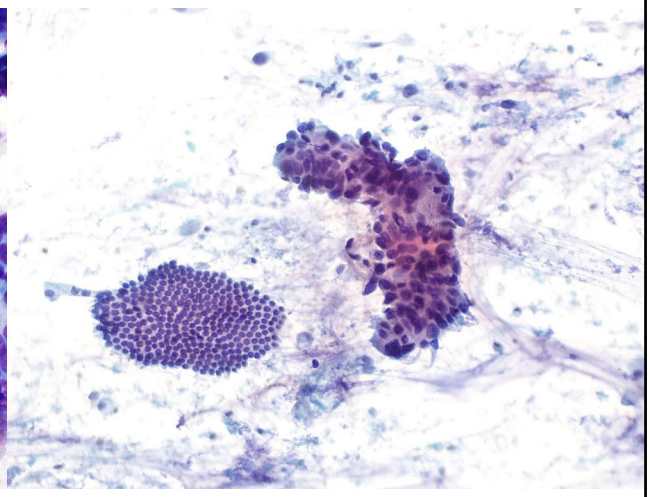
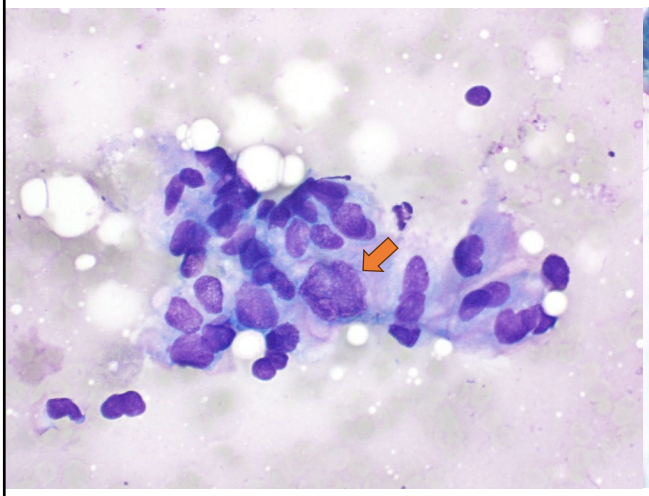


Pap stain

Pancreatic Ductal Adenocarcinoma (PDAC)



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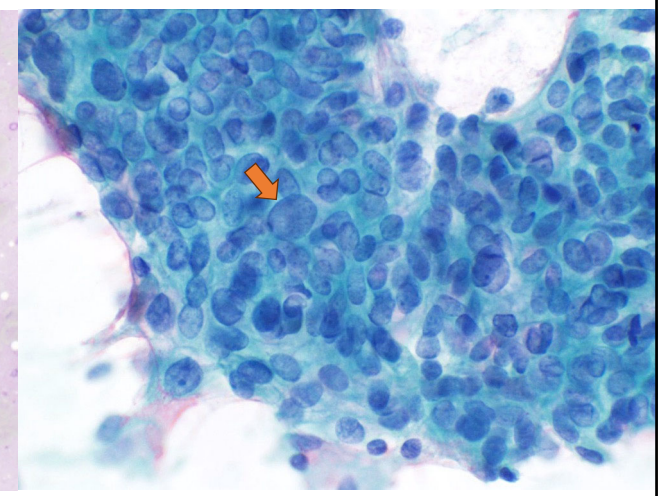


Pap stain

Reactive ductal atypia

Clinical scenario:

inflammatory process that appears mass-forming on imaging

→ FNA to rule out malignancy

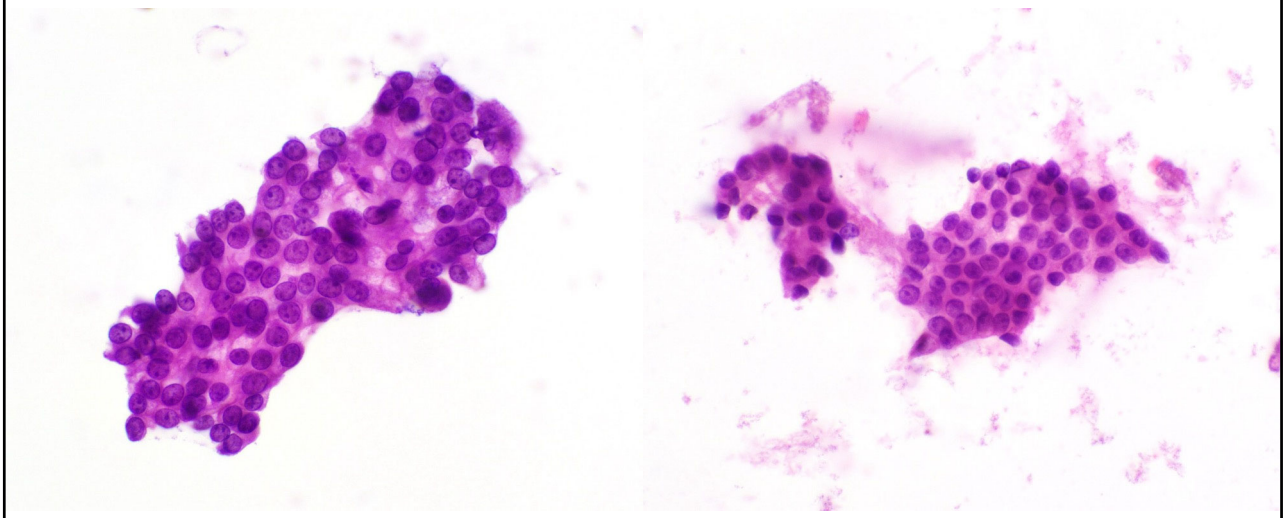
Chronic pancreatitis	Background amorphous/granular debris
	Variable mixed inflammation
	Fibrotic tissue fragments
	Late stage: loss of acinar tissue
Autoimmune pancreatitis	Type 1 (IgG4-related): lymphoplasmacytic sclerosing
	Type 2: granulocytic epithelial lesions (more marked atypia)

Table 1. Comparison of Reactive Atypia, Well-Differentiated Adenocarcinoma, and Moderately or Poorly Differentiated Adenocarcinomas in Fine-Needle Aspiration Samples

Criteria	Reactive Atypia	Well-Differentiated Adenocarcinoma	Moderately or Poorly Differentiated Adenocarcinoma
Cellularity	<6 atypical groups	Variable	Variable
Background	Inflammatory, clean, debris	Clean or bloody	Coagulative necrosis
Architecture	Minimal crowding, loss of polarity	Large, folded groups, nuclear crowding, and overlapping	More 3-dimensional groups; smaller atypically formed groups
Dyshesion	Cohesive	Infrequent; cohesion more typical	Present
Anisonucleosis	Mild: 2:1 to 3:1; moderate: 3:1 to 4:1 (not >4:1)	>4:1	More variability in the degree of anisonucleosis
Nuclear enlargement	Nuclear size increases	1.5× red blood cells on air-dried smears, 2.5× normal duct nuclei on alcohol-fixed smears	Larger than well differentiated, more variability in nuclear size
Chromatin appearance	Granular, evenly distributed	More often hypochromatic	Hyperchromasia and abnormal parachromatin clearing
Nuclear membrane abnormalities	Minimal	Elongations and angulations	More obvious notches and convolutions
Mitoses	Can be present, no abnormal forms	Infrequent	Abnormal forms, more frequent
Macronucleoli	Present in moderate atypia	Absent	Present

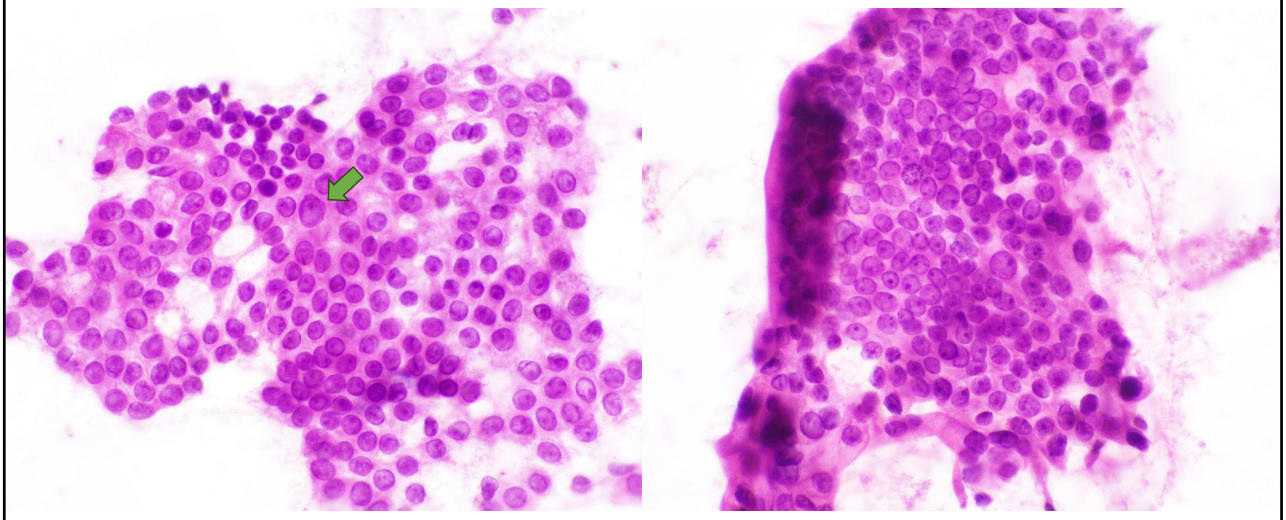
Centeno BA. Arch Pathol Lab Med 2023.

Well-diff adenocarcinoma vs. reactive atypia?



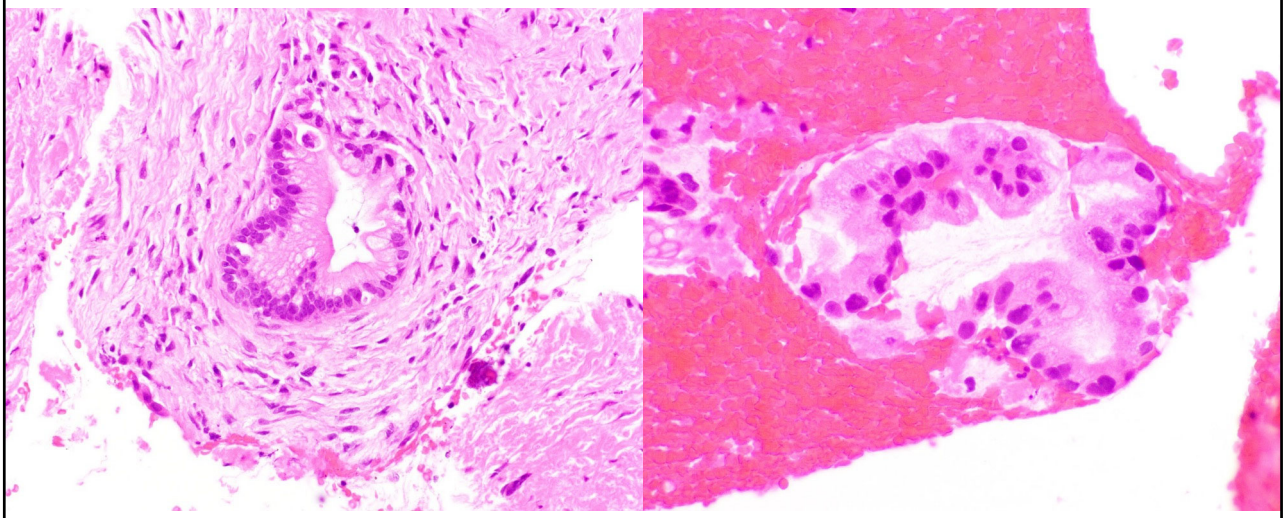
Rapid H&E stain, on-site evaluation

Well-diff adenocarcinoma vs. reactive atypia?



Rapid H&E stain, on-site evaluation

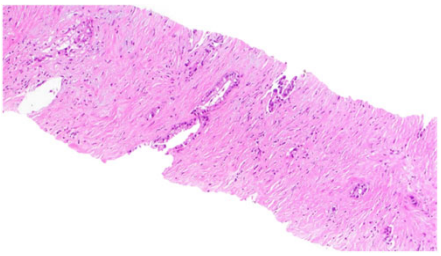
Well-differentiated adenocarcinoma

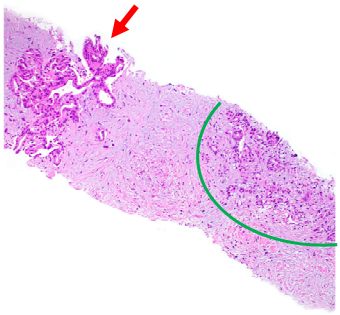


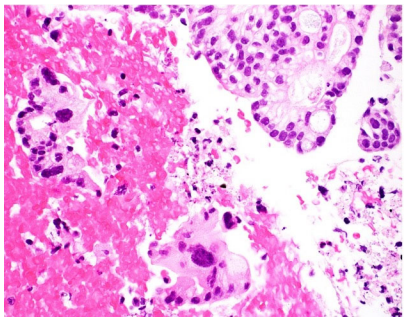
Features of PDAC on small biopsies

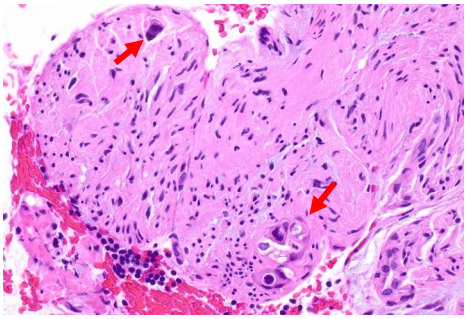
Box 1
Features supporting adenocarcinoma over chronic pancreatitis

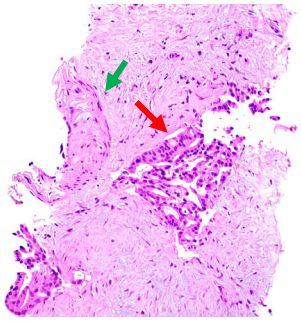
- Haphazard growth pattern
- Incomplete lumina/luminal necrosis
- Nuclear size variation greater than 4:1
- Growth next to muscular vessel
- Perineural invasion
- Vascular invasion
- Ancillary IHC: loss of immunolabeling for Smad4







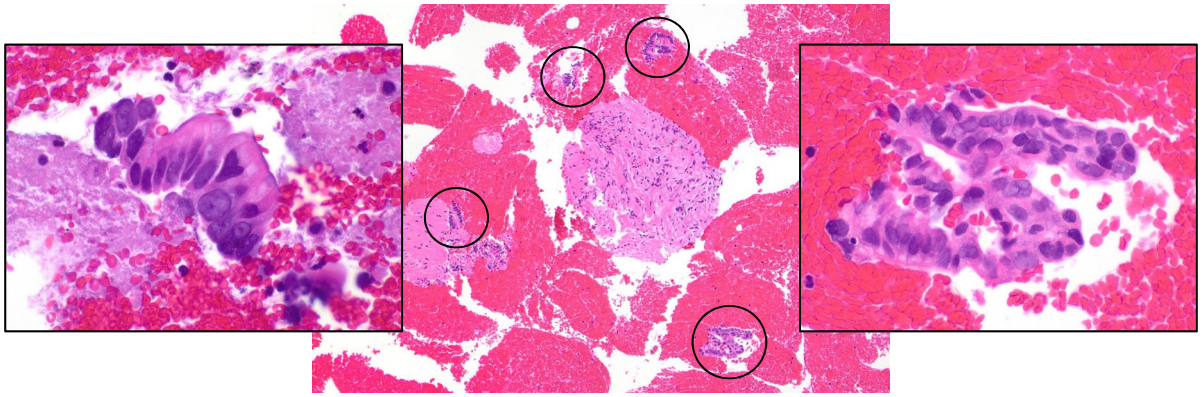




Thompson ED, Zhang ML, VandenBussche CJ. Surg Pathol Clin 2022.

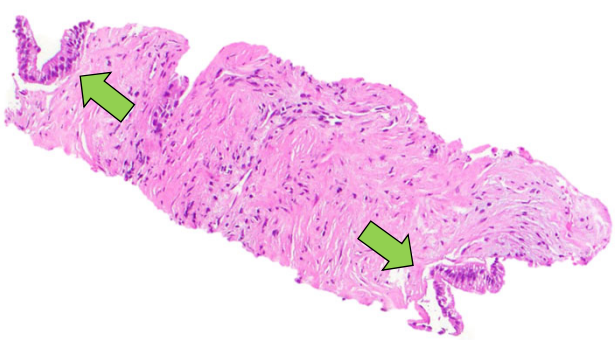
Features of PDAC on small biopsies

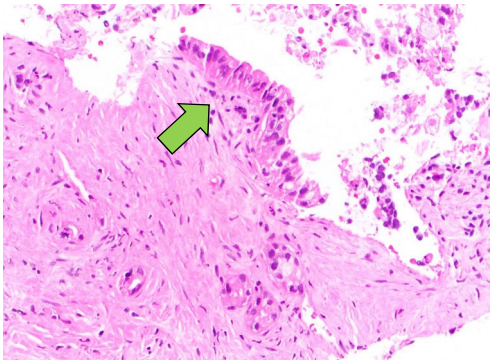
- Detached epithelial strips (floating tumor)



Features of PDAC on small biopsies

- Tumor strips at tissue fragment ends (tumor breakage)





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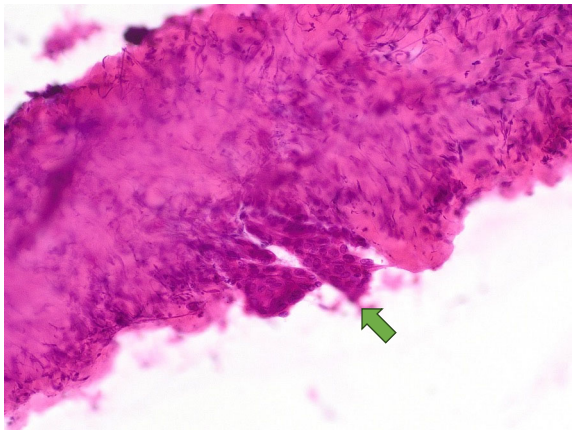
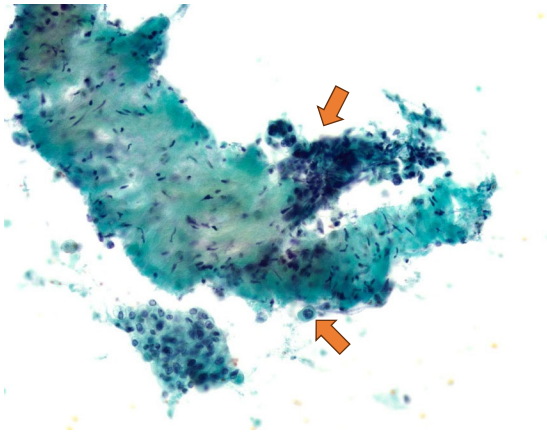




WHO Reporting System for Pancreaticobiliary Cytopathology 2022

Indeterminate diagnostic categories

Table 3 Absolute risk and relative risk of malignancy of the diagnostic categories in the PCS system.

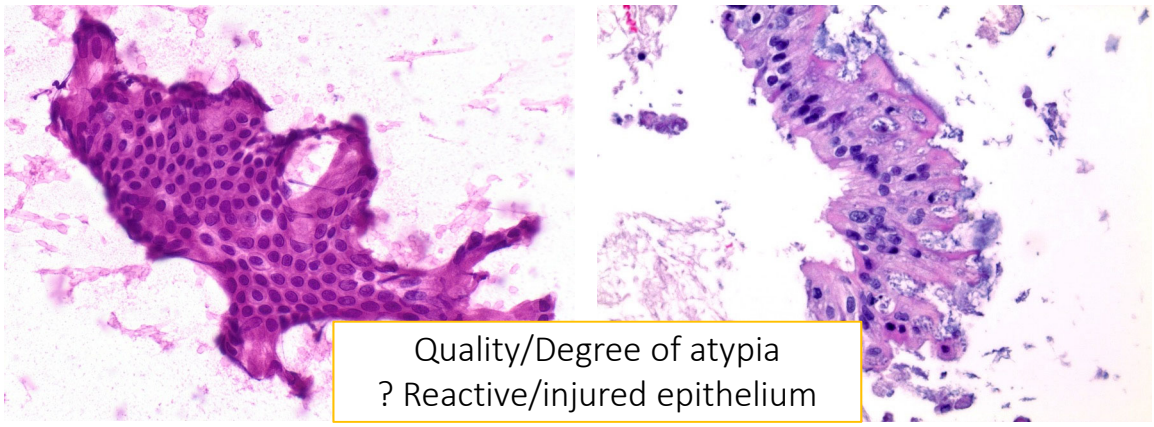
Diagnostic category	Absolute risk of malignancy (%)	Relative risk	*P* value (relative to benign category)
I. Nondiagnostic	7.7	7.7	0.07
II. Negative for malignancy	1.0	1.0	NA
III. Atypical	28.0	28.0	0.001[a]
IV. Neoplastic: benign	0.0	0.0	1.00
IV. Neoplastic: other, all grades of atypia	30.3	30.3	<0.001[a]
With low-grade atypia	4.3	4.3	0.23
With high-grade atypia	90.0	90.0	<0.001[a]
V. Suspicious for malignancy	100.0	100.0	<0.001[a]
VI. Positive or malignant	100.0	100.0	<0.001[a]

Abbreviations: NA, not applicable; PCS, Papanicolaou Society of Cytopathology.
[a]Statistically significant ($P < 0.05$).

Hoda RS et al. J Am Soc Cytopathol. 2019

Example case: final diagnosis "Atypical"

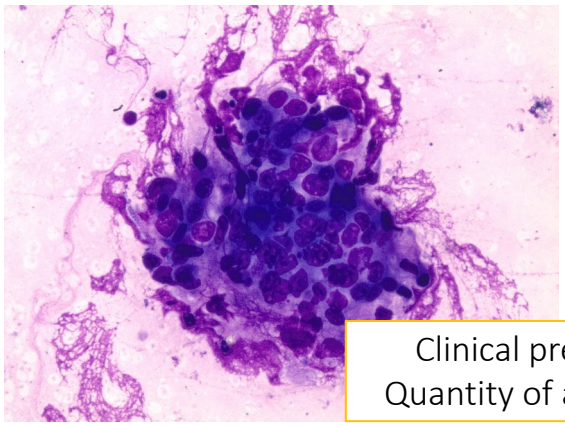
- 81-year-old female with pancreatic head mass, prior biopsy with "reactive epithelial changes and acute inflammation"

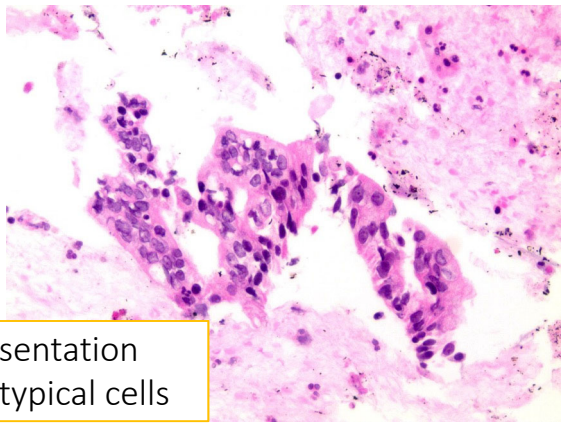


Quality/Degree of atypia
? Reactive/injured epithelium

Example case: final diagnosis “Atypical”

- 29-year-old female with pancreatic duct dilatation and possible obstructive mass in the pancreatic head, ?pancreatitis vs. PDAC

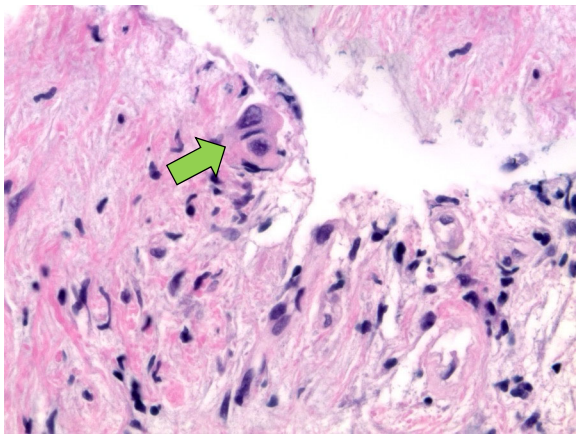


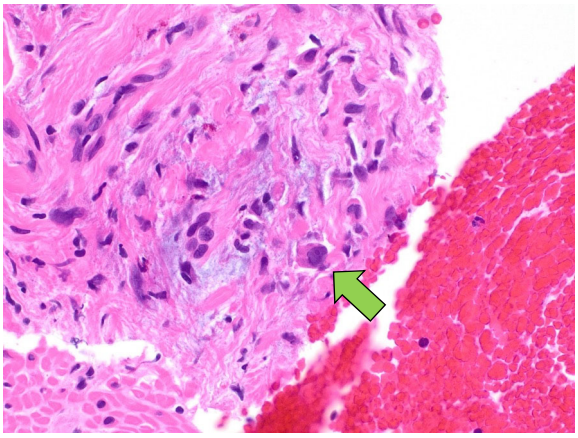


Clinical presentation
Quantity of atypical cells

Example case: final diagnosis “Suspicious”

- Very rare highly atypical cells in a background of desmoplastic stroma

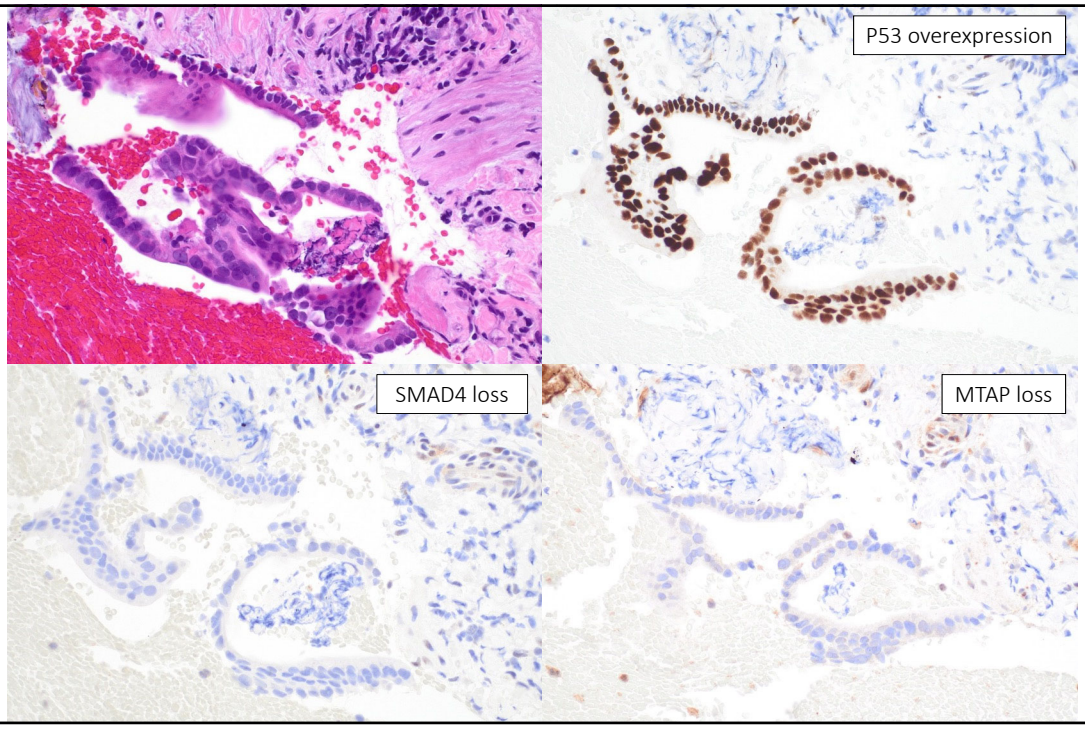




Immunohistochemistry (1st tier panel)

- SMAD4/DPC4: complete loss of expression in 50-55% of PDAC
  - Also lost in variety of other primary carcinomas (caution in metastatic setting)
- p53: mutant expression in 50-75% of PDAC (overexpression > loss)
  - >90% reported concordance between P53 IHC and mutation status
- S100P: strong diffuse nuclear+cytoplasmic expression in >90% of PDAC
  - Strong expression in gastric epithelium
  - Rare false positives (patchy or cytoplasmic only) in reactive ductal epithelium
- MTAP: complete loss of expression in ~30% of PDACs
  - Surrogate marker for *CDKN2A* deletion

Sweeney J et al. J Am Soc Cytopathol. 2018.
Hutchings D et al. Am J Surg Pathol. 2018.
Lin F, Chen ZE, Wang HL. Arch Pathol Lab Med. 2015.
Yu S et al. Cancer Cytopathol. 2023.



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  - Immunohistochemistry
- PDAC variants

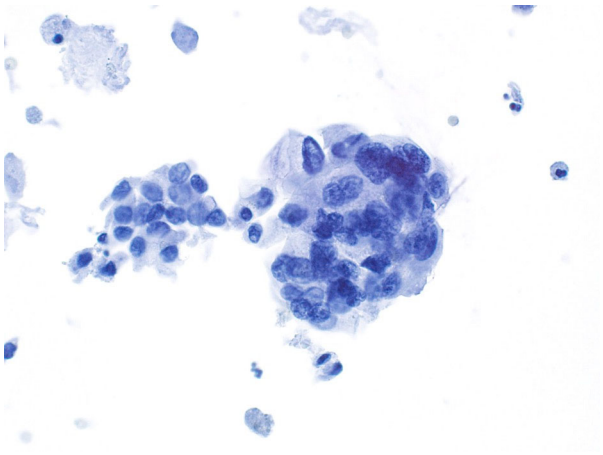
Morphologic patterns vs. Histologic subtypes

- Morphologic patterns
  - Large duct pattern
  - Cystic papillary pattern
  - Foamy gland pattern
  - Clear cell pattern

- Histologic subtypes
  - Adenosquamous
  - Colloid
  - Hepatoid
  - Medullary
  - Invasive micropapillary
  - Signet-ring cell
  - Undifferentiated
    - Anaplastic
    - Sarcomatoid
    - Carcinosarcoma
    - Osteoclast-like giant cells

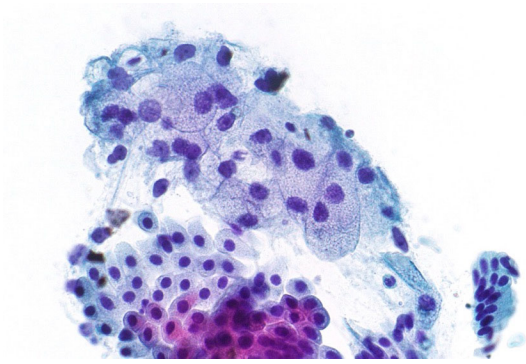
Cystic PDAC

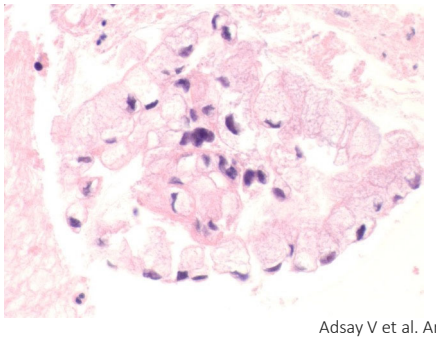
- Scenario 1: Not arising in mucinous cyst
  - Secondarily cystic due to necrosis
  - Large duct or cystic papillary patterns (mimic IPMN)
- Scenario 2: Arising in mucinous cyst (IPMN or MCN)
- Similar cytomorphologic features as usual solid PDAC



Foamy gland pattern

- Morphologic pattern, not histologic subtype – not prognostically distinct from conventional PDAC
- Important to recognize because deceptively bland morphology
- Large cell size
- Low N/C ratio
- Abundant foamy, lacy, microvesicular cytoplasm
- Basally-oriented hyperchromatic nuclei
  - Relatively bland, rasinoid
- Some PDACs have mixture of foamy and more conventional tumor cells

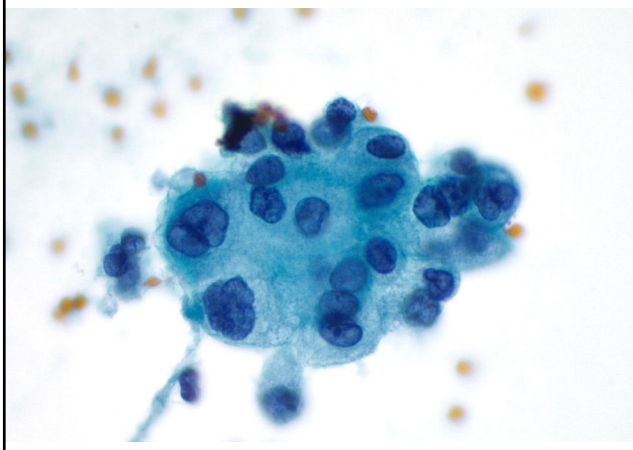




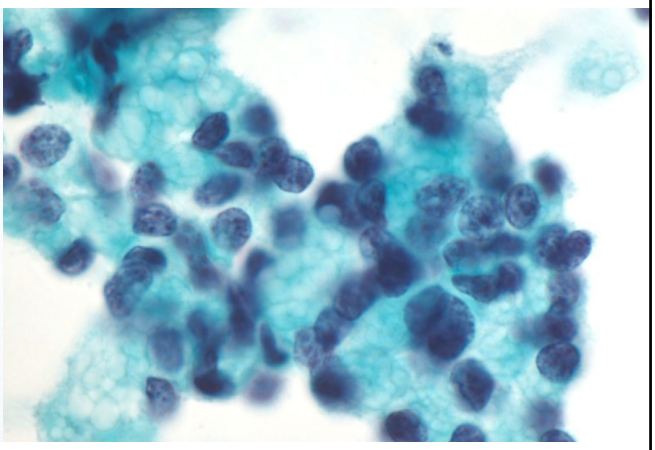
Images courtesy of Dr. Martha Pitman

Adsay V et al. Am J Surg Pathol. 2000.

Metastatic renal cell carcinoma



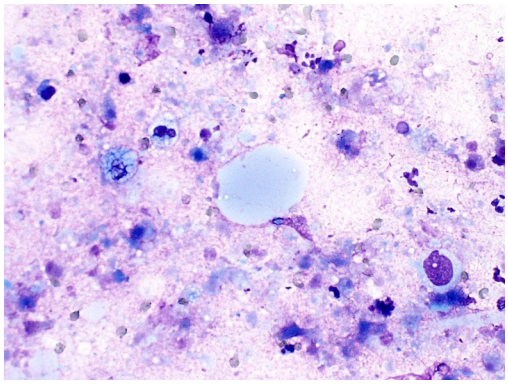
PanNET, lipid-rich variant

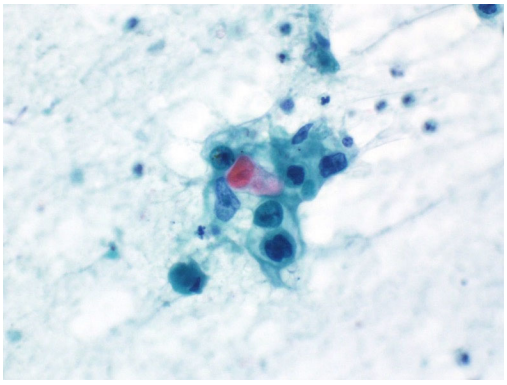


Images courtesy of Dr. Martha Pitman

Adenosquamous carcinoma

- Histologic diagnosis requiring ≥30% of each component, but can suggest based on cytology
- Worse prognosis than conventional PDAC



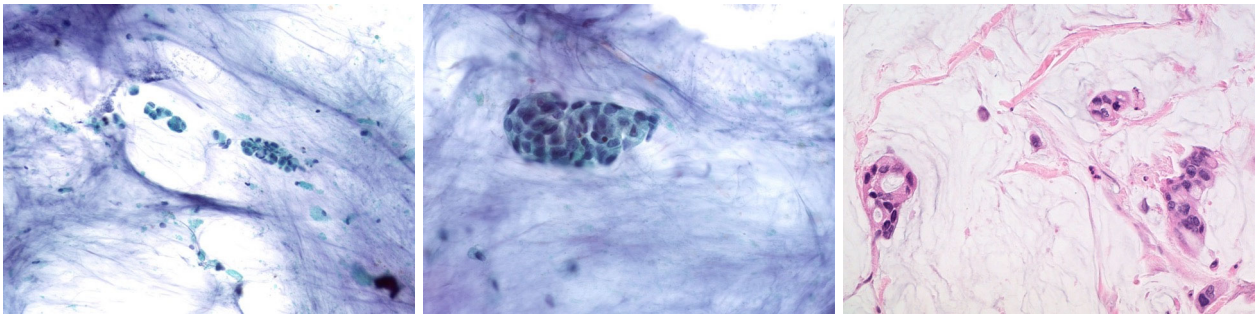


Example report

- Carcinoma with squamous differentiation (see note).
- Note: The differential includes adenocarcinoma with squamous differentiation, primary adenosquamous carcinoma, or metastatic squamous cell carcinoma.

Colloid carcinoma

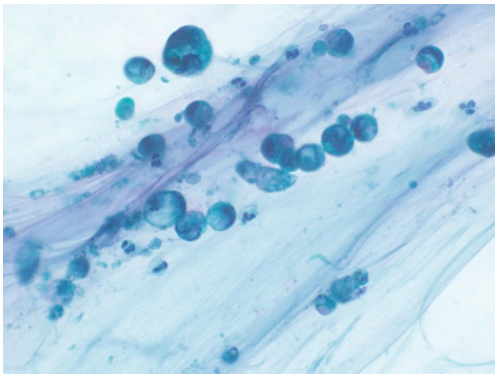
- Histologic diagnosis requiring ≥80% of neoplastic epithelium to be suspended in extracellular mucin pools
- Better prognosis than conventional PDAC

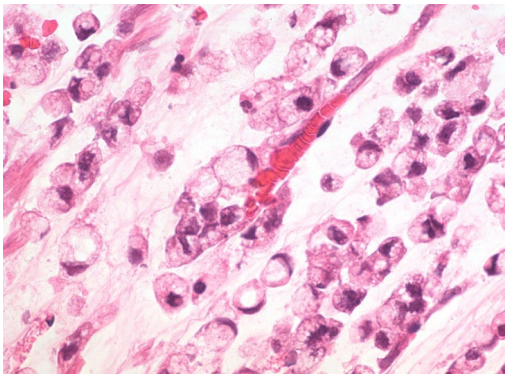


Images courtesy of Dr. Martha Pitman

Signet-ring cell carcinoma

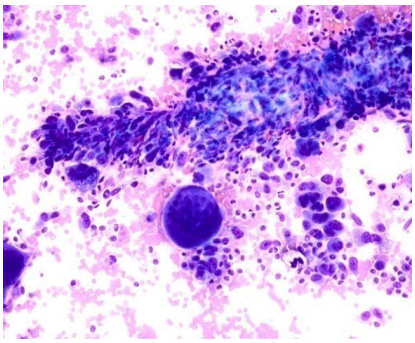
- Histologic diagnosis requiring ≥80% poorly cohesive signet ring cells
- Worse prognosis than conventional PDAC
- Rule out metastatic gastric or breast carcinoma

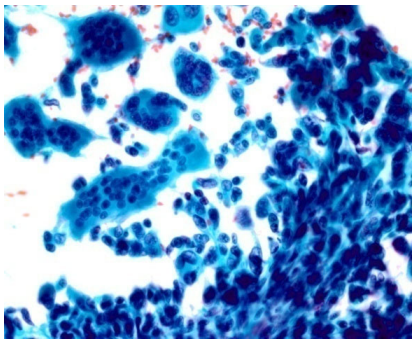




Undifferentiated carcinoma with osteoclast-type giant cells

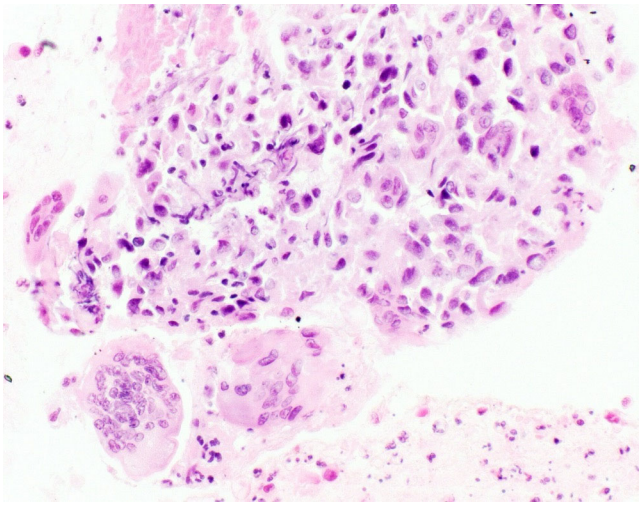
- Distinctive components
  - Non-neoplastic osteoclast-like giant cells (histiocytic)
  - Neoplastic mononuclear cells
- 40% associated with gland-forming epithelial component (conventional PDAC, IPMN, MCN)
- Many patients have relatively favorable prognosis

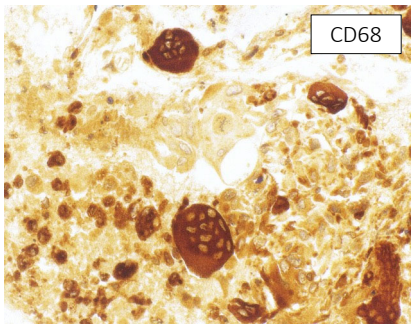


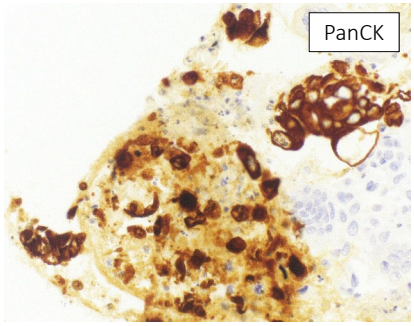


Images courtesy of Dr. Martha Pitman

Undifferentiated carcinoma with osteoclast-type giant cells







WHO Reporting System for Pancreaticobiliary Cytopathology 2022.

Summary

- By far the most common pancreatic lesion is PDAC (>90%)
- FNA cytology is often diagnostic, but combination with core biopsy findings can be helpful
- Distinguishing well-differentiated PDAC from reactive atypia can be challenging, particularly at the time of rapid on-site evaluation
- Ancillary studies (SMAD4, p53, S100P, MTAP) can be helpful in select cases on small core biopsies
- Be aware of the histologic subtypes and morphologic variants of PDAC

Thank you!