Pancreatic Neoplasms with Acinar Differentiation

PRESENTED BY
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**Laura D. Wood, MD, PhD** reported the following relevant financial relationship(s) during the content development process for this activity: *Consultant, Personal Genome Diagnostics*
Case 1

This 60-year-old man presented with arthralgias, peripheral eosinophilia and pockets of fat necrosis in the subcutaneous tissues of his legs. A distal pancreatectomy was performed for a solid pancreatic mass.
If Solid: Hypocellular vs. Cellular

Nature of epithelium & stroma
- Individual glands
- Dendriform pattern
- Myoepithelial neoplasm
- Solid cellular epithelium
- Minimal stromal fibrosis

Pattern of growth
- Adenomatous
- Ribbons or nests
- Mixed mucus

Nuclear features
- Single prominent nucleolus
- Salt & pepper nuclei
- Nuclear grooves
- Ploid cellular nuclei
- Hyperchromatic nuclei

Immunolabeling
- Tropinin: negative
- Synaptophysin: negative
- CD10: negative

Squamous nests
- Yes
- Chronic pancreatitis
- Ductal adenocarcinoma
- Yes
- Pancreatic blastoma
- Acinar cell carcinoma
- Pancreatic neuroendocrine tumor (PanNET)
- Solid pseudopapillary neoplasm
- No
- Serous cystic neoplasm
- Mucinous cystic neoplasm
- Intraductal papillary mucinous neoplasm

Gross configuration
- Solid neoplasm
- Cystic neoplasm

Degenerative vs. True epithelial lining
- Degenerative
- True epithelial lining

Type of epithelium
- Serous
- Mucinous

Type of stroma
- Ovarian
- Collagenous

Six useful features
- Hyperplastic growth pattern
- Intracystic luminal neoplastic necrosis
- Nuclear variability > 2:1
- Growth next to muscular vessel
- Perineural invasion
- Vascular invasion

Based on AFIP Fascicle, 4th Edition
Nature of Epithelium and Stroma

- Hypocellular with desmoplastic stroma
- Cellular with minimal or hyalinized stroma

Solid cellular neoplasms
Solid Cellular Neoplasms

1. Pattern of Growth
2. Nuclear Features
3. Immunolabeling
Pattern of growth: acinar
Pattern of growth: acinar
Nuclear Features: Single Prominent Nucleolus
Nuclear Features: Single Prominent Nucleolus
**Pattern of growth**
- Acinar
- Ribbons or nests
- Insidious invasion

**Nuclear features**
- Single prominent nucleolus
- Salt & pepper nuclei
- Nuclear grooves
  - Poorly cohesive cells
  - Foam cells
  - Cholesterol clefs

**Immunolabeling**
- Trypsin
- Chymotrypsin
- Synaptophysin
- Chromogranin
- CD10
- Nuclear beta-catenin

**Diagnosis**
- Acinar cell neoplasm
- Pancreatic neuroendocrine tumor (PanNET)
- Solid-pseudopapillary neoplasm
Acinar Cell Carcinoma – Staining

- Zymogen granules – PAS positive, diastase resistant

- Immunohistochemistry
  - 90-100% Bcl10 (homology with carboxyl ester lipase)
  - 90-100% trypsin
  - 75% lipase
  - 40% chymotrypsin
  - 30% amylase
  - 42% synaptophysin/chromogranin (focal)

If >30% of malignant cells show neuroendocrine differentiation:
  mixed acinar–neuroendocrine carcinoma

Capella, Virchow Archives, 2009;454:133-42
BCL10
(carboxyl ester lipase)
Potential IHC Pitfall

- Expression of markers of hepatocellular differentiation
  - >50% positive for at least 1 marker (glypican 3, AFP, albumin mRNA)
  - Arginase uniformly negative

Acinar Cell Carcinomas Involving the Duct System

• Acinar cell carcinomas can involve the pancreatic duct system

• Grow along the pancreatic ducts as extending polypoid projections, filling the ducts and destroying the duct walls

• Metastases to the liver with subsequent intraductal growth in the liver have also been reported

Ban et al, AJSP 34:1025-36.
Intraductal growth can trigger mucin production and mimic mucinous adenocarcinoma
Neoadjuvant treatment can significantly alter morphology

Images from Liz Thompson, MD, PhD
Acinar Cell Carcinomas - Clinical

- Age – mostly adults (mean 62 years)
- Gender – male > female
- Symptoms – usually non-specific with weight-loss, abdominal pain, and nausea and vomiting
- Lipase – about 15% develop the syndrome of arthralgias, eosinophilia and subcutaneous fat necrosis
Stage is the only independent prognostic factor.

Mean Survival = 18.1 mos.

Survival:
- 1 year = 56.5%
- 2 years = 40.0%
- 3 years = 26.3%
- 5 years = 5.9%
Acinar Cell Carcinomas - Molecular

- Striking genetic heterogeneity
  - Microsatellite instability (MSI) in ~10% (no distinctive morphology)
  - Variable allelic losses, sometimes involving a large fraction of the genome – loss of 11p is common (~50%)
  - No gene altered by somatic point mutation in >30%
    - SMAD4 in 30%, also TP53, GNAS, RNF43, APC, CTNNB1, BRAF, PTEN…
    - APC and CTNNB1 mutations raise possibility of overlap with SPN on β-catenin IHC
    - Mutations in DNA repair genes in ~50% - BRCA1, BRCA2, ATM, PALB2, MSH2

- RAF fusions in ~25%, SND1-BRAF most common
  - Result in downstream MAPK activation
  - Can be identified by FISH

Chmielecki et al, Cancer Discov, 2014;4(12):1398-405;
Wang et al, Mod Pathol, 2018;31(1):132-140;
Acinar Cell Carcinomas – Targetable Alterations

• Mostly treated with same chemotherapy regimens as PDACs: minimal data on other approaches

• Genomic data suggests several targetable alterations:
  • **Microsatellite Instability**
    • Immune checkpoint inhibitors
  • **Defects in DNA repair** (*BRCA2*, *ATM*, etc)
    • Platinum agents, PARP inhibitors
  • **RAF fusions**
    • MEK inhibitors
Pancreatic Acinar Cell Carcinoma Demonstrates an Active Tumor Immune Microenvironment

Poster #137, Wed March 20, 1-4pm

David Peske & Liz Thompson
This 10-year-old boy complained for weeks of abdominal pain. Imaging revealed a 10 cm solid mass in his pancreas.
Poll: Which of the following morphological features supports a diagnosis of pancreatoblastoma?
Which of the following morphological features supports a diagnosis of pancreatoblastoma?

A. Acinar differentiation of neoplastic cells

B. Squamoid nests

C. Discohesive architecture
If Acinar: Squamoid Nests?
Acinar Cell Carcinoma
Squamoid Nests Absent

Pancreatoblastoma
Squamoid Nests Present
Pancreatoblastoma - Clinical

- Occurs primarily in children (1-15 years), but there is bimodal age peak
- Malignant neoplasm – 40% present with metastases
- Mean survival 17 months
- Poorer survival in adults
- Can occur as part of inherited syndromes – Beckwith Wiedemann, FAP

Am J Surg Pathol 19:1371
Pancreatoblastoma

- Histologically recapitulates embryologic development

- Acinar component dominates in most cases and merges with squamoid nests
  - Majority of cases show abnormal nuclear and cytoplasmic $\beta$-catenin in squamoid nests
  - Other components:
    - Endocrine
    - Ductal
    - Stromal – can show osseous and cartilaginous areas

- Undifferentiated/primitive component
Squamoid nests
Pancreatoblastoma - Molecular

- Allelic loss of 11p is most common genetic alteration
  - Disrupts imprinting at IGF2, leading to overexpression
  - Imprinting at this locus can also be disrupted by methylation

- Activating CTNNB1 mutations are also common
  - APC inactivation can also occur, especially in tumors associated with FAP
  - Abnormal nuclear β-catenin labeling is often present but can be patchy

- Far fewer somatic mutations per tumor than ACC (18 vs 131)
  - No gene other than CTNNB1 reported to have recurrent mutations
  - Larger number of mutations in metastatic samples

Pancreatoblastoma – abnormal β-catenin labeling in squamoid nests
What about cystic lesions with acinar differentiation?
Cystic acinar lesions

- **Acinar cell cystadenoma**
  - Cysts lined by acinar or mixture of acinar/ductal cells
  - Minimal atypia
  - Random X-chromosome inactivation = non-neoplastic
  - May be caused by acinar dilation = “acinar cystic transformation”

- **Acinar cell cystadenocarcinoma**
  - Acinar cell carcinoma characterized by variably sized cysts
  - Malignant neoplasm
  - Very rare

Singhi et al, AJSP, 2013;37(9):1329-35
Colombo et al, Hum Pathol, 2004;35(12):1568-71
Pancreatic Neoplasms with Acinar Differentiation

• **Acinar cell carcinoma**
  - Affects older adults
  - Acinar architecture, single prominent nuclei, BCL10/trypsin IHC+
  - Can involve pancreatic duct system
  - Genomic instability, targetable alterations: MSI, DNA repair defects, RAF fusions

• **Pancreatoblastoma**
  - Most frequent pancreatic neoplasm in children but also affects adults
  - Squamoid nests, other components
  - 11p loss, *CTNNB1* mutations (aberrant β-catenin IHC)
Many images provided by Ralph Hruban, MD
Elizabeth Thompson, MD, PhD
THANK YOU