HEPATIC ADENOMAS
SORTING THE GOOD FROM THE BAD

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Learning Objectives

1. Describe the defining imaging characteristics (with a focus on MRI) of the differing subtypes of hepatic adenomas.

2. Justify when hepatic adenomas can be safely managed conservatively (based on imaging characteristics), and when further evaluation is required.

3. Understand the complications and management pathways of the different subtypes of hepatic adenomas.
What are hepatic adenomas (HA)?

HAs are a rare benign liver tumour.

Histologically, they display well differentiated atypical hepatocytes without bile ducts.¹

General risk factors²:
Women of reproductive age
Further risk factors:
• Oral contraceptives
• Obesity
• Androgen steroid administration
The Four Subtypes

Inflammatory (Inf) HA - 50%

Hepatic Nuclear Factor-1-α (HNF) HA - 35%

The "Good"

β-catenin (β) HA - 10%

Unclassified (U) HA - 5%

The "Bad"
Associated with obesity, diabetes, and hepatic steatosis³
- Mutations in genes that regulate inflammatory pathways⁴
- Result in inflammatory cell infiltration in the tumour and dilated sinusoids and thickened arteries⁵
- Hence have the highest risk (30%) for haemorrhage due to vascular characteristics

Inf-HA

Why are they good?
These subtypes have a low risk of malignant transformation⁷

HNF-HA

- Associated with women who use oral contraceptives⁶
- Mutations in genes that regulate fatty acid binding proteins⁴
- Result in lipogenesis and marked steatosis⁵
β-HA

- Associated with glycogen storage diseases, familial adenomatous polyposis, and androgen administration
- Mutations in genes that regulate hepatocellular function, including cell proliferation
- Highest risk of transformation to hepatocellular carcinoma (HCC)
- HCC found in ~50% of β-HA mutations

Why are they bad?
These subtypes have the highest risk for malignant transformation. They need to be further investigated with biopsy, and surgically removed.

U-HA

- Poorly understood
- Lack specific genetic or phenotypic abnormality
- No known identifying imaging characteristics
How can we distinguish the good from the bad?

Whilst these lesions are often picked up on US or CT, the modality of choice is MRI - of which recent research has made progress in identifying individual imaging characteristics of the different subtypes.

Lucky for us, the good subtypes have defining characteristics with a high sensitivity and specificity.

When evaluating a suspected HA, we use a hepatobiliary contrast agent, like Gadoxetate disodium (Eovist/Primovist) - more on this later.
Inflammatory HA: Two key features

1. T2 Hyperintense\textsuperscript{10}(due to dilated sinusoids):
   - Diffusely
   - OR peripheral rim (atoll sign)

2. Intense arterial enhancement that \textbf{persists} on portal venous and delayed phases\textsuperscript{10}

Identifying the above combination has a high \textbf{sensitivity} (88%) and \textbf{specificity} (94%) for Inf-HA\textsuperscript{11}, hence these lesions can be safely managed conservatively with surveillance MRI.\textsuperscript{6} This will help reduce \textbf{unnecessary} biopsy and patient anxiety!
The liver lesion shows a peripheral rim of T2 hyperintensity - mimicking an atoll. This hyperintense rim enhances on arterial phase and persists on portal venous/delayed sequences.¹⁰ Whilst considered a characteristic sign of Inf-HA, it is only seen in 1/3 of cases.

An Atoll - a ring shaped coral reef/island

Whilst considered a characteristic sign of Inf-HA, it is only seen in 1/3 of cases.
HNF-1-α HA: Two key features

1. Diffuse signal loss on in/out of phase sequences (due to intracellular fat content)¹⁰

2. Variable arterial enhancement that does not persist on portal venous sequences⁷

Case: Mohamed Saber rID: 85535

Identifying diffuse signal loss on in/out of phase imaging has a high sensitivity (87%) and specificity (100%) for HNF-HA¹¹, hence these lesions can be safely managed conservatively with surveillance MRI.⁶ This will avoid unnecessary referral to the loco-regional MDT and help alleviate capacity!
**β-HA**

No specific imaging features!

Commonly...
- Arterial enhancement
- Washout on portal venous/delayed phases (mimicking HCC)$^7$

Sometimes...
- May stay hyperintense on hepatobiliary phase
- T2 hyperintense scar, that may enhance on PV phase$^{10}$

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**U-HA**

No known identifying imaging characteristics

Referral to the loco-regional MDT and biopsy is needed for these lesions (aka those that cannot be confidently recognized as Inf-HA or HNF-HA)$^{12}$
<table>
<thead>
<tr>
<th>MRI Sequences</th>
<th>Inf-HA</th>
<th>HNF-HA</th>
<th>β-HA</th>
<th>U-HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>-/↑</td>
<td>-/↑↑</td>
<td>-/↑↑</td>
<td>No known findings</td>
</tr>
<tr>
<td>T2</td>
<td>↑↑↑ Atoll sign</td>
<td>-/↑</td>
<td>Possibly T2 hyperintense scar</td>
<td>No known findings</td>
</tr>
<tr>
<td>Contrast</td>
<td>Arterial enhancement that persists on PV and delayed phase</td>
<td>Variable enhancement on arterial phase which does not persist on PV and delayed phases</td>
<td>Can often mimic HCC - arterial enhancement + washout If central scar, may enhance on PV phase ↓/-/↑ on HBP phase</td>
<td>No known findings</td>
</tr>
<tr>
<td>In/out of phase</td>
<td>Possible mild, focal signal loss</td>
<td>Diffuse signal loss</td>
<td>Often, no signal loss</td>
<td>No known findings</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>5-10%</td>
<td>Virtually no risk</td>
<td>Up to 46%</td>
<td>14%</td>
</tr>
</tbody>
</table>
HAs and the Hepatobiliary phase (HBP)

Traditionally: HAs are hypointense on HBP due to the lack of functioning hepatocytes (and bile ducts)\(^\text{14}\).

Recent research has found a small proportion of HAs; β-HAs, and a minority of Inf-HA (with β-catenin mutations) will continue to enhance on HBP\(^\text{15}\).

This is helpful, as we can use this to differentiate HA from focal nodular hyperplasia (FNH) (which remains enhancing, or isointense to background parenchyma).

This is because mutations in β-catenin, can cause over-expressions in OATP1B3 (a membrane carrier molecule), which transports gadoxetate disodium into hepatocytes.

Whilst this is a limitation to keep in mind (for a minority) - further studies have found that FNH seems to uniformly and intensely uptake contrast on HBP, and tends to have a lobulated contour and central scar (compared to β-HA)\(^\text{16}\).

Case: Paul Simkin rID: 33368
Management of HA (based on MRI)

Female:
- Inf-HA
- HNF-1-α HA

Lifestyle modification
- < 5 cm or decreased size
  - Continued surveillance
- > 5 cm or growth (> 20% diameter)
  - Repeat MRI after 6 months

Male:
- β-HA
  - Resection is advised in male patients (regardless of size), due to the higher chance of β-HA being present
  - > 5 cm or growth (> 20% diameter)
  - Resection

Biopsy is considered for lesions that cannot be confidently recognized as Inf-HA or HNF-HA¹²
HAs are usually incidental and asymptomatic until rupture

Haemorrhage and pain (usually Inf-HA)

> 10 adenomas = hepatic adenomatosis

Malignant transformation and conversion to HCC

Not usually significant - the severity would guide any management (transfusions, or even embolization)

Case: Matt Morgan  rID: 42155
Peripheral T1 bright haemorrhage

Case: Chris O'Donnell  rID: 26904
Multiple T2 hyperintense HAs

Case: Bruno Di Muzio  rID: 61506
Heterogenous HCC - arterial enhancement with washout on PV phase
Other imaging modalities usually pick up the HA lesion first, with a wide range of appearances.² The characteristics on each modality depend on the HA subtype, the amount of fat content (hypoattenuating), and whether haemorrhage is present (hyperattenuating).

**Ultrasound**

Case: Natalie Yang  rID: 6951

Hyperechoic lesion on ultrasound, found to be HNF-HA - representing it's fatty content

**CT**

Case: Abraão Kupske  rID: 43106

Portal venous CT - lesion with hyperdense rim, found to be Inf-HA

**Nuclear medicine**

Tc99m sulfur colloid study - usually **photopenic** due to dysfunctional Kupffer cells (compared to FNH which show uptake due to functioning Kupffer cells)

Usually lack of HIDA uptake due to absence of biliary ducts
Inf-HA and HNF-HA both have specific MRI imaging features with a high sensitivity and specificity. This helps reduce biopsies, patient anxiety, and workload to improve capacity. These subtypes have a very low risk of malignant transformation. Therefore, if we can identify these imaging features, the patient can be safely followed up with repeat MRI.

Inf-HA: High T2 + intense arterial enhancement that persists on delayed sequences

HNF-HA: Diffuse signal loss on in/out of phase sequences