Cholangiocolocellular Carcinoma: where we are now?

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Short Course: Joint Session Digestive Diseases Pathology & Hans Popper Hepatopathology Society: Hepatocellular carcinoma: from the basic to the complex
Hepatocellular carcinoma (HCC)

Cholangiolocarcinoma (CLC)

Hyper vascular tumor
Chronic hepatitis
Increased serum AFP
Cholangiocarcinoma is an HCC mimicker

Hypervascular tumor

Mass forming
Co-existence of chronic liver disease
Increased serum AFP level
Categorization of CLC in the WHO classification

• 2000 (3rd Ed.): Intrahepatic cholangiocarcinoma (iCCA)

• 2010 (4th Ed.): Combined Hepatocellular and cholangiocarcinoma (cHCC-CCA) with stem cell features, cholangiolocellular subtype

• 2019 (5th Ed.): iCCA small duct type or cHCC-CCA
Outline of my presentation:

1. Intrahepatic cholangiocarcinoma:
   • Large duct type
   • Small duct type
     • Pathological features
     • Immunohistochemistry
     • Clinical features

2. Cholangiolocarcinoma
   • Pathological features
   • Categorization of CLC in the new WHO classification

3. Differential diagnosis:
   • Combined HCC-CCA

4. Future perspectives
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Heterogeneity of the cholangiocytes

Bile Duct Anatomy

Small BD/Ductule:
Mucin negative cuboidal cholangiocytes

Large BD:
Mucin producing cylindrical cholangiocytes
New WHO classification of iCCA

Large BD: Mucin (+) cholangiocytes

Ductules/HPCs: Mucin (-) cholangiocytes

Small duct iCCA
Mucin (-)

Large duct iCCA
Mucin (+)
Heterogeneity of the cholangiocytes proved by IHC

EMA staining

- Ductules
  - Small BD
  - Inter lobular BD
  - Apical positivity

- Large BD
- Segmental - septal BD
- Hepatic BD

Cytoplasmic positivity
EMA staining is effective in iCCA categorization

Small BD: Mucin (-) cholangiocytes

Large BD: Mucin (+) cholangiocytes

Apical positivity

Cytoplasmic positivity

Small duct iCCA

Large duct iCCA
Large-and small duct iCCA: Pathological aspects
Large duct iCCA (proximal to hepatic hilar area)

- Periductal infiltrating type
- Periductal infiltrating & mass forming type
- Glandular or tubular pattern
- Mucin secretion (+)
- Cytoplasmic positivity (EMA)

Risks
- Primary sclerosing Cholangitis
- Hepatolithiasis
- Liver fluke infection

Precursors
- Biliary intraepithelial neoplasia
- Intraductal papillary neoplasm

- Perineural invasion
- Lymphatic invasion

KRAS mutation (30%)
SMAD4 loss (33%)
Small duct iCCA (peripheral location)

Mass forming type

Risks
- Chronic viral hepatitis
- Non-biliary cirrhosis

Precursors: unknown
Perineural/lymphatic invasion: +/-

Tubular pattern, mucin(-)
Ductular or cord like pattern
Mucin (-)

IDH1/2 mutation (15-40%)
FGFR2 translocation (11%)
Prognosis is better in small duct iCCA than large duct iCCA

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Mass forming type. Co-existence of chronic liver disease
Ductular reaction - like tumor structure: >80%

Non-tumoral ductular reaction
Innocent-looking...
Replacing growth pattern in the periphery
Cholangiocellular carcinoma (CLC)

A

CC area (C)

B

Ductular reaction-like area (D)

E

HCC-like area (E)

Cholangiolocellular carcinoma (CLC)
Hepatocytic differentiation

Morphological findings:
- A trabecular and/or solid growth pattern
- Large polygonal cells with eosinophilic cytoplasm without mucin secretion

Immunohistochemical findings:
- Canalicular pattern: pCEA, CD10, BSEP
- Cytoplasmic pattern: Hep Par 1, Arginase-1
Early lesion
8mm
HCC mimicker

Hypervascular tumor

Hepatocytic differentiation

Edematous stroma
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New WHO classification

Cholangiolicarcinoma belongs to two categories:
  Small duct iCCA
  Combined HCC-CCA
Categorization of cholangiocolocarcinoma

- Non-mucin secreting ductular configuration (>80%)
  - Apical expression (EMA)

Hepatocytic differentiation
- Absent
  - Small duct iCCA category
- Present
  - Combined HCC-CCA category

Mucin-secreting iCCA (large duct type iCCA)
CLC is a distinct molecular entity with biliary derived origin

<table>
<thead>
<tr>
<th>Biliary-derived tumor</th>
<th>Mixed HCC-CCA tumors</th>
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<tbody>
<tr>
<td>CLC</td>
<td>Stem-cell</td>
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<tr>
<td>NCAM+</td>
<td>SALL4+</td>
</tr>
<tr>
<td>Biliary-like</td>
<td>Biphenotypic (hepatocyte and biliary marker genes)</td>
</tr>
<tr>
<td>S1 (TGF-WNT)</td>
<td>IGF1R, NOTCH</td>
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<tr>
<td>Late TGF-beta</td>
<td></td>
</tr>
<tr>
<td>Immune response and inflammation related signaling</td>
<td>Poor prognostic signatures (i.e. Proliferation, G3, S2, Cluster A)</td>
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<tr>
<td>Chromosomal stability</td>
<td>Chromosomal instability (Gains: 1q, 8q; Losses: 4q, 8p, 9q, 16q, 16p)</td>
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<tr>
<td>IDH1 TP53</td>
<td>FGFR2-BICC1</td>
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Histological markers
Gene expression
Gene signatures enrichment
Copy Number Variation
Common HCC or iCCA driver mutations

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Combined HCC-CCA

Transitional features
Combined HCC-CCA

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<th>HCC component</th>
<th>CC component</th>
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HE

Hep Par 1

K19
CLC features may exist in cHCC-CCA as a minor component
WHO classification of Combined HCC-CCA

- Classical cHCC-CCA
- cHCC-CCA with stem cell features
  - Typical
  - Intermediate cell
  - Cholangiolocellular

- No subtype
- Unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor
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Identification of hepatocytic differentiation
Lack of standardization in Hepatocytic differentiation

• Hep par 1, Arginase-1, CD10 or polyclonal CEA (both with canalicular pattern), or bile salt export pump (BSEP)
• Sensitivity is different
• Categorization issue
Tumor with small- and large duct iCCA with predominant large duct iCCA...

Large duct type? 
Or 
Small duct type?
>10% small duct iCCA area

Conclusions

- Cholangiocarcinoma is an HCC mimicker.
- Non-mucin secreting ductular configuration >80%

- Identification of hepatocytic differentiation is key for categorization in small duct iCCA or combined HCC-CCA.

- Standardization is required in hepatocytic differentiation.
- Further investigation is required to validate the hypothesis if small duct iCCA component determines the character of iCCA.
Acknowledgement

Prof. Dr. Masamichi Kojiro