Non-focal liver signal abnormalities on hepatobiliary phase of MR imaging post injection of Gd-EOB-DTPA: A review and differential diagnosis

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GOALS AND OBJECTIVES

 ✓ To review the properties of Gd-EOB-DTPA and its current indications in liver MR imaging.
 ✓ To discuss different etiologies that may result in non-focal signal alteration on hepatobiliary phase of MR imaging post injection of Gd-EOB-DTPA.
 ✓ To provide pearls and clues for differential diagnosis.

TARGET AUDIENCE

 ✓ Fellow and attending radiologists specializing in abdominal imaging
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Gd-EOB-DTPA = Gadolinium ethoxybenzyl di-ethylenetriamine penta-acetic acid (Gadoxetic disodium, Eovist™, Primovist™, Bayer HealthCare, Germany)
Introduction

- Indications for use of Gd-EOB-DTPA in liver imaging
- Chemical properties and Pharmacodynamics of Gd-EOB-DTPA

Causes of non-focal signal alteration on hepatobiliary phase of MRI:

1. Fibrosis
2. Steatosis
3. Iron deposition
4. Infiltrative tumors
   - Infiltrative HCC
   - Cholangiocarcinoma
   - Metastases, lymphoma
5. Inflammatory/Infectious etiologies
6. Vascular etiologies

Conclusion
Background

• Use of Gd-EOB-DTPA (also known as Gadoxetate disodium, Eovist™, or Primovist™, Bayer HealthCare, Germany), has been shown to improve sensitivity and specificity for evaluation of focal hepatic lesions. Common indications include characterization of focal hepatic lesion, detection of liver metastases, and HCC surveillance in cirrhotic patients.

• A variety of disease processes also result in non-focal signal abnormalities in hepatobiliary phase of imaging which will be discussed in this presentation.
Chemical Properties of Gd-EOB-DTPA

- Paramagnetic contrast with features of both extracellular contrast agent and hepatocyte-specific agent (uptake by hepatocytes with subsequent biliary excretion).
- Paramagnetic component, gadopentete dimeglumine, is covalently linked to lipophilic ethoxybenzyl (EOB) moiety.
- Relatively high T1 relaxivity allows lower dosage compared to other gadolinium chelates.
- Its blood pool properties are less intense and shorter than extracellular agents.
Pharmacokinetics of Gd-EOB-DTPA

- Lipophilic ethoxybenzyl (EOB) side chain has high affinity to ATP-dependent organic anion transporter polypeptide 1 (OATP1). OATP1 transports Gd-EOB-DTPA from extracellular space into hepatocytes.
- Subsequent excretion into the biliary canaliculi via the canalicular multispecific organic anion transporter (cMOAT).
- With normal liver and renal function, approximately 50% is excreted via the hepatobiliary pathway, with the rest through renal excretion. Plasma half-life is approximately 56 minutes (shorter compared to conventional extracellular contrast agents).
- The hepatobiliary phase occurs approximately 20 minutes after administration and lasts for 120 minutes.

Introduction

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Mechanisms of signal alteration on hepatobiliary phase
1. Decreased uptake of Gd-EOB-DTPA by OATP1 transporter
   - Decreased expression or concentration of OATP1 transporter
     - Such as with loss of hepatocytes and infiltration with non-hepatocellular tissue (infiltrative tumor, severe fat deposition, etc.)
   - Decreased function of OATP1 transporter
     - Seen with hepatocellular dysfunction
2. Decreased excretion of Gd-EOB-DTPA by cMOAT transporter
   - Seen with hepatocellular dysfunction and high-grade biliary obstruction
3. Signal confounding factors
   - Iron deposition (causing accelerated signal decay)
   - Steatosis (causing chemical shift)
**Fibrosis: Confluent Fibrosis**

**Confluent Fibrosis.** Axial post-contrast T1W MRI (A), obtained 20 minutes following injection of Gd-EOB-DTPA, in 55 year-old male with a history of cirrhosis shows a non-focal area of decreased signal (arrow) in left medial and right anterior segments. Corresponding T2W MRI (B) shows T2 hyperintensity in this region. Also note marked volume loss, architectural distortion, and capsular retraction denoting fibrosis.

*Findings of volume loss (such as capsular retraction) are features that may help differentiate confluent fibrosis from tumor. T2 hyperintensity is believed to be due to edema.*
**Fibrosis**: *Lace-like Fibrosis*

**Fibrosis.** Axial post-contrast T1W MRI (A), obtained 30 minutes following injection of Gd-EOB-DTPA, in 41 year-old male with history of alcoholic cirrhosis shows lace-like areas of low signal (arrow) with peri-portal sparing.
Fibrosis: *Lace-like Fibrosis*

**Fibrosis (continued).** Axial T2W (B), axial arterial-phase T1W (C), and axial late-venous-phase T1W (D) MRI through the same section show corresponding T2 hyperintensity and mild retention of contrast (arrow). Note extensive vascular shunts in areas of fibrosis.

*Fibrosis is often hypovascular but may show delayed retention of contrast due to pooling effect of fibrotic tissue.*
**Fibrosis: Segmental Fibrosis**

Segmental Fibrosis. Axial post-contrast T1W (A), obtained 20 minutes following injection of Gd-EOB-DTPA, in 21-year-old male with history of PSC shows a peripheral wedge-shaped area of low signal (arrow). This area enhanced slightly on venous-phase post-contrast T1W (B) and is hyperintense at T2WI image (C). Although no signs of volume loss were seen, this was felt to be due to fibrosis. Presence of enhancement was helpful to differentiate this finding from infarction.
**Diffuse Fibrosis.** Axial post-contrast T1W MR image (A), obtained 20 minutes following injection of Gd-EOB-DTPA, in 62 year-old male with history of recurrent PSC shows diffuse areas of signal alteration in both lobes suggestive of recurrent fibrosis, post OLTX. The diagnosis was confirmed on subsequent MR elastography (B). The average stiffness of liver was calculated at 11 kPa, compatible with cirrhosis.
**Steatosis:** Geographic Fat Deposition

**Steatosis.** Axial post-contrast T1W MRI (A), obtained 20 minutes following injection of Gd-EOB-DTPA, in 65 year-old female with history of primary biliary cirrhosis shows vague geographic areas of low signal (arrows) in right posterior and left medial segments.
Steatosis: Geographic Fat Deposition

**Steatosis (continued).** Corresponding axial dual-echo in-phase (B) and opposed-phase (C) GRE MRI images show signal drop (arrows) in these areas compatible with geographic steatosis. Fat-only reformatted image from 3-point Dixon technique better depicts areas of fat deposition (arrows).

- Liver steatosis is caused by accumulation of triglyceride within hepatocytes. Fat and water protons present in the same voxel accounts for signal drop on opposed-phase of imaging.
- Chemical shift imaging (with dual-echo in-phase & opposed-phase GRE series) is helpful to confirm the diagnosis.
Iron Deposition. Axial post-contrast T1W (A), obtained 20 minutes following administration of Gd-EOB-DTPA, in 51 year-old male with a history of hemochromatosis and cirrhosis shows linear areas of low T1 signal (arrows), with peri-vascular distribution.
Iron Deposition

- **Susceptibility artifact**, caused by a distorted and inhomogeneous magnetic field, results in accelerated signal decay and loss of signal (which is more pronounced on gradient-echo sequences).

- The distribution of iron accumulation differs between hemosiderosis and hemochromatosis.

Iron Deposition (continued). Axial dual-echo gradient echo images (B & C), through the same section show accelerated signal decay in those areas seen on longer TE image (arrows in C) compatible with iron deposition. Axial T2W MRI (D) obtained more inferiorly shows markedly low T2 signal in pancreas (encircled) compatible with intra-pancreatic (non-reticuloendothelial) iron deposition - a feature of primary hemochromatosis.
**Vascular Pathologies: Segmental Infarction**

**Segmental Infarction.** Axial post-contrast T1W (A), obtained 20 minutes following the administration of Gd-EOB-DTPA, in a 36 year-old male with history of ulcerative colitis and recent surgical resection shows wedge-shaped areas of low signal in periphery of segments VIII and VIII (arrows). Axial venous-phase post-contrast T1W (B) and axial T2W (C) show lack of enhancement and corresponding T2 hyperintensity (arrows), respectively. No major vascular pathology was seen in this case.

*Morphology (peripheral, wedge-shaped) and lack of enhancement are clues for a diagnosis of hepatic infarction (which is rare).*
**Vascular Pathologies: Budd-Chiari Syndrome**

**Budd-Chiari Syndrome.** Axial post-contrast T1W (A), obtained 20 minutes following administration of Gd-EOB-DTPA, in a 35 year-old male with a history of chronic Budd-Chiari syndrome shows enlargement of caudate lobe (*) with relatively lower signal in the remainder of liver. Decreased signal in these areas is likely due to a combination of hepatocyte dysfunction and edema. Axial T2W MRI (B) in the same patient shows markedly low renal cortical signal; a finding seen with paroxysmal nocturnal hematuria (PNH) which was the underlying disease in this patient.

*Regenerative nodules (not shown here) in setting of chronic Budd-Chiari may retain contrast on hepatobiliary phase.*
Infiltrative Tumor: Infiltrative Hepatocellular Carcinoma

**Infiltrative HCC.** Axial post-contrast T1W (A), obtained 20 minutes following administration of Gd-EOB-DTPA, in a 51 year-old male with a history of cirrhosis shows abnormal low signal throughout the entire right lobe.
Infiltrative Tumor: *Infiltrative Hepatocellular Carcinoma*

- Infiltrative type accounts for 7-20% of HCC.
- Diffuse, permeative appearance, with lack of well-demarcated boundaries contributes to poor prognosis due to difficult early detection and frequent portal vein invasion.

**Infiltrative HCC (continued)**. Corresponding arterial-phase post-contrast T1W (B), T2W (C), and DWI (D) show arterial hyperenhancement, T2 hyperintensity, and restricted diffusion in the right lobe - features highly concerning for infiltrative HCC. Note expansile, enhancing right portal vein thrombus (*).
**Recurrent infiltrative HCC.** Axial post-contrast T1W (A), obtained 20 minutes following administration of Gd-EOB-DTPA, in a 65 year-old male with a remote history of poorly differentiated infiltrative HCC of left lobe (status post chemoembolization) shows a segmental area of low T1 signal in anterior segment (*). There is subtle associated restricted diffusion seen on axial DWI \([b \text{ value } = 500 \text{ s/mm}^2]\) (B). No corresponding arterial hyperenhancement was present. Axial hepatobiliary-phase post-contrast T1W (C), performed 4 months earlier, shows that the area of abnormal signal was much smaller. Signal characteristics of this lesion were very similar to patient’s original tumor and interval increase in size was strongly suggestive of recurrent infiltrative HCC. Hepatobiliary phase of imaging was extremely helpful in this case since to depict the tumor since the was no or very subtle signal abnormalities on other sequences.
**Infiltrative Tumor:** *Intrahepatic Cholangiocellular Carcinoma*

**Intrahepatic Cholangiocarcinoma.** Axial post-contrast T1W (A), obtained 20 minutes following administration of Gd-EOB-DTPA, in a 44 year-old male with history of PSC shows a large segmental area of low signal involving segment VIII.
**Infiltrative Tumor:** *Intrahepatic Cholangiocellular Carcinoma*

*Intrahepatic Cholangiocarcinoma (continued).* Axial post-contrast arterial-phase T1W (B) shows peripheral enhancement. Vague centripetal enhancement of lesions was noted on more delayed images (not shown). Axial T2W (C) and ADC map (D) show corresponding T2 hyperintensity and restricted diffusion. Although not specific, imaging findings were highly suggestive of cholangiocarcinoma which was confirmed on biopsy.

*Based on the growth pattern, intrahepatic cholangiocarcinoma is further divided into mass-forming, infiltrative periductal, and intraductal subtypes*
**Melanoma Metastasis.** Axial post-contrast T1W (A), obtained 30 minutes following administration of Gd-EOB-DTPA, in 68 year-old male with history of melanoma shows diffuse low signal in right lobe. Corresponding T2W (B) and DWI [b value = 500 s/mm²] (C) images show T2 hyperintensity and restricted diffusion in right lobe. Note right lobe enlargement. These findings are nonspecific and can be seen in the setting of a variety of infiltrative processes. History was key to make the diagnosis.
Non-focal signal alterations on hepatobiliary phase MRI following injection of Gd-EOB-DTPA can be seen with an array of different disease processes and are commonly encountered in clinical practice. Familiarity with their causes and mechanisms can help the radiologist to come up with reasonable differential diagnosis.
Selected References


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