Hepatocellular Adenomas: Genetics and Imaging

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Provide a current update on genetics & molecular biology of hepatocellular adenomas

Correlate imaging findings with genotype-phenotype tumor features

Discuss implications on management
Hepatocellular Adenomas: Introduction

- Monoclonal, hepatocellular neoplasms typically described in young women on oral contraceptives
- Increased proclivity to bleed & rupture
- Rare malignant transformation
- Serial surveillance or surgical resection

Hepatocellular Adenomas: Epidemiology

- Hormone dependent tumor
- Occur predominantly in young women
- >90% women with HCA have h/o OC pill use
- Grow in pregnancy and regress with cessation of OC use
- Other risk factors: Anabolic steroid intake, Glycogen storage disorder (Ia, III, IV, VI), Tyrosinemia, familial Diabetes, Galactosemia, Steatohepatitis & Hemochromatosis

Katabathina et al. Radiographics 2011.
Pathology of HCAs: What is New?

- Inflammatory
- Steatotic
- β-catenin mutated
- Unclassified

Pathology
Complications
Clinical Presentation
Management
Pathological features of HCA subtypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Steatotic HCA (35-50%)</th>
<th>Inflammatory HCA (40-55%)</th>
<th>β-catenin mutated HCA (10-18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Hallmark’ histology</td>
<td>Marked steatosis</td>
<td>Marked peliosis, polymorphous inflammatory infiltrates, thick tortuous arteries</td>
<td>Cholestasis No significant peliosis or steatosis</td>
</tr>
<tr>
<td>Immuno-staining</td>
<td>Lack of expression of Liver Fatty Acid Binding Protein (LFABP)</td>
<td>Strong expression of serum amyloid associated protein A2 (SAA-2) and CRP</td>
<td>Strong, diffuse, over-expression of glutamine synthetase &amp; nuclear β-catenin staining</td>
</tr>
</tbody>
</table>

Pathogenesis of HCAs: A tale of 3 major pathways

- Inflammatory HCA: Activation of Jak-Stat pathway
- Steatotic HCA: HNF-1α gene mutation
- Malignant HCA: β-catenin gene mutation

Pathogenesis of HCA: Inflammatory HCA

**Interleukin-6 pathway**
- Interleukin 6
- gp130
- IL6Ra
- IL6Ra
- gp130
- JAK1
- STAT1/3
- STAT3
- JAK2

**Interferon pathway**
- IFN
- IFNα/β
- IFNγ
- IFNAR1
- IFNAR2
- IFNGR1
- IFNGR2
- TYK2
- JAK1
- STAT1/2
- ISGF3G
- ISGF3
- STAT1/2

**Sustained activation of JAK-STAT pathway**

**Inflammatory HCA**
- Polymorphous inflammatory infiltrates
- Hepatocellular proliferation
- Marked peliosis

**Overexpression of chemokine CCL20**

**Chemoattractant for B, T, & dendritic cells**

**Suppression of ALB, IGF1, TTR**

Rebouissou S et al. Nature 2009
Inflammatory HCA

Pathogenesis of Steatotic (HNF-1α mutated) HCA

- **HNF-1α mutation**
  - Suppression of gluconeogenesis
  - Activation of glycolysis
  - Promotion of fatty acid biosynthesis
  - Increased lipogenesis
  - Cellular proliferation
  - Suppression of estradiol detoxification

- **Down-regulation of FABP1 (Fatty acid binding protein) results in ‘faulty’ transport of fatty acids**
- **Accumulation of intracellular fat**

- **ErbB2**
- **ErbB2**
- **PI3K**
- **AKT**
- **mTOR**
- **PDGFA**
- **PDGFB**

- **Angiogenesis**

- **Diffuse tumoral steatosis**
- **Hepatocellular proliferation**

Bacq et al. Gastroenterology 2003; 125:1470-1475
Pathogenesis of HCA: Malignant HCA

β-catenin pathway - 20-30%

**Normal**
- β-catenin
- APC
- Axin
- GSK 3β-kinase

Cytoplasmic destruction complex
- Rapid degradation of β-catenin prevents its uncontrolled action
- β-catenin plays vital role in differentiation, zonation, proliferation & regeneration of hepatocytes

**Mutation**
- β-catenin
- APC
- Axin
- GSK 3β-kinase

Failed degradation of β-catenin
- Sustained β-catenin activation results in uncontrolled hepatocellular proliferation and tumor formation

Other pathways
- Gain of Oncogenes
  - Chromosome 6p
- Loss of Anti-Oncogenes
  - IGF2R and LATS1
- Typically described in HCA and HCC in Glycogen Storage Disease

HCAs: Radiologic-Pathologic Correlation

Given the significant differences in pathology, MRI findings are distinct.

Characteristic MRI findings of different adenomas.

Complications

Inflammatory HCA

- Major risk factors: Obesity, alcohol abuse
- Moderate risk for bleed and HCC conversion

Steatotic HCA

- Major risk factors: OCP
- Minimal risk for bleed and HCC conversion
Hepatic Adenomatosis

- Presence of > 10 adenomas in an otherwise normal liver
- HA per se is not a distinct subtype of hepatocellular adenoma, and can be of steatotic or inflammatory subtype
- HA predominantly occurs in females
- Management of HA is similar to other HCAs, directed by histological subtype and size
HCA: Management

Symptomatic patient (Rupture / Bleeding)

Hemodynamically stable
- Surgical resection
- RFA? (Question mark)

Hemodynamically unstable
- Transcatheter Embolization

Katabathina et al. RadioGraphics 2011
Asymptomatic HCA: Management

HCA’s in men, GSD, >5 cm, complications & β-catenin mutations → Resect

Fatty HCAs <5 cm → Stop offending drug surveillance

Katabathina et al. RadioGraphics 2011
Genotype-phenotype classification: a paradigm shift in imaging & management of HCA

Imaging plays a key role in the diagnosis & characterization of HCAs, surveillance & management.
Synopsis of HCA Subtypes

What is worth remembering?...

**Inflammatory HCA**
- 40-55% of all HCAs
- Majority occur in women
- H/o OC use in >90% cases
- Associated with obesity, hepatic steatosis, alcohol use & inflammatory syndrome
- Risk of bleeding-30%
- Risk of Malignancy-5-9%

**Steatotic HCA**
- 35-50% of all HCAs
- Exclusively in women
- H/o OC use in >90% cases
- May be multiple in 50% cases
- Risk of bleeding- low
- Risk of Malignancy-None

**β-catenin mutated HCA**
- 10-18% of all HCAs
- Affects men and women
- Associated with androgen therapy and glycogen storage disease
- May co-exist with inflammatory HCA
- Risk of bleeding- low
- Risk of Malignancy-Definite and significant
## MRI Characteristics of Different Subtypes of Hepatocellular Adenomas

<table>
<thead>
<tr>
<th>MRI Sequence</th>
<th>Inflammatory HCA</th>
<th>HNF-1α mutated HCA</th>
<th>β-catenin mutated HCA</th>
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<tbody>
<tr>
<td><strong>T1W GRE images</strong></td>
<td>Iso- or mildly hyper intense signal without drop out on chemical shift sequences.</td>
<td>Hyper- or iso intense signal with <strong>diffuse signal drop out on chemical shift sequence.</strong></td>
<td>No specific MRI patterns. <strong>Typical vaguely defined scar in select cases.</strong> May mimic HCC on MRI (Strong contrast enhancement during arterial phase with portal venous washout).</td>
</tr>
<tr>
<td><strong>T2W images</strong></td>
<td>Heterogeneous hyper intense signal. <strong>Atoll Sign</strong></td>
<td>Iso- to slightly hyper intense signal.</td>
<td></td>
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<tr>
<td><strong>Gadolinium-enhanced T1W images</strong></td>
<td>Intense contrast enhancement during arterial phase that persists in the portal venous and delayed phases.</td>
<td>Moderate enhancement in the arterial phase with no persistent enhancement in the portal venous and delayed phases.</td>
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