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

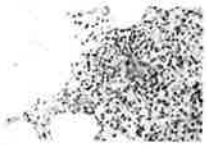
- IgG4-positive plasma cells
- Ampullary vs bile duct vs pancreatic ductal adenocarcinoma
- IPMN
- Acinar cell carcinoma

IgG4-positive plasma cells

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)

Dhall et al. Hum Pathol 2010; 41: 643-52



Periampullary carcinoma

Periampullary carcinoma

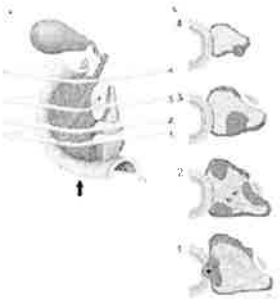
- Identification of cancer origin (ampulla vs common bile duct vs pancreas) can be difficult, particularly with large tumours
- Distinction important clinically: different T-staging criteria, differ in prognosis, participation in clinical trials/adjuvant treatment
- Distinction important for determining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



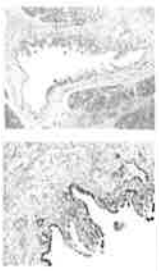
4. Extrapancreatic BD cancer – cranial part of specimen
3. Intrapancreatic BD cancer – in posterior head, above level of ampulla
2. Pancreatic cancer – anywhere in head of pancreas
1. Ampullary cancer – at/around ampulla at mid-craniocaudal height

Precursor lesions

- Found in 80% of ampullary cancer
- Flat dysplasia (BilIN) only found in 10-30% of distal bile duct cancers
- Use of PanIN is limited: low grade PanIN is common finding (especially over 40yrs 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

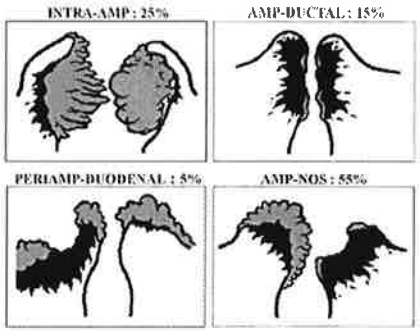


PDAC

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

PDAC

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



Adsay et al. Am J Surg Pathol 2012; 36: 1592-1608

Intraductal papillary mucinous neoplasm (IPMN)

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

	PanIN	IPMN
Clinically detected	No	Yes
Grossly visible	No	Yes
Mucus [illegible]	No	Yes
Duct size	Usually <5 mm diameter	Usually >10 mm diameter
Intraluminal mucin	Minimal	Abundant
Growth pattern	Flat or papillae	Predominantly papillary, rarely flat
Papillae	Microscopic	Taller, more complex, and grossly visible
Associated invasive adenocarcinoma	Conventional type	Conventional type, colloid carcinoma or cystic carcinoma

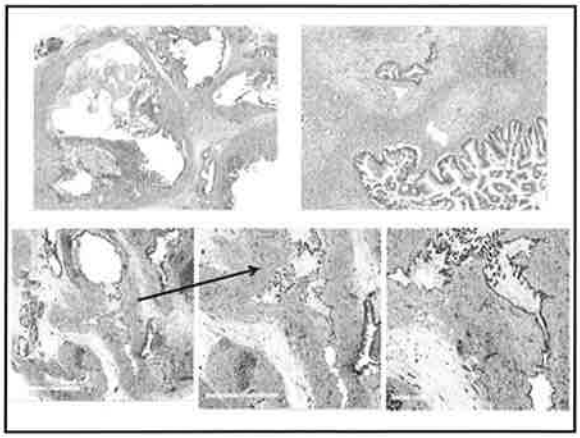
Incipient IPMN

- **Term 'incipient IPMN' introduced for lesions between 5 and 10mm 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**

Matthaei H et al. Am J Surg Pathol 2014; 38: 360-3

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

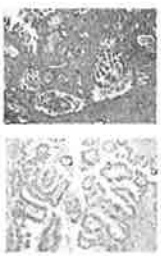
- **Ducts containing IPMN may rupture, resulting in mucus extravasation**
- **Extravasated mucus does not contain epithelium and may evoke an inflammatory response**
- **Colloid carcinoma mucin pools are not related to disrupted ducts and contain floating neoplastic cells with little or no associated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

IPMN vs cystic papillary carcinoma

- **Cystic papillary variant of PDAC may mimic IPMN**

Kelly PJ et al. Am J Surg Pathol 2012; 36: 696-701

- **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

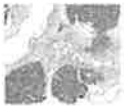
- If the margin is positive for HGD or invasive carcinoma, further resection is warranted
- LGD or IGD at the margin does not require further surgery

Adsay et al. Ann Surg 2015: Mar 13 [Epub ahead of print]

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

Tanaka M et al. Pancreatology 2012; 12: 183-97

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

Sahora K et al. Surgery 2014 Jul 28 [Epub ahead of print]

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

Tanaka M et al. Pancreatology 2012; 12: 183-97
Adsay et al. Ann Surg 2015; March 13 [Epub ahead of print]

- 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

Adsay et al. Ann Surg 2015; March 13 [Epub ahead of print]

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, polyarthritis, 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

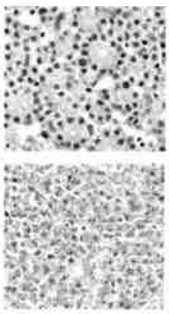
ACC – microscopy

- 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

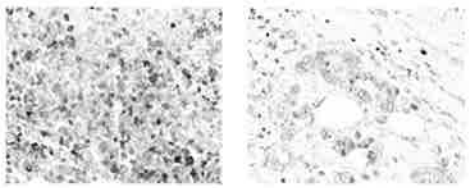


ACC - immunohistochemistry

- 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 86% of cases

  La Rosa S et al. Am J Surg Pathol 2012; 36: 1782-95
- CEA-ve
- Ki67 (mean proliferative index 30%)

ACC - immunohistochemistry



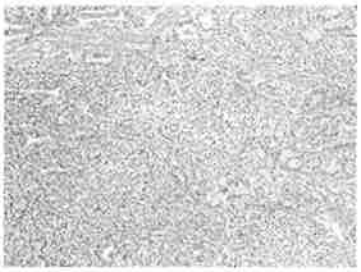
Trypsin

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 PanNEC)
- 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 20.6 Differential diagnosis of pancreatic neuroendocrine tumors

	Pancreatic neuroendocrine tumor	Ductal adenocarcinoma	Acinar cell carcinoma	Pancreatoblastoma	Solid-pseudopapillary neoplasm
Morphology					
Compact, cellular tumor	++	–	++	++	++
Lobulated tumor architecture	+	–	++	++	+
Pseudopapillae	+	–	–	–	++
Dense tumor stroma	+	++	–	++ (often hypercellular)	–
Salt and pepper chromatin	++	–	–	–	–
Nuclear grooves	–	–	–	–	++
Nucleoli	+	++	++	++	–
Intracytoplasmic mucin	–	++	–	–	–
PAS-positive hyaline globules	+	–	–	–	++
Squamoid nests	–	–	–	++	–
Immunohistochemistry					
CK19	+	++	+	+	–
CAM5.2	++	++	++	++	Focal
Vimentin	–	–	+	–	++
Chromogranin/synaptophysin	++	Focal	Focal	+	Focal (synaptophysin only)
NSE/CD56	++	–	+	+	++
Trypsin, chymotrypsin	–	–	++	++	–
Apha-1-antitrypsin	+	–	++	++	++
CD10	+	+	–	–	++
Beta-catenin (nuclear)	+	–	+	+	++
PR	+	–	–	ID	+

++ 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