Primovist MRI Evaluation of FNH vs. Hepatocellular Adenoma

BODY DIVISION GRAND ROUNDS – JANUARY 14, 2018

DR. SAMUEL XU – PGY3
DR. AASHISH GOELA
Conflicts of Interest

None to declare
Agenda

- Introduction to Primovist
- Evaluation of Focal Nodular Hyperplasia
- Evaluation of Hepatocellular Adenoma
- Comparison of the Two Lesions
- Quality Improvement Case
- Questions and QA
What is Primovist?
Primovist

- Gadoxetate Disodium OR Gadoxetic Acid OR Gadoxetate Ethoxybenzyl Dimeglumine
  - Hepatobiliary Specific Contrast Agent approved in Canada in 2010
  - Highest uptake by hepatocytes out of all the agents of 50% in the normal liver

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Abbreviated Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangafodipir trisodium</td>
<td>Mn-DPDP</td>
<td>Teslascan</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>Gd-BOPTA</td>
<td>MultiHance</td>
<td>Bracco</td>
</tr>
<tr>
<td>Gadoxetic acid (or gadoxetate disodium)</td>
<td>Gd-EOB-DTPA</td>
<td>Eovist (United States), Primovist (EU, Australia)</td>
<td>Bayer</td>
</tr>
</tbody>
</table>

Note: —EU = European Union.  

Seale et al, 2009
Primovist

- Review of Microscopic Hepatic Anatomy

Guyton & Hall, 2006
Primovist

- Biochemical level of function

Van Beers et al, 2012
Due to the absence of normal hepatocytes in many pathologic lesions, there is no uptake of the lesion in the delayed phases.

This allows for much higher sensitivity in detection of liver lesions such as HCC or metastatic deposits.

The cost of Primovist is higher than non-specific agents.

Initial cost analysis though showed overall cost savings with the use of Primovist.
Primovist

- Dosage of Primovist is comparably lower compared to non-specific agents – 0.025 mmol/kg vs 0.1 mmol/kg

- Leads to some timing challenges, with solutions including:
  - Dilution of the contrast into normal saline rather than a saline flush immediately following injection
  - Doubling the dose to 0.05mmol/kg which can also be used in patients with poor liver function

- Adverse events similar to non-specific Gadolinium chelates
Primovist

Jhaveri et al, 2015
Characterization of lesions with Primovist adds the benefit of the hepatobiliary phase

- Allows for the detection of smaller, less vascular lesions

Van Beers et al, 2012
Primovist

Van Beers et al, 2012
### Primovist

#### Utility Chart Summary

<table>
<thead>
<tr>
<th></th>
<th>Arterial phase</th>
<th>Portal venous phase</th>
<th>Equilibrium phase</th>
<th>Hepatobiliary phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td>Iso-hypo</td>
<td>Iso-hypo</td>
<td>Iso-hypo</td>
<td>Hypo</td>
</tr>
<tr>
<td>(peripheral nodular enhancement)</td>
<td>(peripheral nodular enhancement)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FNH</td>
<td>Hyper</td>
<td>Iso</td>
<td>Iso</td>
<td>Iso-hyper</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Hypo or hyper</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Hypo (ring enhancement) or hyper</td>
<td>Hypo (ring enhancement)</td>
<td>Hypo</td>
<td>Hypo or hyper</td>
</tr>
<tr>
<td>HCC</td>
<td>Hyper or iso, hypo</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo or hyper</td>
</tr>
<tr>
<td>CCC</td>
<td>Hypo or hyper</td>
<td>Variable, mostly hypo</td>
<td>Variable, mostly hypo</td>
<td>Hypo</td>
</tr>
</tbody>
</table>
Focal Nodular Hyperplasia
Focal Nodular Hyperplasia

- Most common hepatocellular “tumor”
  - Although not a true tumor
  - Localized liver response to small arterial malformations

- Typically found incidentally for other RUQ symptoms
  - Population usually young females taking OCPs
  - Prevalence of 3%
Focal Nodular Hyperplasia

- **Diagnosis**
  - Through imaging, rarely requires biopsy

- **Treatment**
  - Follow up, no surgical resection unless causing symptomatic mass effect
Focal Nodular Hyperplasia

- Appearance on US

Venturi et al, 2007
Focal Nodular Hyperplasia

Venturi et al, 2007
Focal Nodular Hyperplasia

- Appearance on CT

Horton et al, 1999
Focal Nodular Hyperplasia

Horton et al, 1999
Focal Nodular Hyperplasia

- Can also be characterized with Nuclear Medicine
  - Tc-99m SC study uptakes in Kupffer cells, which are present in FNH and thus will have strong uptake in the lesions
  - Tc-99m HIDA uptake theoretically similar in hepatocytes as Primovist so will show persistent retention of the radionucleotide with increased uptake in the lesion
    - However, HIDA scans also has high uptake in other lesions such as adenomas
Hepatocellular Adenoma
Hepatocellular Adenoma

- Second most common benign hepatocellular tumor
  - Estimated incidence of 0.004%
  - Commonly found in younger female patients with use of OCPs, but other patient populations also present
  - Usually asymptomatic

- Subtypes include
  - Inflammatory
  - HFNF1a
  - β-catenin activated
  - Nonspecified/Noninflammatory
Hepatocellular Adenoma

- **HFN1a Subtype**
  - Represents approximately 30-40% of all HCAs
  - Usually the more fat containing HCAs
  - Imaging features of diffuse and homogenous signal dropout on opposed phase T1
Hepatocellular Adenoma

Ax T1 in phase

Ax T1 out-of-phase
Hepatocellular Adenoma

- Inflammatory Subtype
  - Previously identified as telangiectatic FNH, but has been re-classified
  - Accounts for roughly 40-55% of HCAs

- Imaging features of strong hyperintense on T2 compared to other HCAs, with persistent enhancement on delayed phase with extracellular agents
  - However, there have been reports of I-HCA mimicking FNH because it can retain contrast on the hepatobiliary phase and remain hyperintense
Hepatocellular Adenoma

Ax T2
Non I-HCA

Ax T2
Presumed I-HCA
Hepatocellular Adenoma

- Diagnosis
  - Heavily reliant on imaging
  - Definitive diagnosis is through biopsy

- Treatment
  - Surgical resection due to the associated complications of hemorrhage/rupture and malignant transformation
Hepatocellular Adenoma

- Appearance on US

Grazioli et al, 2001
Hepatocellular Adenoma

- Appearances on CT

Ruppert-Kohlmayr et al, 2000
Hepatocellular Adenoma

Seale et al, 2009
Hepatocellular Adenoma

- Can also be evaluated with Nuclear Medicine
  - Due to absence of Kupffer cells, should be photopenic on a Tc-99 sulfur colloid study
    - However, this is not always the case
Comparing the Two
### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with HCA (n = 24)</th>
<th>Patients with FNH (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.4 ± 13.6 (11–79)</td>
<td>41.7 ± 12.7 (14–78)</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1:25</td>
<td>7.51</td>
</tr>
<tr>
<td>Lesion diameter (mm)*</td>
<td>29.5 ± 23.0 (8–110)</td>
<td>38.0 ± 23.7 (6–127)</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>15 Solitary, four multiple</td>
<td>48 Solitary, 10 multiple</td>
</tr>
<tr>
<td></td>
<td>(three patients with three nodules; one patient with four nodules), two patients with liver adenomatosis</td>
<td>(10 patients with two nodules)</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td>Eight lesions resulted in upper quadrant pain, 16 were asymptomatic</td>
<td>Five lesions resulted in abdominal pain, 53 were asymptomatic</td>
</tr>
<tr>
<td>Oral contraceptive use*</td>
<td>8 (7) (4–12)</td>
<td>11 (6.7) (3–8)</td>
</tr>
<tr>
<td>Background disorders</td>
<td>Ovarian cancer (n = 1), breast cancer (n = 1), acute lymphatic leukemia (n = 1)</td>
<td>Colon cancer (n = 5), pulmonary cancer (n = 2), breast cancer (n = 1), melanoma (n = 1), ovarian lymphoma (n = 1), acute lymphatic leukemia (n = 1)</td>
</tr>
<tr>
<td>Other associated hepatic lesions</td>
<td>FNH (n = 7)*, hemangiohoma (n = 1)</td>
<td>HCA (n = 7)*, hemangiohoma (n = 3), cyst (n = 4)</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Diagnostic confirmation</td>
<td>Surgical resection (n = 4), fine-needle biopsy (n = 20)</td>
<td>Fine-needle biopsy (n = 24), follow-up imaging studies (n = 34)</td>
</tr>
<tr>
<td>Histologic subgroups</td>
<td>Steatotic type in 12 patients (23 lesions), inflammatory type in seven patients (12 lesions), and unclassified in five patients (eight lesions)</td>
<td>Intraneudal fat component in two patients (two lesions)</td>
</tr>
</tbody>
</table>

Graziolo et al, 2012
Comparing the Two

Table 3
MR Imaging Findings in HCA and FNH

<table>
<thead>
<tr>
<th>Finding</th>
<th>HCA (n = 43)</th>
<th>FNH (n = 68)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central scar</td>
<td>0</td>
<td>23 (33.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SI dropout on out-of-phase T1-weighted images</td>
<td>23 (53.5)</td>
<td>2 (2.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Arterial phase enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>30 (69.8)</td>
<td>0</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (20.9)</td>
<td>7 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>4 (9.3)</td>
<td>61 (89.7)</td>
<td></td>
</tr>
<tr>
<td>Portal venous phase enhancement</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypointense</td>
<td>25 (58.1)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Iso- to hyperintense</td>
<td>18 (41.9)</td>
<td>67 (98.5)</td>
<td></td>
</tr>
<tr>
<td>Late dynamic phase enhancement</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypointense</td>
<td>31 (72.1)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Iso- to hyperintense</td>
<td>12 (27.9)</td>
<td>66 (97.1)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary phase enhancement†</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypointense</td>
<td>40 (93.0)</td>
<td>6 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Iso- to hyperintense</td>
<td>3 (7.0)</td>
<td>62 (91.2)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data are numbers of nodules, with percentages in parentheses.
* Calculated with Fisher exact test.
† Hepatobiliary phase at 20 minutes.
Comparing the Two

- Pathology staining appearance in the ideal situation

(a) FNH  
(b) HCA  

Walther & Jain, 2011
Comparing the Two

- Possibly thought of on a spectrum?

- Thus, sometimes may be hard to make a definitive distinction on imaging

Walther & Jain, 2011
Quality Improvement Case
38 yo female presented to emergency department with RUQ pain

PMHx includes:
- T2DM
- Asthma
- Hypothyroidism
- Severe OCD/Anxiety Disorder
- Hepatic Steatosis

On OCP
Case

Ax fSPGR in-phase

Ax fSPGR out-of-phase
Case

Ax FRFSE + FS

Cor SSFSE
Case

Unenhanced

Portal Venous

Arterial

Delayed
Case

Hepatobiliary Phase
Case

Unenhanced

Portal Venous

Arterial

Delayed
However....

Given the difference between the two MRI study results, patient’s clinical team wanted confirmation study with Nuclear Medicine
Case
Thoughts?

Probably HCA, inflammatory subtype

Further tests would be warranted
Summary

- Primovist is a hepatobiliary MRI contrast agent helpful in characterization of liver lesions, specifically differentiating FNH from other liver lesions and finding small malignancies.

- FNH is a common liver lesion that is benign and does not require surgical resection, whereas HCA has a similar appearance and patient population, but treatment recommendation is surgical resection.

- Clear communication with clinical team and clarify any possible misunderstandings where applicable.
Questions?

- Thank you!
References


