Pathological Classification of Hepatocellular Carcinoma

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HCC

• Primary liver cancer is the 2\textsuperscript{nd} most common cancer in Asia
• HCC is the most common histological type of primary liver cancer
• Prognosis depends on early detection and management
• Diagnosis can be challenging, especially with scant biopsy specimens and unusual morphology
Gross Features of HCC

- Large, well-circumscribed, bile-stained tumor in a background of cirrhosis
Gross Features of HCC

- Large central mass with small satellite nodules, in a background of cirrhosis
Histopathology of HCC

• Classical HCC
• Special types of HCC
  – Fibrolamellar carcinoma
  – Scirrhous HCC
  – Undifferentiated HCC
  – Lymphoepithelioma-like carcinoma
  – Sarcomatoid HCC
Classical HCC

- Tumor cells resemble normal hepatocytes to a variable extent
- The stroma is composed of sinusoid-like blood spaces lined by endothelial cells
- “Unpaired arteries” or “nontriadal arteries”
- No portal tracts
Comparison

Normal

Malignant
CLASSICAL HCC

- Vary architecturally and cytologically
  - Architectural patterns (trabecular, pseudoglandular or acinar and compact)
  - Cytological variants (pleomorphic cells, clear cells, spindle cells, fatty change, bile production, hyaline bodies, pale bodies, ground glass inclusions)
- The different architectural patterns and cytological variants frequently occur in combination
Classical HCC Patterns

• Trabecular (plate-like pattern)
  – Most common in well and moderately differentiated tumors
  – Tumor cells grow in cords of >3 cell plates thick that are separated by sinusoid-like blood spaces
  – Reticulin or CD34 stain helps highlight this pattern
Classical HCC Patterns
Reticulin Stain

http://library.utah.med.edu

Normal

Malignant
Classical HCC Patterns

Reticulin
Classical HCC Patterns

• Pseudoglandular or acinar pattern
  – Presence of gland-like spaces or acini lined by hepatocytic tumor cells
  – Modified abnormal bile canaliculi formed between tumor cells
  – Pseudoglands frequently contains bile or proteinaceous material
  – Could lead to a misdiagnosis of adenocarcinoma
  – Frequently admixed, as a minor component, with the trabecular pattern
Classical HCC Patterns
<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmoplastic stroma</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Trabecular growth</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Glandular growth</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bile</td>
<td>50%</td>
<td>No</td>
</tr>
<tr>
<td>Bile canaliculi</td>
<td>Usually</td>
<td>No</td>
</tr>
<tr>
<td>Mucin</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>pCEA</td>
<td>Canalicular</td>
<td>Diffuse</td>
</tr>
<tr>
<td>AFP</td>
<td>50%</td>
<td>Rare</td>
</tr>
<tr>
<td>HepPar-1</td>
<td>90%</td>
<td>Rare</td>
</tr>
<tr>
<td>Pankeratin</td>
<td>Weak</td>
<td>Strong</td>
</tr>
<tr>
<td>MOC-31</td>
<td>10–20%</td>
<td>90%</td>
</tr>
<tr>
<td>Other antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td>Canalicular</td>
<td>Negative</td>
</tr>
<tr>
<td>RCC antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>PAX8</td>
<td>Negative</td>
<td>Unknown</td>
</tr>
<tr>
<td>S-100</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HMB-45</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Mac Sween’s Pathology of the Liver
Classical HCC Patterns

• Compact (Solid) pattern
  – Dense aggregates of tumor cells
  – Compressed or slit-like sinusoid-like blood spaces
  – Common in poorly differentiated tumors
Classical HCC Patterns
Classical HCC Cytological Variants

Pleomorphic cells

Clear cells
Classical HCC Cytological Variants

- Fatty Change
- Bile production
Classical HCC Cytological Variants

Mallory bodies

Pale bodies
Fibrolamellar HCC

• Differ from classical HCC in many aspects
  – Occurs mainly in young adults (less than 35 years of age) without cirrhosis
  – No definitive risk factors have been identified
  – No strong gender predilection
  – Serum AFP levels are usually normal
  – 2/3 of cases involve the left lobe
  – Prognosis is better than classical HCC that arises in cirrhotic livers, but similar to classical HCC that arises in non-cirrhotic livers
Fibrolamellar HCC

- A central scar may be seen in about 75% of cases
- Typically grow with broad pushing borders
- Composed of large polygonal cells with abundant eosinophilic cytoplasm, large vesicular nuclei, and large nucleoli
Fibrolamellar HCC
Fibrolamellar HCC
Scirrhouss HCC

- Characterized by marked fibrosis along the sinusoid-like blood spaces with varying degrees of atrophy of tumor trabeculae
- Most arise immediately below the liver capsule
- A better prognosis has been reported in some, but not all studies
- Treated HCC may become scirrhouss in some areas
Scirrhous HCC
Undifferentiated HCC

- Tumors that are primary to the liver but cannot be further classified
- IHC is needed to confirm its epithelial nature
- More common in men
- Postulated to have a worse prognosis compared with classical HCC
Lymphoepithelioma-like HCC

• Pleomorphic tumor cells intermixed with numerous lymphocytes, which usually outnumber hepatocytes
• Tumor cells are small with focal syncytial growth
• EBV can be demonstrated in some, but not all, tumor cells
Lymphoepithelioma-like HCC
Sarcomatoid HCC

• Poorly differentiated tumor with a significant component of spindle cell differentiation, nuclear pleomorphism and high mitotic rate

• Distinguished from various sarcomas with the use of IHC

• Most sarcomatoid HCC will show areas of classical HCC in a sufficiently sampled tumor

• Sarcomatoid change is more frequent in HCC with repeated chemotherapy or transarterial chemoembolization
Sarcomatoid HCC
## Immunohistochemical markers for hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pattern in HCC</th>
<th>Pros/Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepPar-1</td>
<td>Intracytoplasmic granules</td>
<td>Most specific marker for hepatocellular differentiation; not as useful in PD lesions</td>
</tr>
<tr>
<td>Polyclonal CEA</td>
<td>Canalicular pattern</td>
<td>Less useful in PD HCCs</td>
</tr>
<tr>
<td>CD34</td>
<td>Strongly positive in sinusoid-like vessels</td>
<td>Weak or negative in early (&lt;1 cm) HCCs</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Cytoplasmic and/or membranous, focal/patchy to diffuse</td>
<td>GPC-3, HSP-70, GS and clathrin: Limited usefulness when used alone. Highly specific if combination of three or four markers. Limited sensitivity (~60%). Limited data for PD HCCs</td>
</tr>
<tr>
<td>HSP-70</td>
<td>Nuclear and cytoplasmic granules, patchy to diffuse</td>
<td></td>
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<tr>
<td>Glutamine synthetase</td>
<td>Strong diffuse cytoplasmic</td>
<td></td>
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<tr>
<td>Clathrin heavy chain</td>
<td>Diffuse cytoplasmic, variable intensity</td>
<td></td>
</tr>
<tr>
<td>EZH-2</td>
<td>Nuclear staining</td>
<td></td>
</tr>
<tr>
<td>Arginase-1</td>
<td>Nuclear positivity in HCC</td>
<td>Stronger staining of early HCC compared to HG-DN; use in combination with HSP-70 and GPC-3</td>
</tr>
</tbody>
</table>

WD: well-differentiated; PD: poorly differentiated; HG-DN: high grade dysplastic nodules.