Hepatocellular Carcinoma
Quest for an Ideal Immunohistochemical Panel

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UCSF

Differential diagnosis of HCC
• Hepatocellular lesions
  Adenoma, FNH, HG dysplasia
• Adenocarcinoma
  CholangioCA, metastasis
• Polygonal cell tumors
  NE tumors, RCC, ACC, AML, melanoma, epithelioid sarcomas

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Sir Isaac Newton
• 1643-1727
• Newton’s laws of motion

Results 1 - 10 of about 217,000 for HCC immunohistochemistry (0.33 sec)
Laws of Immunohistochemistry

Newton’s 1st law
• Every object tends to remain in a state of uniform motion unless an external force is applied to it.

UCSF 1st law
• Every new stain tends to be 100% specific unless results from a few more papers is applied to it.

Newton’s 2nd law
• Acceleration is proportional to force applied; the more the mass the more the force needed.

UCSF 2nd law
• The diagnostic confusion is proportional to the number of stains applied; the more the stains the more the trouble.

Newton’s 3rd law
• For every action, there is an equal and opposite reaction.

UCSF 3rd law
• For every diagnostic claim of an antibody, there is another paper with an opposite conclusion.

HCC: immunohistochemistry
• Commonly used markers
  - strengths and limitations
• Immunohistochemical panel
  - algorithms for diagnosis
  - different clinical situations
HCC immunohistochemistry

Hepatocellular differentiation
- Hep Par 1
- Polyclonal CEA
- Glypican-3
- Others: AFP, CD10, villin, TTF-1

Hep Par 1 in HCC

Advantages
- Sensitivity ~90%, specificity ~ 80%
- Most cholangiocarcinomas, metastatic adenocarcinomas: -ve
- Polygonal cell tumors: -ve

Pitfalls in diagnosis
- Focal positive in 10-20%
- Sensitivity low in poorly differentiated, scirrhous HCC
- Adenocarcinomas: stomach, esophagus, lung can be +ve
**Hep Par 1 in HCC: focal expression**

**Hep Par 1 in gastric adenocarcinoma**

**Polyclonal CEA in HCC**

**Advantages**

- Canalicular pattern specific for HCC
- Sensitivity ~80% for moderate and well-differentiated HCC
- Increases sensitivity when combined with Hep Par 1

**HCC**

**Adenocarcinoma**
Polyclonal CEA in HCC

Pitfalls in diagnosis
- Diffuse cytoplasmic staining can occur in HCC
- Canalicular pattern can be difficult to interpret
- Sensitivity in poorly differentiated HCC is low

Glypican-3 in HCC

Advantages
- Higher sensitivity in poorly differentiated HCC
- Negative in adenoma and most high grade dysplastic nodules
Glypican-3 in HCC

Pitfalls
- Low sensitivity in well-differentiated HCC
- Occasional reactivity in cirrhosis
- Positive in yolk sac tumor, melanoma
- Relatively new antibody

Glypican-3 in cirrhotic nodule

Glypican-3 in melanoma

Glypican-3 in metastatic breast CA
Other hepatocellular markers

- AFP
- CD10, villin: canalicular pattern
- TTF-1: cytoplasmic staining
- CD34
- Albumin in situ hybridization

HCC immunohistochemistry

Adenocarcinoma markers

- MOC-31
- CK7, CK19
- Site specific markers: TTF-1, ER, PR, GCDFP-15, PSA

MOC31

Advantages

- Diffuse membranous expression
- Cholangiocarcinomas, metastatic adenocarcinomas: 80-100%
- NE tumors, RCC: 70%
- Negative or weak positive in HCC

MOC31: diffuse membrane staining
MOC 31

Pitfalls in diagnosis
- 10% HCC can be positive
- Diffuse strong expression in 5% HCC

Keratins
- CAM 5.2 and AE1/AE3: positive in both HCC and adenoCa
- HCC:
  CK7, CK19: 10-20%
  Stronger in poorly-differentiated

Decisions on needle biopsy
- Working with limited tissue
- Second Law: less stains less trouble
  Minimalist immunohistochemical approach
**Needle biopsy for HCC**

Immunohistochemical approach
- Hep Par 1
- MOC 31
- Unstained slides

**Four groups**

<table>
<thead>
<tr>
<th>Hep Par 1</th>
<th>MOC31</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>+</td>
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<td>Group 2</td>
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<tr>
<td>Group 3</td>
<td>+</td>
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<td>Group 4</td>
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</table>

**Hep Par 1 + MOC31 –**

- Establishes the diagnosis of HCC in most situations
- Approach: additional work-up if
  - clinical info/morphology not typical
  - staining pattern focal
  - p-CEA (or glypican-3)
  - CK19 or CK7

**Hep Par 1 – MOC31 +**

Differential diagnosis
- Adenocarcinoma
- Polygonal cell tumors:
  - RCC, NE tumors
- Rare cases of HCC: 2-3%
**Hep Par 1 – MOC31 +**

**Approach**
- p-CEA (or glypican-3)
- Site specific markers: TTF-1, CDX-2, CK7/20, PSA, ER/PR
- Markers for RCC, NE tumors

**Hep Par 1 + MOC 31 +**

**Differential diagnosis**
- HCC with MOC 31 expression
- Adenocarcinoma with Hep Par 1 expression
  - Stomach, esophagus, lung

**Hep Par 1 + MOC31 +**

**Approach**
- p-CEA or glypican-3
- CK7 or CK19
- Site specific markers: TTF-1, CDX-2, PSA, ER/PR

**Hep Par 1 – MOC31 –**

**Differential diagnosis**
- HCC lacking Hep Par 1
- Adenocarcinoma lacking MOC31
- Polygonal cell tumors
  - Neuroendocrine tumors, RCC, Melanoma, Adrenocortical CA, AML, Epithelioid sarcoma
**Hep Par 1 – MOC31 –**

**Approach**
- p-CEA or glypican-3
- CK7 or CK19

<table>
<thead>
<tr>
<th>Keratin +</th>
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<tbody>
<tr>
<td>HCC</td>
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<tr>
<td>Adenocarcinoma</td>
<td>Adrenocortical CA</td>
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<tr>
<td>NE tumors, RCC</td>
<td>Angiomyolipoma</td>
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<tr>
<td>Urothelial CA</td>
<td>Sarcomas with epithelioid pattern</td>
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**Synaptophysin**

**HCC vs. neuroendocrine CA**
- Neuroendocrine tumors:
  - Hep Par 1 -
    - Chromogranin, synaptophysin +
- CD56: not reliable
HCC or renal cell carcinoma

HCC vs. clear cell renal cell CA

Hep Par 1 and PAX-2
- RCC: Hep Par 1-
  PAX-2 nuclear + (85-90%) Other markers
- RCC marker
- PAX-2: ovarian clear cell CA, parathyroid carcinomas

60M, multiple liver and lung masses

Negative
HepPar 1
m-CEA
CK7
TTF-1
PSA
PAX-2 nuclear+: metastatic RCC

HCC vs other polygonal cell tumors

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<tr>
<th>Adrenocortical CA</th>
<th>Inhibin</th>
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<td></td>
<td>Melan A</td>
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<td>Epithelioid AML</td>
<td>SMA</td>
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<td>HMB-45, Melan A</td>
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<td>Melanoma</td>
<td>S-100</td>
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<td>HMB-45, Melan A</td>
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50F, no cirrhosis, 5 cm liver tumor

Negative

Hep Par 1
p-CEA
CK7
MOC 31
Hep Par 1 – MOC31 –

- HCC lacking Hep Par 1, p-CEA
- Adenocarcinoma lacking MOC31, CK7
- Neuroendocrine tumors, RCC, melanoma, ACC, AML

Round 2

- PanCK
- CG, SYN
- SMA
- HMB-45
- PAX2
- Inhibin
- S-100

Polygonal cell tumors

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Kit: Metastatic GIST
Mesothelioma approach

- Poorly differentiated tumors
  - Hep Par 1
  - pCEA or Glypican-3
  - MOC31
  - CK7 or CK19

Summary

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Summary

- Restrict reflex use of large panels
- Hep Par 1 and/or pCEA
  - Glypican-3: poorly differentiated
  - Avoid markers like AFP
- MOC31, CK7, CK19
  - Markers for primary site after confirming adenocarcinoma
Needle biopsy for HCC

No stains necessary
• Bile production
• Characteristic trabecular pattern
  Fat, Mallory hyaline, cirrhotic liver

HCC vs. melanoma

• HCC: negative for S-100, melanoma markers
• Melanoma: negative for Hep Par 1
• Glypican-3: can be positive in melanoma

HCC vs. adrenocortical CA

• ACC: Hep Par 1 – MOC 31 –
  Cytokeratin -
• Inhibin, melan A
• PAX-2 negative
Hepatic angiomyolipoma

- Monotypic: lacks ‘lipoma’ component
- Myo component is often epithelioid
- Not associated with TS
- IHC: Hep Par 1, MOC31, CK: -ve
  Smooth muscle, HMB 45: +ve