Diagnostic pitfalls in pancreatic pathology

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Introduction

Already discussed:
- Cysts - denuded, sampling (diagnosis, highest grade dysplasia, invasive carcinoma)
- Chronic pancreatitis vs PDAC
- Metastases

Diagnostic pitfalls

- IgG4-positive plasma cells
- Ampullary vs bile duct vs pancreatic ductal adenocarcinoma
- IPMN
- Acinar cell carcinoma

IgG4-positive plasma cells

Periampullary carcinoma

IgG4+ plasma cells

- Can be seen in chronic pancreatitis and in PDAC
- CP - 40% had focal (but not dense) IgG4+ plasma cells
- PDAC - 40% had focal IgG4+ plasma cells
- This peritumoural pancreatitis can include periductal inflammation and venulitis (diagnostic problem in bx)

(Hash et al. Hum Pathol 2010; 41: 869-82)
Periampullary carcinoma

- Identification of cancer origin (ampulla vs common bile duct vs pancreas) can be difficult, particularly with large tumours.
- Distinction important clinically: different T-staging criteria, differ in prognosis, participation in clinical trials/adjuvant treatment.
- Distinction important for determining possible differences in epidemiology, aetiology and molecular biology.

Identifying cancer origin

- Relationship of the centre of the tumour to the ampulla, common bile duct and pancreas.
- Macroscopic examination of the 3-dimensional relationship of the cancer to the key anatomical structures is important.
- Microscopy and immunohistochemistry are shared among the 3 cancer groups.

Axial slicing technique

Origin of periampullary cancer

1. Ampullary cancer – around ampulla at mid-cranio-caudal height.
3. Intrapancreatic BD cancer – in posterior head, above level of ampulla.
4. Extrapancreatic BD cancer – cranial part of specimen.

Precursor lesions

- Found in 80% of ampullary cancer.
- Flat dysplasia (BIIIN) only found in 10-30% of distal bile duct cancers.
- Use of PaniN is limited: low grade PaniN is common finding (especially over 40 yrs of age) in any pancreas.
- Cancerization of ducts or other structures.
Cancerization

- Duct cancerization (intraductal tumour spread) is found in up to 70% of PDACs
- Multifocal and affect pancreatic ducts of any calibre
- Can also affect the common bile duct, ampulla or duodenal crypts
- Presence of tumour glands in the vicinity of the involved duct and the abrupt transition from atypical to normal epithelium

PDAC

- When PDAC invades the duodenal mucosa, it can mimic duodenal dysplasia by growing along the basement membrane of the crypts and villi

PDAC

- When PDAC infiltrates the muscularis propria of the duodenum, it can acquire an intestinal phenotype (mimic duodenal carcinoma)

Intraductal papillary mucinous neoplasm (IPMN)

- IPMN vs PanIN
- Extension into smaller ducts
- Colloid carcinoma vs mucus extravasation
- IPMN vs cystic papillary carcinoma
- Concomitant PDAC
- Frozen sections
- T-staging

# IPMN vs PanIN

<table>
<thead>
<tr>
<th>Clinicopathological</th>
<th>PanIN</th>
<th>IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closely related</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth within</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mucin-secreting cells in lining of duct</td>
<td>Rarely within duct</td>
<td>Present in IPMN</td>
</tr>
<tr>
<td>Duct size</td>
<td>Variable diameter</td>
<td>Usually &lt; 500 μm diameter</td>
</tr>
<tr>
<td>Intraductal papillae</td>
<td>Rarely</td>
<td>Abundant</td>
</tr>
<tr>
<td>Cystic dilatation</td>
<td>Rarely</td>
<td>Frequently</td>
</tr>
<tr>
<td>Regional capsule</td>
<td>Rarely</td>
<td>Usually</td>
</tr>
<tr>
<td>Presence of adenocarcinoma</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

# Incipient IPMN

- Term 'incipient IPMN' introduced for lesions between 5 and 10 mm in size
- Overlap between gastric-type IPMN and low-grade PanIN (involve branch ducts, similar morphology & mucin profiles)
- Do incipient IPMNs belong to the IPMN pathway or the PanIN-associated pathway?
- GNAS mutations in 33% of incipient IPMNs; postulate that some are in fact small IPMNs


# Extension into smaller ducts

- IPMNs may grow into smaller ducts and mimic PanIN or be mistaken for invasive carcinoma
- Knowledge of this phenomenon helps
- Extension into smaller ducts: lobular architecture & stroma, smooth outline of the involved ducts, morphological similarity to the main lesion
- If severe atrophy, small involved ducts may resemble well-differentiated invasive carcinoma, but these ducts are widely spaced and not surrounded by desmoplastic stroma (elastin stain will outline the native ducts)

# Colloid carcinoma vs mucus extravasation

- Ducts containing IPMN may rupture, resulting in mucus extravasation
- Extravasated mucus does not contain epithelium and may evoke an inflammatory response
- Colloid carcinoma mucin pools are not related to disrupted ducts and contain floating neoplastic cells with little or no associated inflammation

# IPMN vs cystic papillary carcinoma

- Cystic papillary variant of PDAC may mimic IPMN
- Large malignant glands containing abundant mucin and papillary projections
- Does not involve the duct system (no elastic fibres around the malignant glands)
Concomitant PDAC

- IPMN and PDAC may be present in the same specimen, but the PDAC may develop independently of the IPMN (so-called concomitant PDAC), rather than arise from the IPMN.
- IPMN-associated invasive carcinoma will show histological transition from IPMN to invasive adenocarcinoma, whereas concomitant PDAC does not.
- Carcinoma arising in an IPMN, and PDAC concomitant with IPMN, can be detected at an earlier stage (see IPMN on imaging) than ordinary PDAC; consequently may have a better prognosis.

IPMN – frozen section

- Transection margin: duct(s) involved by IPMN (with or without invasive carcinoma) or dilatation secondary to obstruction
- Limitations: IPMN can be multifocal with 'skip' lesions, grade of dysplasia can vary within an IPMN, duct erosion/inflammation with reactive epithelial atypia
- Duct epithelium can also be denuded: deeper sections should be cut from tissue block and/or further tissue samples should be requested from the surgeon.

IPMN – frozen section

- If the margin is positive for HGD or invasive carcinoma, further resection is warranted.
- LGD or IGD at the margin does not require further surgery.


- Some still advocate further excision for LGD in main duct-type IPMN


Mixed duct-type IPMN

- Mixed duct-type IPMN thought to have same malignant potential as MD-type IPMN
- Now shown that minimal (microscopic) involvement of the main pancreatic duct in mixed duct-type IPMN shares clinicopathological features and (less aggressive) biology with BD-IPMN
- ?progression of BD-IPMN
- Separate classification.


What is ‘minimally’ invasive?

- ‘Minimally’ invasive PDACs are detected in IPMNs, ITPNs and MCNs.

Definitions:
- ‘≤5mm in depth’
- ‘Minute focus/foci of invasion’
- ‘Cancer discovered only on microscopy’
- ‘T1 cancer’

- Suggested now that this term is abandoned

Subdividing pT1

- Proposed subdividing T1 into
  pT1a  ≤0.5cm
  pT1b  >0.5 & ≤1cm
  pT1c  1-2cm

for cancers arising in IPMNs, ITPNs and MCNs


- Needs validation/acceptance by AJCC/UICC TNM
IPMN – size of invasive cancer

- Important prognostic factor
- Size of overall tumour (non-invasive & invasive components together) is often used interchangeably with size of invasive carcinoma
- Measure size of invasive carcinoma
- For multifocal invasive tumours, measure diameter of largest tumour & overall estimated size of all foci in aggregate. Not yet clear which one of these better reflects tumour burden


Acinar cell carcinoma

Acinar cell carcinoma (ACC)

- Accounts for 1-2% of pancreatic exocrine neoplasms
- Mean age 60yrs, age range 3-90yrs
- Male:female ratio 2:1
- Non-specific symptoms: abdominal pain, nausea & vomiting, weight loss
- 15% of patients may present with lipase hypersecretion syndrome (elevated serum lipase, diffuse subcutaneous fat necrosis, polyarthritides, with or without eosinophilia)
- Up to 50% present with metastatic disease (LNs, liver, lungs, peritoneum)

ACC - macroscopy

- Large, well-circumscribed, soft solitary tumour with pushing (expanding) border
- Men size 10cm (range 2-30cm)
- Lobulated cut-surface
- Haemorrhage, necrosis and cystic degeneration
- Intraductal growth

ACC – microscopy

- Lobulated cellular tumour separated by hypocellular fibrous bands
- Carcinoma cells are arranged in acinar pattern, solid sheets, trabecular or gyriform pattern; mixture of growth patterns can occur in the same tumour
- Often numerous small blood vessels around the nests of carcinoma cells

ACC – growth patterns
**ACC - cytology**
- Minimal to moderate amounts of amphophilic to eosinophilic granular cytoplasm
- Granularity is due to zymogen granules
- Uniform round/oval nuclei with single central nucleolus, but well-differentiated carcinomas may have inconspicuous nucleoli
- Mitoses readily found

**ACC - immunohistochemistry**
- Trypsin, chymotrypsin, lipase (diffuse cytoplasmic in solid areas, or apical cytoplasmic in acinar areas)
- Alpha-1-antitrypsin, AE1-AE3, CAM5.2, CK8, CK18, EMA
- Conflicting results with CK7 & CK19 (traditionally markers of ductal differentiation)
- Recent study, CK7+ in 73% of cases and CK19+ in 85% of cases
  
- CEA-ve
- Ki67 (mean proliferative index 30%)

**ACC - immunohistochemistry**

Trypsin

**ACC – differential diagnosis**
Pancreatic endocrine neoplasms
- Both can have lobulated appearance, acinar growth pattern and scanty stroma within the tumour lobules
- ACC – mitotic, necrosis (so can PanNET)
- ACC – uniform vesicular nuclei, central nucleolus
- ACC (well-differentiated) – PAS-positive granules in apical cytoplasm
- ACC (IHC) - trypsin, chymotrypsin, lipase, and only scattered endocrine cells (synaptophysin, chromogranin)

**ACC vs PanNET**

**ACC – differential diagnosis**
Solid pseudopapillary neoplasm
- Both can have solid growth pattern
- SPN – young females
- SPN – nuclear grooves, PAS-positive globules
- SPN – vimentin, CD10, PGR and beta-catenin (abnormal nuclear & cytoplasmic)
- SPN – not express trypsin
ACC – differential diagnosis

Pancreatoblastoma
- Extremely uncommon malignant epithelial neoplasm
- Prominent acinar differentiation and squamoid nests (morules)
- Can also have ductal and endocrine differentiation, and small immature cells
- Hypercellular stroma
<table>
<thead>
<tr>
<th><strong>Morphology</strong></th>
<th><strong>Pancreatic neuroendocrine tumor</strong></th>
<th><strong>Ductal adenocarcinoma</strong></th>
<th><strong>Acinar cell carcinoma</strong></th>
<th><strong>Pancreatoblastoma</strong></th>
<th><strong>Solid-pseudopapillary neoplasm</strong></th>
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<tbody>
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<td>Pseudopapillae</td>
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</table>

++ usually positive, + may be positive, - usually negative, ID insufficient data

**Campbell F, Verbeke CS. Pathology of the pancreas – a practical approach. Springer-Verlag, London, 2013**