Arterial Enhancing Nodules in Cirrhosis

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Purpose

To define the nature of an “Arterial Enhancing Nodule” (AEN) and devise a rational management strategy.
AEN

- An MRI finding describing a <20mm mass lesion in a cirrhotic liver which demonstrates early enhancement on dynamic scanning, variable T1 signal intensity and hypo- or iso-T2 signal intensity. The lesion may or may not be associated with elevated AFP levels.

- *The lesion may represent a small hepatocellular carcinoma.*
HCC

- HCC is the most common primary hepatic malignancy worldwide.
- Incidence has doubled in the past 20 years and long term survival is poor.
- Patients with cirrhosis have a much greater chance of developing HCC.

Sholz, Lahey Clinic, 2004
HCC

• Early diagnosis and resection or transplantation substantially increases survival
• Survival rate 85% in limited disease
  – One lesion <5cm or up to three lesions less than or equal to 3cm.

Courtesy Lahey Clinic, 2004
Management

It is therefore critical to detect nodules that contain HCC at an early stage both to control tumor burden while awaiting transplantation and to distinguish those patients who may have favorable long-term results with transplantation from those who will not, because cadaveric organs are in short supply.
AEN, Management?

- Finding of an AEN in patients with cirrhosis raises questions of management (is it HCC?) because the most effective treatment is surgical resection or local ablation when the tumor is small.
- But what do AENs represent?
Cirrhosis in North America

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>16</td>
</tr>
<tr>
<td>Hepatitis C and EtOH</td>
<td>10</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>9</td>
</tr>
<tr>
<td>EtOH</td>
<td>9</td>
</tr>
<tr>
<td>PSC</td>
<td>7</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>6</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>5</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>2</td>
</tr>
<tr>
<td>PBC</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis B and EtOH</td>
<td>1</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1</td>
</tr>
<tr>
<td>Hemosiderosis</td>
<td>1</td>
</tr>
<tr>
<td>a-1-antitrypsin deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>


Sholz, Lahey Clinic
Hepatocarcinogenesis

Acute HCV infection

- Weak CTL response
  - 85%
  - Chronic HCV infection
  - Mild and moderate immune responses
    - Chronic hepatitis
      - Cirrhosis
        - End-stage liver disease
        - HCC
  - Strong immune responses
    - Cirrhosis
      - End-stage liver disease
      - HCC

Acute HBV infection

- Fulminant hepatitis (< 1%)
  - Weak Th1 & CTL response
    - Chronic infection (HBs [+] for > 6 mo.)
      - 10%
      - Asymptomatic chronic carrier (no liver disease)
          - Regression
            - Cirrhosis
              - Regression
                - Hepatocellular carcinoma
      - 70-90%
      - Chronic hepatitis
          - Regression
            - Cirrhosis
              - Regression
                - Asymptomatic (subclinical) seroconvert to viral antibodies
      - 10-30%
      - 25%
      - Strong Th1 & CTL response
          - Death or recovery
          - Acute hepatitis
  - 25%
  - Strong Th1 response
    - Death or recovery
    - Acute hepatitis

- 65%
  - Death or recovery
Hepatocarcinogenesis

Multistep anaplastic process
Hepatocarcinogenesis

- Neoangiogenesis and capillarization leads to gradual change in blood supply

Portal Venous Supply | RN | DN | HCC | Hepatic Arterial Supply

T2 Signal Intensity

hypointense | hyperintense
Hepatocarcinogenesis

Although neovascularity within HCC can be used for early detection and characterization of liver lesions the overlap in blood supply patterns of various types of cirrhotic nodules makes definitive diagnosis challenging.
## HCC in North America

<table>
<thead>
<tr>
<th>Signal Intensity</th>
<th>Lesions</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1W</strong></td>
<td><strong>T2W</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypointense</strong></td>
<td>Hyperintense</td>
<td>189</td>
<td>54</td>
</tr>
<tr>
<td><strong>Isointense</strong></td>
<td>Isointense</td>
<td>58</td>
<td>16</td>
</tr>
<tr>
<td><strong>Hypointense</strong></td>
<td>Isointense</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>24</td>
<td>6.8</td>
</tr>
<tr>
<td>Isointense</td>
<td>Hyperintense</td>
<td>22</td>
<td>6.2</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>Isointense</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypointense</td>
<td>Hypointense</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>Hypointense</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Isointense</td>
<td>Hypointense</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Kelekis et al, AJR:170, 4/98
## Immediate GdE Findings in HCC in 126 Histologically Proven Lesions

<table>
<thead>
<tr>
<th>Enhancement</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Heterogeneous</td>
<td>95</td>
<td>75.4</td>
</tr>
<tr>
<td>Peripheral Rim</td>
<td>17</td>
<td>13.5</td>
</tr>
<tr>
<td>Diffuse Homogeneous</td>
<td>10</td>
<td>7.9</td>
</tr>
<tr>
<td>Diffuse Hypovascular</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>126</td>
<td>100</td>
</tr>
</tbody>
</table>

Mitchell et al AJR:170, 4/98
MRI and HCC

- Most cases of HCC reported in the literature have shown HSI on T2WI and enhancement during early phase dynamic MRI.
- Typical example, the diagnosis is straightforward.
Cirrhotic nodules, classical teaching

<table>
<thead>
<tr>
<th>Lesion</th>
<th>T1W</th>
<th>T2W</th>
<th>HAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Hypointense</td>
<td>Hyperintense</td>
<td>heterogeneous</td>
</tr>
<tr>
<td>Dysplastic Nodule</td>
<td>Hyperintense</td>
<td>Hypo/isointense</td>
<td>Iso/Hypointense</td>
</tr>
<tr>
<td>Regenerative Nodule</td>
<td>Isointense</td>
<td>Isointense</td>
<td>Iso/Hypointense</td>
</tr>
</tbody>
</table>
Pt with hep C, cirrhosis and elevated AFP

Lesion slightly hypointense of T1W sequence

4.5 cm heterogeneous lesion segment V with T2 signal hyperintensity
Heterogeneous early arterial enhancement indicating hepatic arterial vascular supply, diagnosis HCC.
Hep C, Cirrhosis. Normal AFP

8mm T2 hyperintense lesion segment IV a

T1 hypointense
Early arterial enhancement. Is this an AEN?

No, the lesion demonstrates T2 hyperintensity. This is an HCC or “atypical” dysplastic nodule.
Pt with Hemochromatosis, Cirrhosis and Elevated AFP

Signal drop in liver parenchyma on T1W ip GRE sequence. Lesion relatively hyperintense.

40mm T2 hyperintense lesion segment VIII.
PV phase 3D T1W FFE sequence demonstrates peripheral rim enhancement. Heterogeneous enhancement on arterial phase (not shown).

T2W SS TSE, TE 180, low signal intensity of liver consistent with iron deposition. Note lesion conspicuity despite long TE.
There is a subset of small (<20mm) hepatic nodules that do enhance during arterial phase MR images but do not demonstrate HSI on T2WI.

These fall into the category of AENs
AEN

- It has been hoped that MRI could aid in distinguishing HCC from regenerative nodules and dysplastic nodules based on signal characteristics.
- Kelekis et al reported that a substantial number (30%) of HCCs were isointense on T2WI – Thus there is considerable SI overlap between HCC and other cirrhotic nodules (notably dysplastic nodules).
Examples
Pt with Hep B and C, cirrhosis

What are they?
Only segment IV lesion demonstrates early arterial enhancement, no associated T2 abnormality, our typical AEN. Lesion in segment V/VIII typical of dysplastic nodule.
Pt with Hep C, Cirrhosis, Normal AFP

Lesion isointense on PV phase imaging

Segment VII enhancing nodule, HAP
No associated T2 signal abnormality

Isointense to liver parenchyma on T1W image
Hep C, Cirrhosis, Normal AFP

Same pattern. AEN.

Management?
Hep B, Hep C, Cirrhosis. Normal AFP

4mm T1 hyperintense lesion segment V, no associated T2 signal abnormality
Unusual rim enhancement on HAP

T2 hypointense – although early enhancement is unusual, still classified as AEN.

Management?
Pt with Hep C, Cirrhosis.

Normal AFP
The more you look....
AENs

• Things in common
  – All lesions <20mm
  – Variable T1 SI
  – Hypo- or iso- T2 SI
  – All lesions demonstrate early arterial enhancement (pattern may be variable) and wash out on PV and Equilibrium phase imaging
What do they represent?
MRI Findings in 40 pts with 68 AENs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T1W Images</th>
<th>T2W Images</th>
<th>Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Iso</td>
<td>Low</td>
</tr>
<tr>
<td>HCC 9</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Benign 59</td>
<td>12</td>
<td>43</td>
<td>4</td>
</tr>
</tbody>
</table>

Initial MRI study

Only those lesions that were T2 isointense or hypointense, what we call AENs

Kamishima et al, AJR:178, 6/02
Management Strategy?
What happens to these lesions over time?

<table>
<thead>
<tr>
<th>HCC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in signal intensity</td>
<td>60%</td>
<td>91%</td>
</tr>
<tr>
<td>Change in enhancement pattern</td>
<td>63%</td>
<td>94%</td>
</tr>
<tr>
<td>Change in size</td>
<td>100%</td>
<td>98%</td>
</tr>
</tbody>
</table>

- In patients with follow-up MRI and HCC lesions
Management Strategy

Signal intensity and contrast enhancement patterns in the arterial phase cannot be used for definitive diagnosis of HCC in AENs

However, interval growth is highly predictive of HCC
Management Strategy

• Assess signal characteristics of all cirrhotic nodules

• AENs are defined as arterially enhancing nodules, < 20 mm, with no associated T2 hyperintensity

• Followup of these lesions is recommended in 2-4 months, allowing for the doubling time of HCC (approx 2-3 months)
• Jeong et al, Small (<20mm) Enhancing Hepatic Nodules Seen on Arterial Phase MR Imaging of the Cirrhotic Liver: Clinical Implications, AJR2002;178:1327-1334.
• Carlos et al, Developing a Prediction Rule to Assess Hepatic malignancy in Patients with Cirrhosis, AJR2003;180:893-900.
• Krinsky et al, Nondysplastic Nodules That Are Hyperintense on T1w GRE MR Imaging: Frequency in Cirrhotic Patients Undergoing Transplantation, AJR2003;180:1023-1027.
References

• Byun et al, Contrast-Enhancing Hepatic Eosinophilic Abscess During the Hepatic Arterial Phase: A mimic of Hepatocellular Carcinoma, AJR2006;186:168-173.
• Ito et al, Multiarterial Phase Dynamic MRI of Small Early Enhancing Hepatic Lesions in Cirrhosis or Chronic Hepatitis: Differentiating Between Hypervascular Hepatocellular Carcinomas and Pseudolesions, AJR2004;183:699-705.