

Objectives

- To understand EUS/FNA technique and ways to improve its diagnostic yield
- To understand how frozen section diagnosis and final pathologic diagnosis impact patient care
- To review basic cytologic and histologic features of important pancreatic lesions
- To foster improved communication between the pathologist and clinician in care of patients with pancreatic disease

Fine Needle Aspiration Biopsy and Cytologic Features of Pancreatic Lesions

Cynthia Behling M.D. Ph.D
Associate Professor of Clinical Pathology

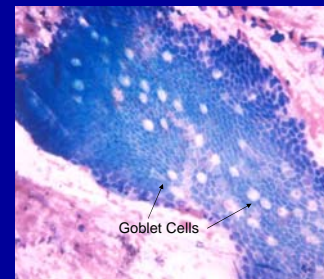
University of California, San Diego

Cytology of Pancreatic Lesions

- Cytologic Features of
 - Pancreatic Ductal Adenocarcinoma
 - Chronic Pancreatitis
 - Cystic Lesions
- Technical Aspects of EUS/FNA which impact cytologic diagnosis

Pancreatic FNA: Normal Pancreas

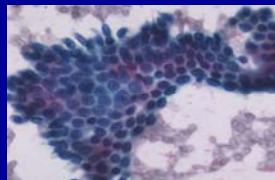
- "Contaminants" from the normal gastrointestinal tract may be present in any aspirate.



Sheet of benign duodenal epithelium

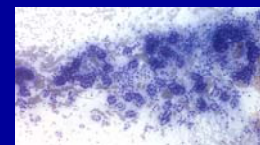
Cytologic Findings: Normal Pancreas

- Less cellular
- Proportional mix of bland ductal cells and acinar cells
- 80% of the cells are acinar cells
- Normal ductal cells
- Islet cells resemble acinar cells, rare

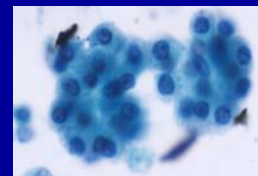


Normal Pancreatic Elements: Acini

- Acinar cells
 - round nuclei
 - well-defined cell borders
 - abundant granular cytoplasm



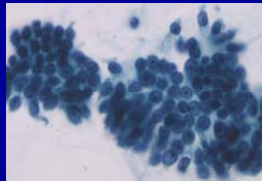
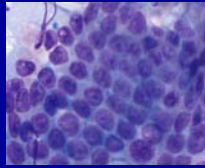
Microarchitecture: Acinar arrangement



Granular cytoplasm, round uniform nuclei

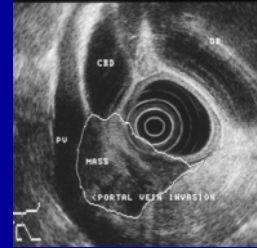
Normal Pancreatic Elements: Ductal Cells

- Orderly, regularly arranged cohesive sheets of columnar cells
- Vary in size proportionally to the duct from which they were aspirated.
- Basally located nuclei, round to oval with smooth nuclear contours and fine chromatin.



Regular arrangement

Pancreatic Ductal Adenocarcinoma



Pancreatic Cytology: Features of Carcinoma

Mitchell 1985 AJCP	3-D clusters, disoriented or crowded cells	Nuclear enlargement	Nuclear membrane irregularities
Cohen 1991 Diagn Cyto	Large Nuclei	Molding	Anisonucleosis
Robins* 1995 Acta Cyto	Nuclear crowding/overlapping	Irregular chromatin	Nuclear contour membrane irregularity
David 1998 Diag Cyto	Disorderly groups	Nuclear enlargement	Nuclear membrane irregularities

*Robins Minor criteria (nuclear enlargement, single cells, necrosis, mitoses)

Pancreatic Cytology: Features of Carcinoma

- Well differentiated tumors can be difficult to diagnose.

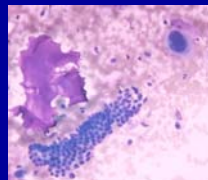
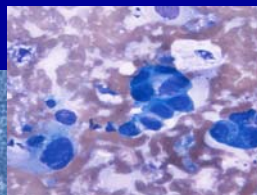
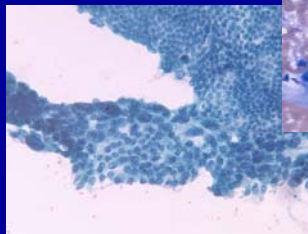
Comparison of Cytologic Features of Confirmed Pancreatic WDAs and Benign Lesions

Criteria no.	Cytologic feature	WDA (n = 24) (%)	Suspicious (n = 6) (%)	False negative (n = 4) (%)	Benign (n = 23) (%)
1	Anisonucleosis (greater than four times)	57	100	75	0
2	Nuclear membrane irregularity	97	83	50	4
3	Nuclear crowding/overlapping/three-dimensionality	97	67	50	17
4	Nuclear enlargement (>2 RBC)	99	83	100	17
5	Gap vs. confluent cell spacing	84	16	25	4
6	Hyperchromasia	36	0	25	7
7	Macronucleoli	14	0	0	0
8	Mitosis	22	0	25	7
9	Chromatin clumping	14	33	0	4
10	Necrosis	7	0	0	0

WDA, well differentiated adenocarcinoma; RBC, red blood cells.

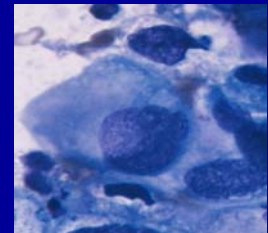
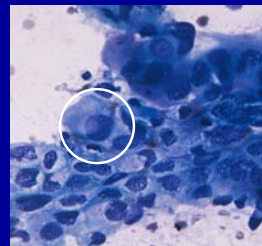
Lin F, Steiertel G. Cytologic Criteria for Well Differentiated Adenocarcinoma of the Pancreas in Fine Needle Aspiration Biopsy Specimens. Cancer Cytopathology. 99(44-50)2003

Features of Malignancy: Anisonucleosis

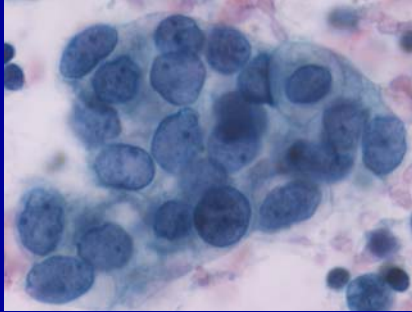


Greater than 4 fold variation in nuclear size within a group

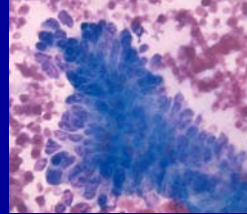
Features of Malignancy: Nuclear membrane irregularities



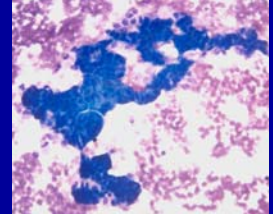
Features of Malignancy: Nuclear Membrane Abnormalities



Features of Malignancy: Architecture

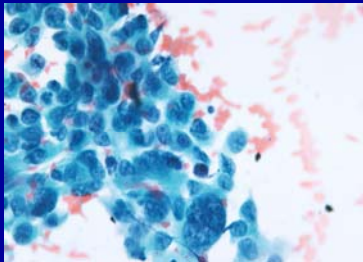


Crowded, overlapping nuclei



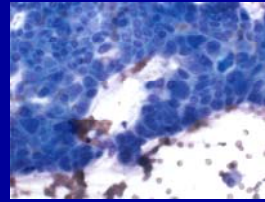
Three dimensional structures

Features of Malignancy: Nuclear Enlargement

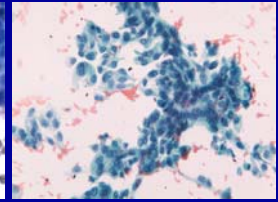


Nuclei more than twice the size of a red blood cell

Pancreatic Carcinoma: Other Cytologic Features

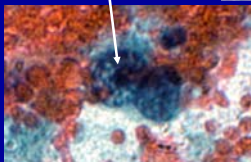
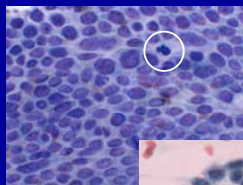


Gap vs confluent spacing (Sheet dyshesion)

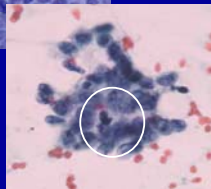


Hyperchromasia

Pancreatic Carcinoma: Other Cytologic Features

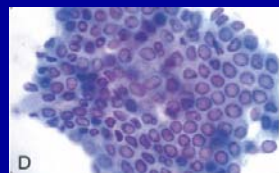


macronucleoli

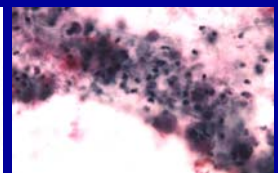


mitoses

Pancreatic Carcinoma: Other Cytologic Features



Chromatin Clearing
Photo from Lin and Staerkel 2003



Necrosis

Chronic Pancreatitis

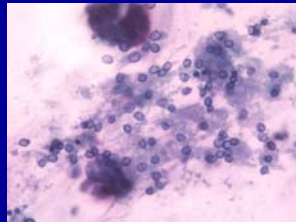


Chronic Pancreatitis

- Chronic pancreatitis may mimic cancer in its clinical presentation
- Chronic pancreatitis is a risk factor for the development of pancreatic adenocarcinoma
- Chronic pancreatitis is often present in the tissue around pancreatic adenocarcinoma

Chronic Pancreatitis: Cytologic Features

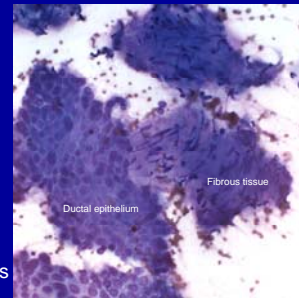
- Less cellular
- Disproportionate ratio of ductal to acinar cells
- Inflammation varies, acute or chronic
- Fat necrosis
- Debris, mucin, fibrous tissue, calcification



Degenerated Acini

Chronic Pancreatitis: Cytologic Findings

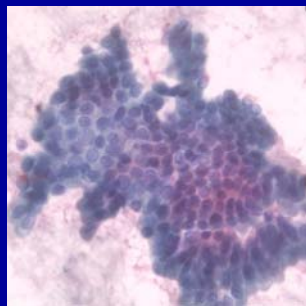
- Most helpful cytologic features*
 - Fibrotic acinar tissue
 - Fibrosis
 - Calcific debris
- Ductal atypia is worrisome
- A cytologic diagnosis of chronic pancreatitis does not exclude carcinoma



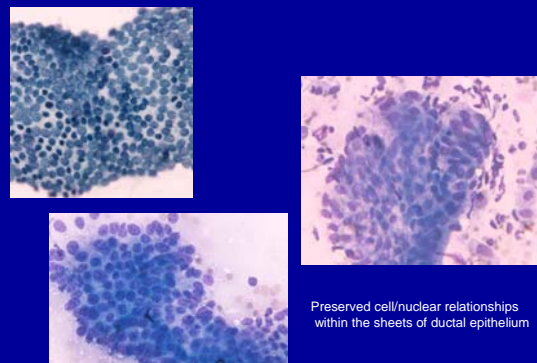
*Sietow EB, Bardales RH, Lei R, Mallory S, Linzie BM, Cray GS, Stanley MW. The Cytologic Spectrum of Chronic Pancreatitis. Diagnostic Cytopathology 32(2): 65-69, 2005

Chronic Pancreatitis: Ductal Epithelium

- **Cohesive**
 - Few if any single cells
- **Orderly** arrangement
- **Uniform** nuclei (little variability)
- **Smooth** nuclear contours



Chronic Pancreatitis: Ductal Epithelium



Preserved cell/nuclear relationships within the sheets of ductal epithelium

Chronic Pancreatitis: Problems in Interpretation

- Ductal epithelium can be very atypical secondary to reactive changes
- Stents cause reactive changes
- Squamous met can be seen in both benign and malignant
- Adenocarcinoma can be deceptively bland
- Chronic pancreatitis and cancer coexist
- Underdiagnosis is more of a problem than overdiagnosis

Pancreatic Cystic Lesions

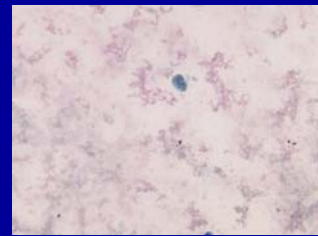


Pancreatic Cystic Lesions

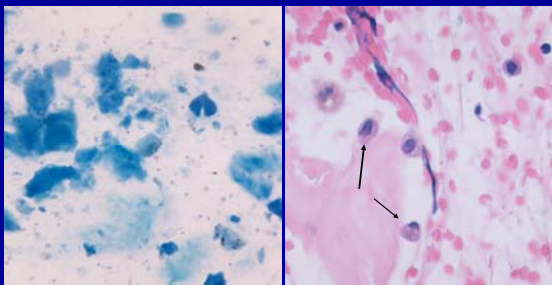
- Non Neoplastic (Pseudocysts)
- Neoplastic
 - Benign
 - Malignant

Pancreatic Pseudocyst Cytology

- Inflammatory cells
- Macrophages (hemosiderin)
- Debris, blood, sometimes bile
- No cyst lining
- Fibroblasts
- Normal pancreatic elements



Pseudocyst: Cytology



Debris

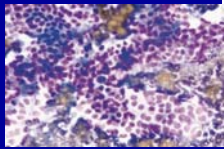
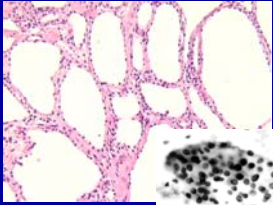
Macrophages

Cystic neoplasms

- Serous
- Mucinous

Serous cystadenoma: Cytology

- Scant cellularity, may be non diagnostic
- Proteinaceous background, blood
- Monolayer sheets, bland nuclei clear or vacuolated cytoplasm, distinct cytologic borders
- Glycogen present (PAS/PASD)

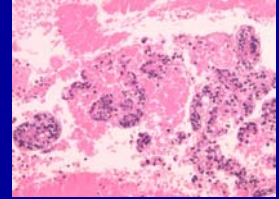


Logrono R, Vyas SH, Molina CP, Wasman I. Microcystic Adenoma of the Pancreas. *Diag Cyto* 20(5):298-301, 1999

Rampry BA, Wasman I, Xiao SY, Logrono R. Serous Cystadenoma of the Pancreas with Papillary Features. *Arch Path Lab Med* 125:p1591-1594, 2001

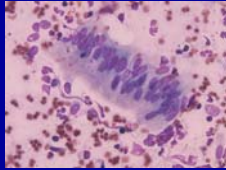
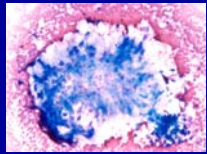
Mucinous Cystic Neoplasms

- Benign, Borderline, Malignant
- Multilocular cysts with variability
- Columnar epithelium

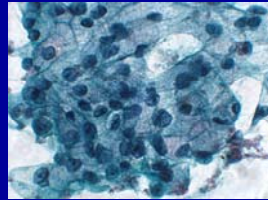


Mucinous Cystic Neoplasms

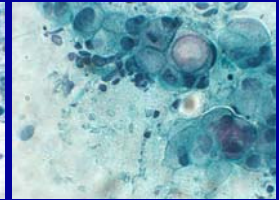
- Background **Mucin**
- **Columnar cells** whose arrangement varies from flat to papillary to pseudoacinar
- Well defined **cytoplasmic borders**
- **Variable nuclear atypia.**



Mucinous Cystic Neoplasms

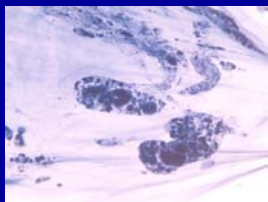


"Drunken Honeycomb"

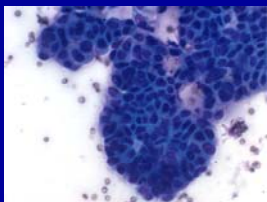


Intracytoplasmic Mucin

Mucinous Cystic Neoplasms



Necrosis



Nuclear pleomorphism architectural atypia

Pancreas Cytology: Technical Issues

Pancreatic FNA: Technical Features

- Technical aspects of the procedure may make a difference in diagnostic yield
- Sample preparation: Optimum preservation of diagnostic features
 - Staining
 - Cell Block
 - Liquid Based
- Immediate Cytologic Evaluation
- Pathologist's Interpretation

Cytology Preparation

Preparation	Advantages	Disadvantages
Air Dried Smears	Speed of preparation, Exaggerate pleomorphism if present	Require technical proficiency
Alcohol Fixed Smears	Excellent preservation of nuclear detail	Require technical proficiency
Cell Block	Familiarity, Less technically demanding on site	Suboptimal preservation of cells
Liquid based	Potentially less technically demanding on site	Limited data regarding pancreatic cytology

Air dried, Alcohol fixed and cell block preparations are complimentary and ideally are used in combination.

Immediate Cytologic Evaluation

- Provides real time feedback about the content and quality of the aspirate
- Maximizes efficiency of the procedure
- Most effective way to reduce sampling error (and false negative diagnoses)
- Allows triage of specimen for culture, flow cytometry, molecular diagnostics etc
- Disadvantage-Pathologist time and potential cost

Compromise solutions include use of runners from endoscopy suite to lab, cytotechnologist for screening, review of several passes at one time

Pathologist's Interpretation

Experience with and bias toward tissue sections

Screening vs diagnostic procedure

Learning curve

False negative pancreatic FNA are due to sampling

False positive (rare) are due to pathologist inexperience

Communication between pathologist and endoscopist regarding the purpose of the procedure in the diagnostic algorithm, technical aspects of slide preparation and discussion of results will optimize patient care

Pancreatic Cytology: Summary

- Criteria based diagnosis of FNA of pancreatic lesions is clinically useful and accurate
- Communication between the endoscopist and the pathologist regarding specific issues is critical
 - Technical quality of the material
 - Immediate Cytologic Evaluation (Adequacy of specimens)
 - Integration of clinical data and pathologic findings.