Current Topics in Liver Pathology:
Hepatocellular Adenomas – New Classification

Oyedele A. Adeyi

oyedele.adeyi@uhn.ca

Nov. 9, 2013
Disclosure Information
Oyedele A. Adeyi, M.D., FRCPC

• I have no financial relationships to disclose.

- and -

• I will not discuss off label use and/or investigational use in my presentation
Learning Objectives

• Discuss genetic classification of hepatocellular adenomas

• Present an algorithmic approach to evaluating hepatocellular neoplasms

• Answer questions
The feature in this adenoma stained with CD34 that is indicative of a specific sub-type is:

A. Inflammation

B. Diffuse sinusoidal CD34 positivity

C. Scar

D. None
Case presentation

• A 32 yo woman presented with a "large" mass on the right liver lobe, referred to UHN as FNH

• MRI showed heterogenous mass with fat content, but predominantly hypervascular with delayed washout in the venous phase.
  – Atypical for FNH
  – Has an eccentric scar
  – Underwent US-guided needle biopsy
32 yo woman with 10-cm Rt. Lobe Mass
32 yo woman with 10-cm Rt. Lobe Mass
32 yo woman with 10-cm Rt. Lobe Mass
32 yo woman with 10-cm Rt. Lobe Mass
32 yo woman with 10-cm Rt. Lobe Mass
Reticulin: none-to minimal plate thickening
32 yo woman with 10-cm Rt. Lobe Mass
Reticulin: focal loss of reticulin fibers
32 yo woman with 10-cm Rt. Lobe Mass:
CD34: sinusoidal Capillarization
32 yo woman with 10-cm Rt. Lobe Mass: Beta Catennin: nuclear localization
Nuclear beta catenin as seen in this adenoma implies:

A. This is not an adenoma but a metastatic hepatoid carcinoma

B. This is an adenoma but there is very little risk for transformation to hepatocellular carcinoma

C. This is an adenoma, beta catenin is mutated therefore LFABP immunostain will be positive

D. This is an adenoma; I can’t say why it’s an adenoma just yet, but isn’t that why I’m here?
32 yo woman with 10-cm Rt. Lobe Mass

- LFABP positive

**Diagnosis:**
Hepatocellular neoplasm, well-differentiated, with beta catenin mutated phenotype: Complete resection recommended
Hepatocellular Adenoma: Epidemiology

• Rare neoplasms most-often in young-middle-aged women women
• Incidence 3-4 /100,000 in N/America and Europe
• Must be in a non-cirrhotic background
• Associated with OCP
  – 25% occur with women with no OCP history
• Also occurs in children, older women and male patients
Table 1: Hepatocellular adenomas: Bordeaux cases.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>H-HCA</th>
<th>IHCA</th>
<th>b-IHCA</th>
<th>b-HCA</th>
<th>UHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>184*</td>
<td>66</td>
<td>68</td>
<td>13</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>n W</td>
<td>163</td>
<td>62</td>
<td>59</td>
<td>8</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Mean age (extreme)</td>
<td>40 (21–66)</td>
<td>41 (23–60)</td>
<td>40 (25–54)</td>
<td>35.5 (26–46)</td>
<td>35 (21–66)</td>
<td>36.5 (22–52)</td>
</tr>
<tr>
<td>n W (OC)</td>
<td>146</td>
<td>52</td>
<td>54</td>
<td>7</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>n W BMI &gt; 25</td>
<td>52</td>
<td>13</td>
<td>24</td>
<td>0</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>n M</td>
<td>19</td>
<td>3**</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

n: number; W: adult women; M: adult men; BMI: body mass index; OC: oral contraceptives; *includes 2 children; **2 patients with MODY3.

Hepatocellular Adenoma: Risk factors

– Oral contraceptives
– Androgens
– MODY3 (maturity-onset DM of the young type 3)
– Glycogenosis
– Tyrosinemia
– familial polyposis coli
– Vascular diseases e.g. Abernethy malformation
– Obesity
Hepatocellular Adenomatosis

• Genetic factors:
  – Tyrosinoses
  – MODY3
  – FAP syndrome
  – Glycogenosis
  – (Obesity)

• Underlying vascular abnormalities
  – Abernethy malformation (cong. Absence of portal vein)
    • Schaeffer & Adeyi *Mod. Pathol* 2013;44(3):432
Hepatocellular Adenoma: New Classification
Mass Lesions: Hepatocellular Adenoma Clinical Variants

*Hepatology*. 2006;43(3):515-24

- **HNF-1α-mutated:**
  - Steatotic adenoma

- **β-Catenin mutated**
  - ↑Risk for HCC progression

- **Inflammatory**
  - (prior telangiectatic FNH)

- **Non-mutated, non-inflammatory**
HNF-1α-mutated adenoma

- *HNF-1α* (aka *TCF1*) gene encodes the hepatocyte nuclear factor
- Biallelic-inactivating mutations lead to tumour suppression (hence classified as a tumor suppressor gene)
- HNF-1α germline mutations:
  - Predisposition for MODY3 and liver adenomatosis
- Most HNF-1α mutated adenomas are somatic mutations
Maturity-Onset Diabetes of the Young Type 3 (MODY3)

- MODY3, rare autosomal dominant subtype of NIDDM with early onset DM in early 20s
- Primary defect in insulin secretion and an altered renal tubular glucose reabsorption
- Patients have heterozygous germline mutations of TCF1/ HNF1-α
- Patients traditionally known to develop multiple hepatic adenomas
HNF-1α mutated

- *HNF-1α* gene positively regulates the *FABP1* gene, *that codes for* LFABP (Liver fatty acid binding protein)

- Inactivated *HNF-1α* HA demonstrates:
  - Steatotic phenotype
  - Loss of staining for LFABP
  - Small risk, ~7% for HCC progression
  - Could be multifocal, especially in patients with germline inactivation
  - Seen in 35-40% of all adenomas
HNF-1α mutated

Courtesy Dr. Sanjay Kakar, UCSF
HNF-1α mutated

L-FABP in lesion

L-FABP in normal liver

Courtesy Dr. Sanjay Kakar, UCSF
Mass Lesions: Hepatocellular Adenoma Clinical Variants

*Hepatology*. 2006;43(3):515-24

- **HNF-1α-mutated:**
  - Steatotic adenoma

- **β-Catenin mutated**
  - ↑ Risk for HCC progression

- **Inflammatory**
  - (prior telangiectatic FNH)

- **Non-mutated, non-inflammatory**
β-Catenin mutated HA

• β-catenin protein:
  – encoded by the CTNNB1 gene
  – a subunit of the cadherin protein complex
  – regulates cell–cell adhesion, and also
  – is an intracellular signal transducer in the Wnt signaling pathway
**β-Catenin mutated HA**

- **β-catenin protein:**
  - Located in the membrane normally
  - Mutated phenotype leads to non-transient nuclear localization
  - Approx. 10% of human cancers have β-catenin mutation or overexpression
    - E.g.: hepatocellular carcinoma, colorectal carcinoma, lung cancer, malignant breast tumors, ovarian and endometriophelial cancer.
β-Catenin mutated HA

• Present in 10-15% of all HA
• Highest risk of malignant transformation among all HA (~46% risk)
• Commonest type in men, androgen steroid use
• Over-represented in glycogenoses and FAP patients
**β-Catenin mutated HA**

- Aberrant nuclear and cytoplasmic β-catenin staining by IHC
  - random & heterogenous

- Also **diffuse** glutamine synthetase (GS)
  - Due to upregulation of *Glul*, a β-catenin target gene coding for GS

- Some inflammatory HA also β-catenin
  - in up to 10% of IHA
Nuclear beta catenin as seen in this adenoma implies:

A. This is not an adenoma but a metastatic hepatoid carcinoma

B. This is an adenoma but there is very little risk for transformation to hepatocellular carcinoma

C. This is an adenoma, beta catenin is mutated therefore LFABP immunostain will be positive

D. This is an adenoma because that’s why we are here, but I still don’t get it!
Mass Lesions: Hepatocellular Adenoma Clinical Variants

*Hepatology.* 2006;43(3):515-24

- **HNF-1α-mutated:**
  - Steatotic adenoma

- **β-Catenin mutated**
  - ↑ Risk for HCC progression

- **Inflammatory HA**
  - (prior telangiectatic FNH)

- **Non-mutated, non-inflammatory**
Inflammatory Hepatocellular Adenoma, IHA

• Accounts for up to 50% of all adenomas
• In the past called telangiectatic FNH
• Now known to be clonal, hence neoplastic
• Up to 10% of IHA could also have β-catenin mutation
  – Classify as β-catenin mutated subtype
• 60% of IHA have small in-frame deletions that target the binding site of gp130 for IL-6
Inflammatory Hepatocellular Adenoma, IHA
Inflammatory Hepatocellular Adenoma, IHA

- Inflammation
- Ductular reaction
- Vessels sometimes thick-walled
- Telangiectatic sinusoidal dilatation
- SAA and CRP (inflammatory markers) by IHC & mRNA level)
Inflammatory Hepatocellular Adenoma, IHA
Inflammatory Hepatocellular Adenoma, IHA
Inflammatory Hepatocellular Adenoma, IHA
Inflammatory Hepatocellular Adenoma, IHA

CD31
Mass Lesions: Hepatocellular Adenoma Clinical Variants

*Hepatology*. 2006;43(3):515-24

- **HNF-1α-mutated:**
  - Steatotic adenoma

- **β-Catenin mutated**
  - ↑ Risk for HCC progression

- **Non-mutated, inflammatory**
  - (prior telangiectatic FNH)

- **Non-mutated, non-inflammatory**
NOS/Unclassifiable HA

- Less than 10% of HA
- Lacks any of the \( \beta \)-catenin mutated; HNF-1\(^{\alpha} \) inactivated or inflammatory/telangiectatic variants
The feature in this adenoma stained with CD34 that is indicative of a specific subtype is:

A. Inflammation

B. Diffuse sinusoidal CD34 positivity

C. Scar

D. None
Hepatocellular Adenoma: Suggested Immuno Panels

• Must Have
  – Beta catenin
  – CD34, CK7
  – LFABP
  – (Glutamine Synthetase)

• Useful and helpful
  – Glypican 3
  – CRP, SAA
  – (Glutamine Synthetase)
Hepatocellular Adenoma: CD34
Hepatocellular Adenoma: CD34
Glutamine Synthetase

Normal Liver: Perivenular

β-catenin mutated HA: Diffuse

FNH: Map-Like pattern
Brief about glypican 3

- ALL GPC3-positive hepatocellular neoplasms are carcinoma
- Low sensitivity at the well-differentiated end of the spectrum
- Useful ONLY when positive to differentiated WD-HCC from HA
Back to the story of a 32 yo woman with 10-cm Rt. Lobe Mass

• **Diagnosis:**
  – Hepatocellular neoplasm, well-differentiated, with beta catenin mutated phenotype:
    • Complete resection recommended
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection
32 yo woman with 10-cm Rt. Lobe Mass: Liver Resection

GPC3+ Focus
32 yo woman with 10-cm Rt. Lobe Mass:

- **Final Diagnosis**
  Hepatocellular carcinoma, arising within a beta catenin mutated adenoma
Mass Lesions: Hepatocellular Adenoma Clinical Variants

*Hepatology.* 2006;43(3):515-24

- **HNF-1α-mutated:**
  - Steatotic adenoma

- β-Catenin mutated
  - ↑Risk for HCC progression

- Non-mutated, inflammatory
  - (prior telangiectatic FNH)

- Non-mutated, non-inflammatory
Hepatocellular Adenoma:
An Algorithm for Hepatocellular Neoplasms

- **Neoplastic and hepatocellular**
  - Background Cirrhosis

- **Malignant (HCC)**
  - Grade and Stage
  - CK19

- **Benign or uncertain**

- **Beta Catenin Nuclear**
  - LFABP Positive
    - LFABP Negative

- **Inflammatory**
  - None Inflammatory
References

• Bioulac-Sage P et al. Subtype Classification of Hepatocellular Adenoma *Dig Surg* 2010;27:39–45


“Adenoma” in elderly women

Chromosomal abnormalities determined by comparative genomic hybridization are helpful in the diagnosis of atypical hepatocellular neoplasms

Sanjay Kakar, Xin Chen, Coral Ho, Lawrence J Burgart, Oyedele Adeyi, Dhanpat Jain, Viabhav Sahai & Linda D Ferrell

Conclusions: Adenoma-like neoplasms with focal atypical morphological features or unusual clinical settings such as male gender or women outside the 15–50 year age group can show chromosomal abnormalities similar to well-differentiated HCC. Even though these tumours morphologically mimic adenoma, they can recur and metastasize. Determination of chromosomal abnormalities can be useful in the diagnosis of AHN.
The similarity in morphologic and cytogenetic features of β-catenin–activated hepatocellular adenoma–like tumors and HCC suggests that the former tumors represent an extremely well-differentiated variant of HCC.
Thank You for Your Attention

Oyedele A. Adeyi, MD
University Health Network & The University of Toronto
Toronto, ON, Canada

oyedele.adeyi@uhn.ca