biliary tract cytology

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The role of cytology in management of diseases of hepatobiliary ducts

• Diagnosis in patients with radiologically/clinically detected lesions
• Screening of dysplasia/CIS/cancer in risk groups
• Preoperative evaluation of the candidates for liver transplantation (Patients with cytological low-grade and high-grade dysplasia/adenocarcinoma are currently referred for liver transplantation in some institutions).
• Diagnosis of the benign lesions and infestations

Low sensitivity but high specificity!

False positive findings

• majority of false positive cases have a background of primary sclerosing cholangitis.
  – lymphoplasmacytic sclerosing pancreatitis and cholangitis,
  – primary sclerosing cholangitis,
  – granulomatous disease,
  – non-specific fibrosis/inflammation
  – stone disease.

False negative findings

• Poor sampling
• Lack of diagnostic criteria for dysplasia-carcinoma in situ
• Difficulties in recognition of special tumour types
  – well-differentiated cholangiocarcinoma with tubular architecture
  – gastric foveolar type cholangiocarcinoma with mucin-producing tumour cells.
• Underestimating the significance of the smear background
• The causes of false negative cytology
  – sampling error was a major cause (67%),
  – interpretive (17%), Logroño et al

• Repeat brushing increases the diagnostic yield and should be performed when sampling biliary strictures with a cytology brush at ERCP.

• Predictors of positive yield include
  – older age,
  – mass size >1 cm, and
  – stricture length of >1 cm.
 Sampling

• Endoscopic Bile and Retrograde Brush Cytology (ERCP)
• Percutaneous transhepatic cytology
• T-Tube bile drainage
• Endoscopic Ultrasound-Guided aspiration

Histology

• Intrahepatic bile ducts
• Extrahepatic bile ducts
  — Biliary
  — Intestinal
  — Foveolar
  — Squamous

Intrahepatic CholangioCarcinoma (ICC)

Klatskin tumour Cholangiocarcinoma arising from the right and left hepatic ducts at or near their junction is referred to as “hilar CC” and considered to be an extrahepatic lesion.

Extrahepatic CholangioCarcinoma

Etiology

• Alcoholic liver disease
• Hepatitis C virus
• HIV
• Diabetes mellitus
• Inflammatory bowel disease
• Chronic inflammatory biliary disease
• Primary sclerosing cholangitis (PSC) (prevalence 5-15% in USA. Higher risk in Northern European countries)
• Hepatolithiasis (7% of cases develop ICC, 27-65% ICCs are assoc with hepatolithiasis)
• Parasitic biliary infestations
• Biliary malformations
  — Fibropolycystic disease of the liver, Caroli disease, cholangiocystic, solitary unicocular or multiple cysts, congenital hepatic fibrosis
• Non-biliary cirrhosis
• ...
Clinical features

- Relatively early obstructive jaundice
- Right upper-quadrant pain
- Malaise
- Weight loss
- Pruritus
- Anorexia
- Nausea and vomiting
- Chills and fever (in case of cholangitis)

Precursor lesions

- **Biliary Cystadenoma**
  - Intraductal Papillary Neoplasms (IPN) / Intraductal papillomatosis
  - BiliN 1-3 (Biliary Intraepithelial Neoplasia)

- **Intraductal Papillary Neoplasms (IPN) / Intraductal papillomatosis**
  - Pancreatobiliary (most common)
  - Intestinal
  - Oncocytic
  - Gastric

- **Intrahepatic IPN 1/3 Mucinous**
  - Extrahepatic mucinous IPN is rare (looks like pancreatic IPMN)

Pheonotype of Intraductal papillary Neoplasia - WHO 2010

- Tends to occur in women
- Has a well-known tendency for malignant transformation
- Columnar or cuboidal mucin-secreting epithelium
- Mostly uniform
Precursor lesions
BilIN 1-3 (Biliary Intraepithelial Neoplasia)

- Atypical epithelial cells
- Multilayering of nuclei
- Micropapillary projections into the lumen
- Increased nucleus-cytoplasm ratio
- Partial loss of nuclear polarity
- Nuclear hyperchromasia

Biliary Intraepithelial neoplasia – BilIN
WHO 2010

Hyperplasia
Normal

BilIN-1

BilIN-2

BilIN-3
Carcinoma/Histopathology

- Adenocarcinoma biliary type
- Adenocarcinoma gastric foveolar type
- Intestinal type adenocarcinoma
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Carcinosarcoma
- Clear cell adenocarcinoma
- Mucinous adenocarcinoma
- Undifferentiated carcinoma

Epithelium of the Normal Ducts /Cytology

- Flat sheets of cells / honeycomb” pattern
- Columnar or cuboidal
- Suprabasal spherical or ovoid nucleus
- One or two tiny nucleoli
- Generally pale staining cytoplasm
- Granular crystals of yellow or green bilirubinate or crystalline calcium carbonate
- Single cells or clusters of cells
- Feathering of cells: brushing artifact
- Occasional cytoplasmic vacuoles

Normal-TP, pap.

Normal-TP
Benign oncocytic cells/pancreas aspiration/MGG

Cytological findings: adenocarcinoma

• Clusters of cells, disorganised sheets, loose aggregates, small acinar groups and single pleomorphic cells
• Marked overlapping and crowding
• Nuclear enlargement, moulding and irregular nuclear outlines
• Prominent nucleoli
• High N:C ratio
• Coarse chromatin
• Background of necrotic debris.

Biliary brush samples

low-grade dysplasia

• Sheets and clusters with nuclear crowding and overlapping
• Smooth nuclear outline, moderate N:C ratio
• Granular chromatin with mild clumping
• 1–2 small distinct nucleoli.

high-grade dysplasia

• Clusters and groups with prominent nuclear crowding and overlapping
• Irregular nuclear membranes, high N:C ratio
• Coarse chromatin
• Distinct prominent nucleoli.

Cytologic Diagnose

• Non-diagnostic
• Benign
• Atypia
  – Reactive atypia?
  – Dysplasia or neoplastic process?
• Suspicious for malignancy
• Malignant
Cytologic Diagnose

- Non-diagnostic
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FISH

- Chromosomes 3, 7, 17
- CDKN2A (9p21)
Case
• Male, 62, PSC, stenosis in choledochus
• Cytology: benign
• FISH: trisomy 3,7,17
• Liver biopsy: suspicious for cholangiocellular carcinoma
• Liver transplantation...

Case
• Male, 46 y o, stenosis in bile ducts
• PSC + Colitis Ulcerosa
• Cytology: Atypia
• FISH: “Trisomy chro 3, 7, 17, consistant with malignant cells”
• Liver transplantation.
Case

- Male, 41
- Anamnesis: PSC and known cholecystectomy showing dysplasia.
- Finding: Polypoid lesion in the choledochus.
- Cytology: Papillary Neoplastic Lesion with atypia.
- FISH: trisomy chro 3,7,17.
- Liver transplantation:...
Intraductal Papillary Neoplasia Biliary & Intestinal type, BILIN-2

Case

- Female, 62 y o, stenosis in choledochus
- Cytology: Suspicious for malignancy in 2 samples
- FISH:
  - Sample 1 normal.
  - Sample 2 trisomy (chro 3 & 7) in a few cells.
- Surgical material: left lobectomy because of suspicious Klatskin tumor
Intraductal Papillary Neoplasia with 10 mm invasive cancer

**Case**

- Male, 67
- Stenosis in choledochus
- Cytology: Atypia
- FISH: Trisomy chromosom 3, 7, 17
Case

- Female 31 y o!
- PSC and stent in the choledochus. Clinically suspicious for CCCa
- Cytological preliminary diagnosis suspicious for malignancy
- FISH-TP: Normal
- Cell-block:...
Cell block: Malignant adenocarcinoma, adenocarcinoma in situ cannot be ruled out

Cell block FISH: Trisomy 7, 17

Ki67
p53
p16