Liver Fine Needle Aspiration: Classic Morphology and New Concepts

Syed Z. Ali, M.D.
Professor of Pathology and Radiology
The Johns Hopkins Hospital
Baltimore, Maryland

Fine Needle Aspiration of the Liver

Complications
- Tumor Seeding of the Needle Tract (n=12)
  - HCC (n=9)
  - Metastatic Colonic Adenocarcinoma (n=3)
- Bleeding (n=8)
  - HCC (n=5)
  - Hepanglioma (n=2)
  - Angiosarcoma (n=1)
- Bile Peritonitis (n=1)
- Carcinoid Crisis (n=1)
- Lymphorhoea (n=1)
- Biliary Venous Fistula (n=1)
- Sudden Hypoglycemia - Clear Cell HCC (n=1)

Benign Diseases
- Non-neoplastic
  - Granulomatous Disease
  - Infection
    - Hydatid Disease
    - Other (Ambeic, Schistosomiasis)
  - Congenital Cysts
  - Focal Nodular Hyperplasia (FNH)
  - Cirrhosis (Regenerative Nodule)
- Benign Neoplasm
  - Hepatic Adenoma
  - Hemangioma

Malignant Tumors
- Primary
  - Epithelial
    - Hepatocellular Carcinoma
    - Cholangiocarcinoma
    - Neuroendocrine Neoplasm
  - Non-epithelial
    - Angiosarcoma/Other Sarcomas
    - NHL/HL

Malignant Tumors
- Metastatic/Secondary
  - Epithelial
    - Adenocarcinoma
    - Squamous Cell Carcinoma
    - Small Cell Carcinoma
    - Other (Renal Cell Carcinoma etc)
  - Non-epithelial
    - Malignant Melanoma
    - Sarcomas
    - NHL/HL
    - Other
Cystic Lesions

- Congenital/Simple Cyst
- Ciliated Foregut Cyst
- Hydatid Cyst
- Abscess
- Granulomatous Infections
- Cystic Neoplasms

Macroregenerative Nodule

- Cytomorphologic Features
  - Reactive hepatocytes (high N/C ratio, often prominent nucleoli)
  - Higher than normal amount of biliary epithelium
  - Varying amount of fibroconnective tissue fragments
  - Marked focal atypia of hepatocytic or biliary epithelium
  - Varying amount of lympho-mononuclear cells
  - Cholestasis
  - Focal necrosis (rare)
- Differential Diagnosis
  - Normal Liver
  - Focal Nodular Hyperplasia
  - Hepatic Adenoma
  - Well-differentiated HCC
Focal Nodular Hyperplasia

A diagnosis of exclusion

- Differential Diagnosis
  - Normal Liver
  - Cirrhosis
  - Hepatic Adenoma
  - Well-differentiated HCC
  - Clinico-Radiologic Correlation Is Imperative
  - Accurate Sampling of the Lesion Is Critical
Hepatic Adenoma

- Cytomorphologic Features
  - Could Be Entirely Non-specific
  - Abundant Normal-appearing Hepatocytes
  - Lack of Biliary Epithelium, Fibrous Tissue Fragments
  - Lack of Endothelial/vascular Proliferation

- Differential Diagnosis
  - Normal Liver
  - Focal Nodular Hyperplasia
  - Well-differentiated HCC
Cytologic Grading of HCC: Is it possible?

- In our study, the 3-tier cytologic grading of HCC was only moderately accurate.
- Accuracy of cytologic grading was high for WD/PD HCC, and low for MD HCC.
- The inter-observer agreement was highest for WD and lowest for MD HCC.

Cytologic Grading of HCC

Why Do We Grade?

- Differences in Clinical Prognosis and Survival
- Treatment Options
- For Differential Diagnosis

Cytologic Grading of HCC

Well Differentiated
- Cohesive fragments with vascular/endothelial proliferation
- Uniform bland appearance; mildly increased N/C ratio, small nucleoli
- Cytoplasmic vacuolization (steatosis), dense granularity, bile staining
- Single cells and/or naked nuclei seen less often

Moderately Differentiated
- Prominent pleomorphism
- Abundant naked nuclei with prominent nucleoli
- Large discohesive cell population
- Moderately high N/C ratio, macronucleoli, DNs

Poorly Differentiated
- Marked hypercellularity
- Discohesive cellular fragments, 3-D nests, glandular & tubular formations
- Extreme pleomorphism, macronucleoli, focal necrosis
- Endothelial wrappings “packeting” more pronounced
Well Differentiated HCC

Differential Diagnosis

- Normal Liver
- Cirrhosis (Regenerative Nodule)
- Hepatic Adenoma
- FNH
- Metastatic Tumors (RCC)
Moderately Differentiated HCC

Differential Diagnosis

- Metastatic Cancers
  - Renal Cell Carcinoma
  - Melanoma
  - Adenocarcinoma
Poorly Differentiated HCC

Differential Diagnosis

- Metastatic Cancers
- Adenocarcinoma
- Malignant Melanoma
- Other Cancers
- Cholangiocarcinoma
HCC – Immunoperoxidase Profile

- **Conventional Markers**
  - CAM5.2
  - AE1/AE3
  - pCEA (canalicular)
  - CD34/CD31
  - HepPar-1 (Sp-90%, Sn-82%)

- **Newer Markers**
  - CD13 (canalicular) (Sn-94%)
  - Glypican-3 (GPC3) (Sp-100%, Sn-90%)

---

**p53 Immunoreactivity in Hepatic FNA**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 Immunoreactivity</td>
<td></td>
</tr>
<tr>
<td>p53 Immunoreactivity</td>
<td></td>
</tr>
<tr>
<td>Circled (50)</td>
<td>0</td>
</tr>
<tr>
<td>FNH (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic Adenoma (6)</td>
<td>0</td>
</tr>
<tr>
<td>HCC:</td>
<td></td>
</tr>
<tr>
<td>Biopsy(59)</td>
<td>8.5%</td>
</tr>
<tr>
<td>FNA (65)</td>
<td>24%</td>
</tr>
</tbody>
</table>

> p53 Expression Correlated Well With the Tumor Grade

---

Role Of Immunoperoxidase Staining for p53, Ki-67 And Beta-catenin In Hepatocellular Carcinoma and Benign Hepatic Lesions

<table>
<thead>
<tr>
<th></th>
<th>Hepatocellular Carcinoma</th>
<th>Focal Nodular Hyperplasia</th>
<th>Regenerative Nodule</th>
<th>Hepatic Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>6/11 (55%)</td>
<td>0/5 (0%)</td>
<td>0/5 (0%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Beta-catenin</td>
<td>7/11 (64%)</td>
<td>4/6 (67%)</td>
<td>4/6 (67%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Ki-67 (moderate-high)</td>
<td>4/11 (36%)</td>
<td>0/6 (0%)</td>
<td>0/6 (0%)</td>
<td>0/5 (0%)</td>
</tr>
</tbody>
</table>

Ojanguren et al. Histopathology 1995
Well-Differentiated HCC

Cholangiocarcinoma

Diagnosed by
- Biliary Brushing
- Fine Needle Aspiration
Cholangiocarcinoma

Differential Diagnosis
- Normal/Reactive Biliary Epithelium
- Metastatic Adenocarcinoma
- HCC
- Malignant Melanoma

Pediatric Liver Tumors
- Fibrolamellar Hepatocellular Carcinoma
- Hepatoblastoma
- Embryonal Sarcoma
Hepatoblastoma

Differential Diagnosis
- HCC
- Embryonal Sarcoma
- Small Round Blue Cell Tumors

Primary Hepatic Sarcomas
- Angiosarcoma
- Kaposi Sarcoma
- Leiomyosarcoma
- Epithelioid Hemangioendothelioma
Metastatic Neoplasms

- Most Common Cancer In The Liver
- Most Common Indication For Hepatic FNA
- Most Common - Colon, Pancreas, Breast, Lung, Kidney, Melanoma
- Metastasis Could Be From An Occult Primary
- Cytomorphology Alone May Not Be Able To Diagnose An Unknown Primary (IPOX Stains Are Needed)

Metastatic Adenocarcinoma

- Colon
  - Columnar Cells With Oval to Elongated Nuclei, Apically Clear Cytoplasm, Flat Honey-combed Sheets
  - Dirty Necrosis
- Pancreas
- Lung
- Breast
- Kidney
- Prostate
HCC Vs Melanoma

- Closest Mimick of HCC
- Liver Is a Very Common Site for Visceral Spread of MM
- Cytomorphologic Features (MM Over HCC):
  - More Often Single Cells or Sheet-like Arrangement
  - Plasmacytoid Cells (Eccentric Nuclei)
  - More Frequent Bi-nucleation
  - Cytoplasmic Tails/Prolongations
  - Melanin-like Pigment
  - Necrosis

Other Metastatic Cancers

- Squamous Cell Carcinoma
- Small Cell Carcinoma
- Pancreatic Endocrine Neoplasm
- Carcinoid Tumor
- Adrenal Cortical Carcinoma
- Granulosa Cell Tumor
- GIST
- Various Sarcomas
Metastatic Neuroendocrine Tumors
Lymphoid Lesions

- Non-Hodgkin Lymphoma
  - Primary
  - Secondary
- Hodgkin Lymphoma
- Clinical Features:
  - Most Common Presentation Is Pain or Liver Mass
  - Hepatic Involvement Has Important Clinical Significance
  - Usually Multiple Lesions
  - Serum AFP Not Elevated

Most Common Presentation Is Pain or Liver Mass
Hepatic Involvement Has Important Clinical Significance
Usually Multiple Lesions
Serum AFP Not Elevated