Neoplastic progression in macroscopic precursor lesions of the biliary tract

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Professor Yoh Zen reported no relevant financial relationships

USCAP staff associated with the development of content for this activity reported no relevant financial relationships.
Macroscopic precursor lesions of the biliary tract

- Intraductal papillary neoplasm of the bile duct (IPNB)
- Intracholecystic papillary neoplasm (ICPN)
- Intraductal tubulopapillary neoplasm of the bile duct (ITPN)
- Mucinous cystic neoplasm (MCN)
CASE 1

30-year-old lady presented with fever and was found to have a large tumour with complex papillary and cystic appearances in the left lobe of the liver (size: 7 cm).
Extensive intraductal papillary tumour with duct dilatation and mucus accumulation
Intraductal papillary proliferation with an overall regular growth pattern
Low- to high-grade dysplasia
CASE 2

80-year-old man presented with abdominal pain and was found to have an intraductal tumour in the extrahepatic bile duct.
Intraductal papillary proliferation with a complex growth pattern and invasive foci
<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Intrahepatic bile duct</td>
<td>Distal bile duct</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>Regular, homogeneous</td>
<td>Complex, irregular</td>
</tr>
<tr>
<td><strong>Mucin production</strong></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Invasive cancer</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>IPMN-like</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
How often do you see cases like **CASE 1**

- Never seen
- Very rarely (<1 case per year)
- 1-3 cases per year
- ≥4 cases per year
How often do you see cases like **CASE 2**

- Never seen
- Very rarely (<1 case per year)
- 1-3 cases per year
- ≥4 cases per year
Case 1: **Type 1 IPNB** with high-grade dysplasia

Case 2: **Type 2 IPNB** with an associated invasive adenocarcinoma
<table>
<thead>
<tr>
<th>Classification of IPNB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
</tr>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td><strong>Gross appearance</strong></td>
</tr>
<tr>
<td><strong>Gross mucin</strong></td>
</tr>
<tr>
<td><strong>Histological architecture</strong></td>
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<tr>
<td><strong>Histological type</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
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<tr>
<td><strong>Invasive cancer</strong></td>
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<tr>
<td><strong>5-year recurrence free survival</strong></td>
</tr>
</tbody>
</table>
Type 2 IPNB
Incidence of IPNB

Proportions of IPNB in surgically resected biliary neoplasms

(gallbladder neoplasms and small-duct intrahepatic cholangiocarcinoma excluded)

Kobe University, Japan
(2001-2014)

Type 2 IPNB (10%)
Type 1 IPNB (5%)
Non-papillary cholangiocarcinoma (85%)

King’s College Hospital, UK
(2000-2020)

Type 2 IPNB (12%)
Type 1 IPNB (1%)
Non-papillary cholangiocarcinoma (87%)
Incidence of IPNB

*East vs. West*

Papillary neoplasms account of 13-16% of surgically resected biliary neoplasms

<table>
<thead>
<tr>
<th></th>
<th>East (Japan)</th>
<th>West (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPNB type 1</td>
<td>33%</td>
<td>6%</td>
</tr>
<tr>
<td>IPNB type 2</td>
<td>67%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Evolution of IPNB

- Molecular change in tumour-initiating cells
- Formation of microscopic lesion
- Formation of macroscopic / clinical tumour
- Malignant transformation
- Local progression and remote metastasis
Whole exome sequencing of intracholecystic papillary neoplasm (ICPN)

a. Whole-exome sequencing

<table>
<thead>
<tr>
<th>ID</th>
<th>STK11</th>
<th>APC</th>
<th>CTNNB1</th>
<th>TP53</th>
<th>ERBB3</th>
<th>ERBB2</th>
<th>KRAS</th>
<th>NRAS</th>
<th>SMAD4</th>
<th>MLH1</th>
<th>PMS2</th>
<th>AXIN2</th>
<th>SMARCB1</th>
<th>FBXW7</th>
<th>CDKN2A</th>
<th>ARID1A</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICPN1</td>
<td>Y60X</td>
<td>F200X</td>
<td>Q123X</td>
<td>116</td>
<td>121del</td>
<td>c.919+1G&gt;A</td>
<td>F117L</td>
<td>G12D</td>
<td>G386V</td>
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<td>ICPN2</td>
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<tr>
<td>ICPN3</td>
<td>K84X</td>
<td>S45F</td>
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<td>ICPN4</td>
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<tr>
<td>ICPN5</td>
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<td>T41A</td>
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<td>ICPN6</td>
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<td>ICPN7</td>
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<td>Pap1</td>
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<td>Pap2</td>
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<td>Pap3</td>
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<td>Pap5</td>
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</tbody>
</table>

**Type 1 ICPN**

**Type 2 ICPN**

Driver gene mutations in IPNB/ICPN

<table>
<thead>
<tr>
<th></th>
<th>Type 1 IPNB (n=21)</th>
<th>Type 2 IPNB (n=38)</th>
<th>Tubular carcinomas (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>5 (24%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>4 (17%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>STK11</td>
<td>3 (14%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>APC, CTNNB1 or STK11</td>
<td>11 (52%)</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**APC**: Responsible gene for **Familial Adenomatosis Coli**

**STK11**: Responsible gene for **Peutz-Jeghers Syndrome**
Numerous polyps fill the middle and distal common bile duct.

Carcinoma and Polyps of the Gallbladder Associated with Peutz-Jeghers Syndrome

KOICHI WADA, MD, MASAO TANAKA, MD, KOJI YAMAGUCHI, MD, and KOJI WADA, MD

KEY WORDS: Peutz-Jeghers syndrome; gallbladder polyp; gallbladder carcinoma.

Fig 3. The gallbladder polyp is composed of excessive growth of mucous-type glands that contains a few Paneth cells and argentaffin cells. Close to, but not in, the polyp, well-differentiated adenocarcinoma is present (arrows).
GNAS mutations in IPNB

- GNAS is commonly mutated in pancreatic IPMN (~40%).
- GNAS mutations were not identified in any cases of type 1 IPNB / ICPN of our cohorts.
- It is likely due to the lack of intestinal-type cases.

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1 IPNB</th>
<th>Type 1 ICPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatobiliary</td>
<td>6/14 (43%)</td>
<td>2/7 (29%)</td>
</tr>
<tr>
<td>Gastric</td>
<td>5/14 (36%)</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Intestinal type</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>3/14 (21%)</td>
<td>0</td>
</tr>
</tbody>
</table>
**GNAS Is Frequently Mutated in a Specific Subgroup of Intraductal Papillary Neoplasms of the Bile Duct**

Jia-Huei Tsai, MD,* Ray-Hwang Yuan, MD,† Yu-Ling Chen, PHD,‡ Jau-Yu Lianu, MD,* and Yung-Ming Jeng, MD, PHD*†

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**GNAS mutations in 12/41 (29%) cases of IPNB**

<table>
<thead>
<tr>
<th></th>
<th>Intestinal (n=23)</th>
<th>PB / Gastric (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNAS mutated</td>
<td>12 (52%)</td>
<td>0</td>
</tr>
<tr>
<td>GNAS wild-type</td>
<td>11 (48%)</td>
<td>18 (100%)</td>
</tr>
</tbody>
</table>

**Why is the intestinal type common in Taiwan?**

- Hepatolithiasis or liver flukes

### Type 1 IPNB vs pancreatic IPMN

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type 1 IPNB</th>
<th>IPMN</th>
<th>All types</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>30-50%</td>
<td>50-70%</td>
<td>All types</td>
<td>Fujikura K, et al. Am J Surg Pathol 2018</td>
</tr>
<tr>
<td>STK11</td>
<td>20%</td>
<td>15%</td>
<td>Gastric / PB types</td>
<td>Aoki Y, et al. J Pathol 2020</td>
</tr>
<tr>
<td>APC</td>
<td>20%</td>
<td>0</td>
<td>Gastric / PB types</td>
<td>Amato E, et al. J Pathol 2014</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>20%</td>
<td>5%</td>
<td>Gastric / PB types</td>
<td>Omori Y, et al. Ann Surg 2021</td>
</tr>
</tbody>
</table>

The differences between IPNB and IPMN are partly because of the different proportions of histological subtypes.
Recruent Rearrangements in PRKACA and PRKACB in Intraductal Oncocytic Papillary Neoplasms of the Pancreas and Bile Duct

Aatur D. Singhi,1,2 Laura D. Wood,3,4 Emma Parks,5 Michael S. Torbenson,6 Matthäus Felsenstein,3,7 Ralph H. Hruban,3,4 Marina N. Nikiforova,1 Abigail I. Wald,1 Cihan Kaya,1 Yuri E. Nikiforov,1 Laura Favazza,1 Jin He,8 Kevin McGrath,9 Kenneth E. Fasanella,9 Randall E. Brand,9 Anne Marie Lennon,10 Alessandro Furlan,11 Anil K. Dasyam,11 Amer H. Zureikat,12 Herbert J. Zeh,13 Kenneth Lee,12 David L. Bartlett,12 and Adam Slivka9

PRKACA / PRKACB fusions in intraductal oncocytic papillary neoplasm

DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma

Monika Vyas1 · Jaclyn F. Hechtman1 · Yanming Zhang1 · Ryma Benayed1 · Aslihan Yavas1 · Gokce Askan1 · Jinru Shia1 · David S. Klimstra1 · Olca Basturk1

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Evolution of IPNB

1. Molecular change in tumour-initiating cells
2. Formation of microscopic lesion
3. Formation of macroscopic / clinical tumour
4. Malignant transformation
5. Local progression and remote metastasis

APC, CTNNB1, STK11, GNAS, PRKCA, PRKCB
CASE 3

76-year-old lady with an intraductal mass in the left lateral segment of the liver, associated with cystic dilatation of the adjacent ducts.
Type 1 IPNB with high-grade dysplasia
- Localized duct dilatation
- **5-mm** nodule in 2013
- Followed up

- **15-mm** nodule in 2016
- Type 1 IPNB with high-grade dysplasia
Type 1 IPNB

92 months
80 months
64 months
39 months

(years) 8 7 6 5 4 3 2 1 Resection
72-year-old man

- **27-mm** solid mass in 2004
- Suspected haemangioma

- 64 months later
- Progress to a **41-mm** mass
- Type 1 IPNB with high grade dysplasia
All cases already had a tumour. Resected specimens confirmed type 1 IPNB with high-grade dysplasia (one with possible microinvasion).

No cases showed imaging abnormalities suggestive of a biliary neoplasm.

Evolution of IPNB

1. Molecular change in tumour-initiating cells
2. Formation of microscopic lesion
3. Formation of macroscopic / clinical tumour
4. Malignant transformation
5. Local progression and remote metastasis

APC, CTNNB1, STK11, GNAS, PRKCA, PRKCB

Takes ~10 years until forming a clinically relevant tumour
## Evolution of IPNB

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Genes</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Molecular change in tumour-initiating cells</td>
<td>APC, CTNNB1, STK11, GNAS, PRKCA, PRKCB</td>
<td>Takes ~10 years until forming a clinically relevant tumour</td>
</tr>
<tr>
<td>2</td>
<td>Formation of microscopic lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Formation of macroscopic / clinical tumour</td>
<td>TP53, SMAD4</td>
<td>(more studies needed)</td>
</tr>
<tr>
<td>4</td>
<td>Malignant transformation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Local progression and remote metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CASE 4

A 64-year-old lady presented with fever and was found to have a large cystic mass in the right hepatic lobe. After the cyst was aspirated for a suspected infectious liver cyst, an intraductal papillary tumour was detected around the orifice of the right hepatic duct.
26 months later, follow-up CT demonstrated no local recurrence in the left hepatic duct, but detected a separate papillary tumour in the intrapancreatic bile duct. On ERC, the tumour appeared to be a mucin-producing neoplasm with abundant mucus secreted from the dilated ampulla of Vater.
Is this a multifocal neoplasm or intrabiliary dissemination?
Type 1 IPNB (55M)
Perihilar
Distal bile duct
9 years 5 months

BRAF V600E

Type 1 IPNB (59M)
Cystic duct
Distal bile duct
6 years

APC T1556fs*

Type 1 IPNB (73M)
Gallbladder
Mid CBD
Synchronous

CTNNB1 T41A;
SMAD4 G186V

CTNNB1 T41A;
SMAD4 G186V

Type 2 IPNB (45F)
Gallbladder
Distal bile duct
13 years 5 months

GNAS R201H

GNAS R201H
Evolution of IPNB

1. Molecular change in tumour-initiating cells
2. Formation of microscopic lesion
3. Formation of macroscopic / clinical tumour
4. Malignant transformation
5. Local progression and remote metastasis

- APC, CTNNB1,
- STK11, GNAS,
- PRKCA, PRKCB

Takes ~10 years until forming a clinically relevant tumour

- TP53, SMAD4

(more studies needed)

Intrabiliary implantation can also occur.
Summary

- Unique driver genes, slow tumour development and late recurrence in a form of intrabiliary implantation characterise type 1 IPNB.
- Type 2 IPNB shares many features with ‘conventional type’ cholangiocarcinoma (e.g., no unique gene mutations; tumour development within one year). >95% of cases have an invasive cancer at the time of diagnosis. Type 2 IPNB may be better classified as papillary cholangiocarcinoma.
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Dr Krish Menon

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Dr Takahiro Komori

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