Biliary tract tumors

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“I wish you pathologists would find a way to tell us surgeons whether a growth is cancer or not while the patient is still on the table.”

William Mayo, 1905
Case 1
Female, aged 57, epigastric pain and discomfort

- Abdomen CT: Multiple stones in the dilated left intrahepatic duct, gallbladder, and common bile duct
- Left lobectomy was performed
Dilated bile duct, fibrous ductal wall, and inflammatory cells infiltrate
Dysplastic nuclei reaching the luminal surface and pseudostratification
Nuclear hyperchromasia with pseudostratification
Hyperplasia of peribiliary glands
Immunohistochemistry

(+): MUC5AC

(-): MUC1, MUC2, CDX-2
case 1: Biliary intraepithelial neoplasia (Bill N)-2 in hepatolithiasis

Diagnostic criteria

1. Increased cellularity
2. Structural atypia: loss of polarity, nuclei reaching luminal surface
3. Nuclear atypia (evident but not enough for carcinoma):
   nuclear enlargement, hyperchromasia, irregularity of nuclear membrane
WHO histologic classification of tumors of the liver and intrahepatic bile ducts (2000)

**Benign epithelial tumors**
- Intrahepatic bile duct adenoma
- Intrahepatic bile duct cystadenoma
- Biliary papillomatosis

**Malignant epithelial tumors**
- Intrahepatic cholangiocarcinoma
- Bile duct cystadenocarcinoma
- Combined hepatocellular and cholangiocarcinoma
- Undifferentiated carcinoma

**Bile duct abnormalities**
- Hyperplasia (bile duct epithelium and peribiliary glands)
- Dysplasia (bile duct epithelium and peribiliary glands)
- Intraepithelial carcinoma (carcinoma in situ)
Diagnostic approach of biliary tract lesions

Biliary tract lesions

- First: clinical data, gross and microscopic features
- Second: immunohistochemistry, EM, molecular genetics, etc.

Non-neoplastic lesion

Neoplasm

- Line of differentiation

Epithelial

- Nuclear atypia (-)
- Invasion (-)
  - Benign
- Nuclear atypia (+)
  - Premalignant (dysplasia)
- Nuclear atypia (+)
  - Malignant (primary vs. metastatic)

Non-epithelial

- Nuclear atypia, atypical mitosis, necrosis
  - Absent
  - Present

- Benign
- Malignant (primary vs. metastatic)
Familiarity with the normal histology of the biliary tract is important.

<table>
<thead>
<tr>
<th>Diameter (um)</th>
<th>Small intrahepatic bile ducts</th>
<th>Large bile ducts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canals of Hering</td>
<td>Bile ductules</td>
</tr>
<tr>
<td></td>
<td>Cuboidal</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td>Lower columnar</td>
<td>15-100</td>
</tr>
</tbody>
</table>

Peribiliary glands

(Prog Histochem Cytochemistry 2007; 42: 61-110)
Normal large intrahepatic bile duct

A single layer of columnar cells with basally oriented nuclei
Normal small intrahepatic bile duct

Interlobular bile ducts and bile ductules in portal tract, and canal of Hering
Normal peribiliary glands

Peribiliary glands composed of cuboidal cells in lobular arrangement
Grading of biliary intraepithelial neoplasia (dysplasia) based on the degree of structural and nuclear atypia

<table>
<thead>
<tr>
<th>Consensus proposal (Zen, et al 2007)</th>
<th>3 grading system</th>
<th>2 grading system</th>
</tr>
</thead>
<tbody>
<tr>
<td>BilIN-1 (corresponding to low grade)</td>
<td>Mild dysplasia</td>
<td>Low grade dysplasia</td>
</tr>
<tr>
<td>BilIN-2 (corresponding to high grade)</td>
<td>Moderate dysplasia</td>
<td></td>
</tr>
<tr>
<td>BilIN-3 (corresponding to carcinoma in situ)</td>
<td>Severe dysplasia</td>
<td>High grade dysplasia</td>
</tr>
</tbody>
</table>
Classification of biliary intraepithelial neoplasia (Bill N)

Biliary epithelium

- Assess cellularity, structural atypia, nuclear atypia (nuclear enlargement, irregular nuclear membrane, hyperchromasias)

- Cellularity: slightly increased
- Structural atypia: (-) or mild
- Nuclear atypia (-)

Hyperplasia or reactive atypia

BillN

- Cellularity: increased
- Structural atypia (+)
- Nuclear atypia (+)

BillIN-1

- Cellularity: increased
- Structural atypia: pseudostratification, nuclei within lower 2/3 of epithelium
- Nuclear atypia: mild, uniform nuc. size and shape

BillIN-2

- Cellularity: increased
- Structural atypia: loss of polarity (not diffuse), nuclei reaching luminal surface
- Nuclear atypia: evident, but not enough for carcinoma

BillIN-3

- Cellularity: increased
- Structural atypia: loss of polarity (diffuse), nuclei reaching and piling on luminal surface
- Nuclear atypia: severe, overt carcinoma

(Mod Pathol 2007; 20: 701-709)
Hyperplasia or reactive change

Slightly increased cellularity and slightly enlarged nuclei with fine chromatin
Mild nuclear atypia, pseudostatification, nuclei in lower two thirds of epithelium
Enlarged, hyperchromatic nuclei reaching the luminal surface
Diffuse loss of polarity and severe nuclear atypia
Practical points: evaluation of Bill N (dysplasia)

• Three-grade system of BillN has been commonly used
• The identical diagnostic criteria of BillN could be used in the intrahepatic and extrahepatic bile duct lesions irrespective of the preceding biliary diseases
• Any consensus criteria for premalignant lesions in gallbladder and peribiliary glands have been not established
• The diagnostic criteria of BillN would be applicable to gallbladder and peribiliary gland lesions

(Mod Pathol 2007; 20: 701-709) (Pathol Int 2010; 60: 419-429)
## Morphologic changes of biliary tracts in hepatolithiasis

<table>
<thead>
<tr>
<th>Non-neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bile duct fibrosis and inflammatory cells infiltration</td>
</tr>
<tr>
<td>- Necroinflammatory and degenerative change of peribiliary glands</td>
</tr>
<tr>
<td>- Cystic dilatation of peribiliary glands</td>
</tr>
<tr>
<td>- Metaplasia of peribiliary glands</td>
</tr>
<tr>
<td>- Hyperplasia (or reactive change) of bile duct epithelium</td>
</tr>
<tr>
<td>- Hyperplasia (or reactive change) of peribiliary glands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BillN (dysplasia) of bile duct epithelium</td>
</tr>
<tr>
<td>- Dysplasia of peribiliary glands</td>
</tr>
<tr>
<td>- Intraductal papillary neoplasm of the bile duct (IPNB)</td>
</tr>
<tr>
<td>- Intrahepatic cholangiocarcinoma with BillN</td>
</tr>
<tr>
<td>- Intrahepatic cholangiocarcinoma with IPNB</td>
</tr>
</tbody>
</table>
Necroinflammatory/ degenerative change of peribiliary glands

Peribiliary glands with acidophilic cytoplasm, inflammatory cells infiltrate.
Cystic dilatation of peribiliary glands
Pyloric metaplasia of peribiliary glands

Pyloric metaplasia lined by clear columnar cells
Hyperplasia of peribiliary glands

Abundant proliferation of peribiliary glands with lobular arrangement
Dysplasia of peribiliary glands

Peribiliary glands with dysplastic epithelium and nuclear hyperchromasia
Case 2

Female, aged 58, no specific symptoms

- Abdomen CT: Saccular dilatation of the left intrahepatic bile duct, with multiple stones and low density lesion along the dilated bile duct
- Left lobectomy was performed
Large bile ducts and adjacent bile ducts lined by papillary epithelial cells
Papillary epithelial cells and mucin secretion
Mucin secreting cells with hyperchromatic nuclei and pseudostratification
Dysplastic cells with high nuclear/cytoplasmic ratio, pseudostratification
Immunohistochemistry

(+): MUC5AC, MUC2, CDX-2

(-): MUC1

MUC5AC

MUC1

CDX-2
Case 2: Intraductal papillary neoplasm of the bile duct with high grade dysplasia in hepatolithiasis

Diagnostic criteria

1. Intraductal papillary proliferation of mucin secreting cells
2. Mucin hypersecretion
3. Dilatation of affected bile ducts
4. 4 types: intestinal, gastric, pancreatobiliary, oncocytic type
Intraductal papillary neoplasm of the bile duct (IPNB)

• **Definition**
  Biliary papillary neoplasm mainly growing in the bile duct lumen resembling intraductal papillary mucinous neoplasm of the pancreas

• **Morphology**
  - Intraluminal papillary growth of mucin secreting epithelial cells (mucinous cells)
  - Mucin hypersecretion
  - Fibrovascular cores, dilatation of affected bile ducts
  - 4 histologic types of tumor cells:
    - pancreatobiliary, intestinal, gastric, and oncocytic
Types of tumor cells in biliary tract tumors

Pancreatobiliary type
- Columnar cells with eosinophilic cytoplasm and round nuclei
  - MUC1 (+)
  - MUC2 (-)
  - MUC5AC (+)
  - CDX-2 (-)

Intestinal type
- Stratified tall columnar cells with some goblet cells
  - MUC1 (-)
  - MUC2 (+)
  - MUC5AC (+)
  - CDX-2 (+)

Gastric type
- Columnar cells with abundant intracytoplasmic mucin
  - MUC1 (-)
  - MUC2 (-)
  - MUC5AC (+)
  - CDX-2 (-)

Oncocytic type
- Abundant, granular eosinophilic cytoplasm and round nuclei
  - MUC1 (+)
  - MUC2 (focal +)
  - MUC5AC (focal +)
  - CDX-2 (?)
A variety of terms have been used for intraductal papillary neoplasm of the bile duct (IPNB)

- Intraductal papillary neoplasia of the liver
- Intraductal papillary mucinous neoplasm
- Mucin hypersecreting bile duct tumor
- Biliary papillomatosis
- Mucin producing bile duct tumor
- Mucin-secreting bile duct adenoma
- Non-invasive or minimally invasive papillary carcinoma
- Intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma
- Intraductal growth type of cholangiocarcinoma
Until now there is no consensus criteria for grading of IPNB

<table>
<thead>
<tr>
<th>3 grading system</th>
<th>2 grading system</th>
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</thead>
<tbody>
<tr>
<td>IPNB with low grade dysplasia</td>
<td>IPNB-1</td>
</tr>
<tr>
<td></td>
<td>(corresponding to benign and borderline lesions of pancreatic IPMN)</td>
</tr>
<tr>
<td>IPNB with high grade dysplasia</td>
<td>IPNB-2</td>
</tr>
<tr>
<td></td>
<td>(corresponding to carcinoma in situ of pancreatic IPMN)</td>
</tr>
<tr>
<td>IPNB with carcinoma in situ</td>
<td></td>
</tr>
</tbody>
</table>

(Histo Histopathol 2002; 17: 851-861)
## Comparison of BilIN and IPNB

<table>
<thead>
<tr>
<th></th>
<th>BillIN</th>
<th>IPNB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatolithiasis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parasites infestation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gross</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>Microscopic</td>
<td>Macroscopic</td>
</tr>
<tr>
<td>Grossly visible</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Micro</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplastic epithelium</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Flat</td>
<td>+</td>
<td>Rare</td>
</tr>
<tr>
<td>Papillary proliferation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Mucin hypersecretion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Malignant transformation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucinous (colloid) carcinoma</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Intraductal growth type of intrahepatic cholangiocarcinoma arising in IPNB

Key morphologic findings
• 4 types of tumor cells
  1. Pancreatobiliary type
  2. Intestinal type
  3. Gastric type
  4. Oncocytic type
Case 3
Female, aged 46, right upper quadrant pain for 2 days

- Abdomen CT: Intraductal mass with cystic dilation of the bile duct in segment 5
- Segmentectomy was performed
Multiple papillary growing tumors in the dilated bile duct
Papillary structures covered by columnar cells
Complex papillary projections with fibrovascular stalks
Columnar cells with mild cytologic atypia
Immunohistochemistry

(+) MUC5AC

(-) MUC1, MUC2, CDX-2
Case 3: Biliary papillomatosis

Diagnostic criteria

1. Multifocal or diffuse papillary proliferation covered by columnar cells with fibrovascular stalks
2. Histologically papillary (villous) adenoma features
3. No invasion and metastasis
Biliary papillomatosis

- **Definition**
  Multiple, benign papillary lesions with delicate fibrovascular stalks covered with columnar cells

- **Site**
  Any sites in biliary tree

- **Morphology**
  - Papillary (villous) adenoma features
  - Malignant change:
    - Stromal invasion, marked dysplasia, loss of polarity, nuclear hyperchromasia, numerous mitoses
Intraductal growth type of intrahepatic cholangiocarcinoma arising in biliary papillomatosis

**Key morphologic findings**
- Multiple papillary tumors located in intrahepatic and extrahepatic bile duct
- Papillary (villous) adenoma features
- Malignant change: stromal invasion

Female, aged 61, liver and common bile duct

Common bile duct
Intraductal growth type of intrahepatic cholangiocarcinoma arising in biliary papillomatosis

Key morphologic findings
- Resection specimen for biliary papillomatosis should be entirely submitted to exclude a small focus of invasive carcinoma

Female, aged 61, liver
IPNB and biliary papillomatosis share similar morphological features

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>IPNB</th>
<th>Biliary papillomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>No predilection</td>
<td>No predilection</td>
</tr>
<tr>
<td>Biliary stone</td>
<td>Commonly present</td>
<td>Unknown etiologic factor</td>
</tr>
<tr>
<td>Site</td>
<td>Any sites in biliary tree</td>
<td>Any sites in biliary tree</td>
</tr>
</tbody>
</table>

**Morphology**

<table>
<thead>
<tr>
<th>Tumor cells</th>
<th>Usually mucinous (mucin-secreting) cells</th>
<th>Usually biliary columnar cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary (villous) adenoma</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Mucin hypersecretion</td>
<td>+</td>
<td>Variable</td>
</tr>
<tr>
<td>Fibrovascular cores</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Multifocal occurrence</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
IPNB, biliary papillomatosis, and intrahepatic cholangioca.

Liver lesion shows the spectrum of papillary biliary neoplasms
IPNB, biliary papillomatosis, and intraductal papillary cholangiocarcinoma

• IPNB, biliary papillomatosis, and intraductal papillary cholangiocarcinoma belong to the spectrum of papillary biliary neoplasms
Case 4
Female, aged 53, epigastric pain for 3 months

- Abdomen CT: A 20-cm multilocular cystic mass in the left lobe
- Extended left lobectomy was performed
Multilocular cystic neoplasm
Low and high grade dysplastic cells and ovarian-type stroma, goblet cells
Moderately differentiated adenocarcinoma change
Poorly differentiated adenocarcinoma area
Immunohistochemistry

(+) MUC2, MUC5AC, CDX-2

(-) MUC1
Case 4: Bile duct cystadenocarcinoma arising in bile duct cystadenoma

Diagnostic criteria

1. Cyst lined by columnar mucinous epithelium
2. Ovarian-type stroma
3. Malignant change:
   - Stromal invasion, nuclear atypia,
   - loss of polarity
Bile duct (biliary) cystadenoma and cystadenocarcinoma

• **Definition**
  A cystic tumor either benign (cystadenoma) or malignant (cystadenocarcinoma), lined by mucus-secreting or, less frequently serous epithelium

• Exclusively women in cystadenoma, but no predilection in cystadenocarcinoma

• **Morphology**
  - Multilocular cysts (size: 5-15 cm)
  - 2 histologic variants
    1. Mucinous type: columnar, cuboidal cells, mucus secreting cells and ovarian-like stroma
    2. Serous type: cuboidal cells with clear cytoplasm and no ovarian-like stroma
Bile duct cystadenocarcinoma arising in bile duct cystadenoma

Key morphologic findings

- Malignant change:
  stromal invasion, marked nuclear pleomorphism, loss of polarity, multilayering of epithelium, densely packed glands, mitotic figures
- Since malignant change can be focal, extensive sampling is recommended

Male, aged 45, liver
Classification of cystic lesions of the liver

Cystic lesions of the liver

Epithelial cysts

- Simple (solitary bile duct) cyst
- Ciliated foregut cyst
- Peribiliary cyst
- Fibropolycystic liver disease
- Caroli’s disease
- Choledochal cyst

Non-epithelial cysts

- Bile duct cystadenoma
- Bile duct cystadenocarcinoma

Non-neoplastic

- Simple (solitary bile duct) cyst
- Ciliated foregut cyst
- Peribiliary cyst
- Fibropolycystic liver disease
- Caroli’s disease
- Choledochal cyst

Neoplastic

- Bile duct cystadenoma
- Bile duct cystadenocarcinoma

Infectious cysts

- Parasitic cysts
  - Echinococcus
  - Opisthorchis
  - Paragonimus
- Bacterial abscess
- Amebic abscess

Secondary cystic degeneration or pseudocyst

- Neoplasms
- Posttraumatic
- Postinfarct
Ciliated foregut cyst

Key morphologic findings
• A solitary unilocular cyst lined by ciliated, pseudostratified, columnar epithelium and smooth muscle bundles in the wall
• Usually found incidentally
• Arise from the embryonic foregut
Adult type (autosomal dominant) of polycystic liver disease

Key morphologic findings
- Cysts lined by simple biliary epithelium
- Mutation in \textit{PKD1} gene (16q13.3)

Fibropolycystic diseases
- A family of congenital hepatic fibrosis, Caroli’s disease, von Meyenburg complex, choledochal cyst, infantile and adult type of polycystic liver disease
Biliary tract and pancreas have similar pathologic features

<table>
<thead>
<tr>
<th>Biliary tract</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Biliary intraepithelial neoplasia (BilIN)</td>
<td>- Pancreatic intraepithelial neoplasia (PanIN)</td>
</tr>
<tr>
<td>- Intraductal papillary neoplasm of the bile duct (IPNB)</td>
<td>- Intraductal papillary mucinous neoplasia of the pancreas (IPMN)</td>
</tr>
<tr>
<td>- Bile duct cystadenoma/cystadenocarcinoma</td>
<td>- Mucinous cystic neoplasm</td>
</tr>
<tr>
<td>- Cholangiocarcinoma</td>
<td>- Ductal adenocarcinoma</td>
</tr>
</tbody>
</table>

(Pathol Int 2010; 60: 419-429)