Liver Pathology:
The Most Common Problems Seen in Consultation

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Friday 12/6
Microscope Video Tutorial
Topic 1: Fibrosis or Necrosis

• Problem: How to distinguish cirrhosis from regenerative nodules with intervening necrosis?

• One of the most common errors in interpretation seen on our consult service.
Severe Acute Hepatitis

• Generally presents as fulminant liver failure
• Time span can be days to weeks to 3-4 months, dependent on etiology
• Typically correlates with submassive to massive necrosis of the liver
  – *Early stage* — necrosis, Kupffer cells
  – *Subacute* — regeneration, early collapse
  – *Late stage* — nodule formation; fibrosis
Fibrosis or Necrosis

• How to distinguish cirrhosis from regenerative nodules with intervening necrosis?
  – Trichrome
  – Reticulin
  – Orcein

• Reference

Severe Acute Hepatitis with Regenerative Nodules

Viral
Autoimmune
Wilson Disease
Drugs
Idiopathic (15 – 20%)

Toxic / Herpes viruses don’t tend to produce this pattern: patient enters into liver failure before there is time to regenerate
Case 2a,b: Clinical History

- 19-year-old woman
- Fulminant liver failure
- 2 wks prior: vomiting, fatigue
- Negative screens for viral hepatitis
- Sepsis, death
Nodular regeneration in subacute fulminant hepatitis (not cirrhosis).
Trichrome Stain. Very pale zones of blue is the necrosis (compare to darker blue of portal collagen), no fibrosis/cirrhosis.
Trichrome: Changes of severe acute hepatitis with no fibrosis: note two-toned staining
Topic 2. Centrizonal injury

Two major etiologies:
1. NASH and alcoholic injury
2. Ischemia/vascular outflow obstruction
Case 4f

- 28 year old man
- Presented with vague abdominal pain
- Physical Exam: Liver markedly enlarged
- Scan: Hepatomegaly and ascites, no flow in large hepatic vein
- Lab values:
  - Alkaline Phosphatase and Bilirubin increased
  - AST/ALT in normal range
  - Viral, autoimmune markers negative
  - Ceruloplasmin normal
Large Central Vein Occlusion
Large Central Vein: Perivenous necrosis and plate atrophy
Large occluded vein
Small occluded veins
Centrizonal ductular “metaplasia”
Portal zone, and less injured periportal area
Case 4f

- DX: Chronic Venous Outflow Obstruction
- Imaging revealed Budd-Chiari syndrome
- Notable for ductular “metaplasia”
Ischemia / Venous Outflow Obstruction

Three major etiologies:
• Budd-Chiari Syndrome
• Veno-occlusive Disease
• Congestive/Chronic Heart Failure
Ischemia / Venous Outflow Obstruction

Common features include:

• Ischemic change such as cell plate atrophy
• Sinusoidal dilation and/or fibrosis
• In chronic injury, centrizonal fibrosis, either sinusoidal, perivenous, or intravenous
• NOTE: Alk Phos often elevated
Case 4d,e

Similar history of chronic venous outflow obstruction

Trichrome stain:
- Plugs of collagen in central venous zones
- Dilated congested sinusoids
- One core with extensive scar
- No ductular metaplasia
- Centrizonal arterialization (next topic of discussion)
Chronic venous outflow obstruction (CVOO)

TAKE HOME POINTS

• Odd pattern of irregular scarring and dilated sinusoids: consider CVOO
• Trichrome stain may demonstrate early sinusoidal lesions
• Reticulin and Trichrome may highlight atrophy of plates (ischemic injury)
• DON’T be fooled by centrizonal ductular metaplasia
• Central zones can also arterialize
## Central Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>C or I</th>
<th>NASH/ASH</th>
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<tbody>
<tr>
<td>Sinusoidal dilation</td>
<td>++C</td>
<td>-</td>
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<tr>
<td>Compressed (atrophic) liver plates</td>
<td>+C</td>
<td>-</td>
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<tr>
<td>Cholestasis at edge of lesion</td>
<td>+C, I</td>
<td>-N, +A</td>
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<tr>
<td>Pigmented macrophages</td>
<td>C&gt;I</td>
<td>+</td>
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<tr>
<td>Centrilobular hepatocyte necrosis</td>
<td>++I</td>
<td>+/-</td>
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<tr>
<td>Red blood cells in cell plates</td>
<td>++C</td>
<td>-</td>
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<tr>
<td>Ballooned hepatocytes</td>
<td>+I</td>
<td>++</td>
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<tr>
<td>Mallory Hyaline</td>
<td>-</td>
<td>+N,+++A</td>
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C= Cardiac failure, I = ischemia
Topic 3: Regression and Remodeling

Case 1a and 1b
Case 1a: Regression and alcohol

- 61 year old man
- Patient had quit drinking many years ago, but had been diagnosed with cirrhosis due to alcohol
- Clinical condition had improved over time, but developed HCC
- Received ablation therapy
- Transplanted for cirrhosis with HCC
Case 1a: Regression and alcohol
Case 1a: Example of Regression
Case 1b: Regression and HBV

73 year old woman

• History of Hepatitis B cirrhosis by history
• Had received antiviral therapy
  – No evidence of active viral hepatitis
• Developed HCC, which was ablated
• Transplanted for HCC and cirrhosis
Case 1b: Regression and HBV
Case 1b: Regression and HBV
Regression and HBV

Thin septa
Can be difficult to identify without collagen stain

Perforated septa
Plates lined up irregularly
Case 1a and b: Features of remodeling/regression

- “Perforated” septa: Hepatocytes penetrating through thin fibrous septa
- Thin bridging septa between residual central and/or portal tracts
- Irregular placement of portal and central areas
- Hepatocytes entrapped in scars
- Vascular irregularities:
  - Extra vessels in scars or at edge of scar, arterial ingrowth into scars, sclerotic vessels, irregularly dilated sinusoids next to scars, etc
Remodeling in Setting of Necrosis to Fibrosis

- Acute necrosis followed by fibrosis and chronic hepatitis
- Patient was later shown to have LKM antibody, thought to be type 2 AIH
- Responded to steroids and azothiaprine
- Shows similar features of thin septa
Biopsy in acute stage with confluent centrizonal and periportal necrosis
Followup biopsy with minimal inflammation and thin septa
Regression occurs if changes are reversible. *What is NOT reversible?*

- Extensive scar with elastosis and/or parenchymal extinction is unlikely to regress
  - Elastosis occurs in later stages of scarring
  - Often seen with nondegradable forms of highly-complexed collagen (such as Type III)
  - Nondegradable forms of collagen and elastosis seen in parenchymal extinction

- Extensive vascular remodeling may limit reversibility of liver function regardless of regression of fibrosis
Irreversible lesions

Parenchymal Extinction = Extensive scar

• Dark, dense fibers predominate = highly complexed collagen

• Indicates a late stage in the fibrotic process as in Laennec stage 4c

• Much of the extensive scarring probably related to either venous outflow or arterial inflow alterations and chronic ischemic effects in advanced “end-stage” cirrhosis
Irreversible lesions (?)

• Duct loss: dense scar at site of duct loss probably irreversible
  – Small duct loss: may get regeneration
    • Idiopathic forms of ductopenia (personal observation) and chronic ductopenic rejection regrow interlobular bile ducts
  – Large duct loss: dense scars likely not reversible for duct regrowth
    • Example in Primary sclerosing cholangitis
Topic 4: Well-differentiated Hepatocellular lesions

Differential Diagnosis
- Focal nodular hyperplasia (FNH)
- Hepatocellular Adenoma (HCA)
- Hepatocellular Carcinoma (HCC)
FNH: Bile ductules and “Unpaired” artery (no bile duct)
Another FNH: Note abnormal “dystrophic” thick walled vessels, often similar to those seen in AV malformation surrounded by connective tissue.
FNH, Reticulin stain: abundant framework present, but plate width and shape can be variable in rare cases, so can overlap some variants seen in HCC.
FNH – Core Biopsy

- Don’t mistake this lesion for:
  - Scar zones with arteries and lymphoid infiltrates of ductopenic portal areas
    - Hepatocytes at edge of scar zones can be positive for copper in both FNH and chronic obstructive biliary disease
  - Reaction to adjacent lesion
  - Thicker plates of HCC
Hepatocellular Adenoma: Common Features

- Association with estrogen such as OCP (obesity??), diabetes
- Risk of hemorrhage correlates with increase in size (usually >5 cm)
- Rare risk of HCC
- Histology: bland cytology, intact reticulin framework, no mitoses, no ductules
Hepatocellular Adenoma: Common Features

Reticulin framework intact, plate architecture and cytology mimics normal patterns
Adenoma: New Classifications

- **Adenoma: 4 variants**
  - **Variant 1.** HNF1α mutations, 40-50%
    - Fatty change, no atypia, no inflammatory infiltrates
  - **Variant 2.** β-catenin mutation, <10%
    - Very high risk for HCC
  - **Variant 3.** Inflammatory adenoma
    - Formerly known as telangiectatic FNH
  - **Others (Variant 4?)**
    - No specific trait
Variant 1 Hepatocellular adenoma, HNF1α type
Variant 2 Hepatocellular adenoma: B-catenin-mutated type

Rare adenomas with HIGH risk of HCC transformation
Association with male hormone use

B-catenin nuclear staining

Glutamine synthetase: Intense, diffuse staining

Variant 2 Hepatocellular adenoma: B-catenin-mutated type: High risk for HCC

Adenomas with HCC features: Loss of reticulin
Variant 3 Hepatocellular adenoma, inflammatory type

- Formerly known as Telangiectatic FNH
- Features include:
  - Dilated sinusoids
  - Focal inflammatory change around arteries
  - Arteries can be in clusters
  - Mild ductular reaction
- Association with obesity
- Also seen in males
Variant 3 Hepatocellular adenoma, inflammatory type

Dilated sinusoids, focal inflammation around arteries

Ductules with artery and inflammation
Ductule present in this zone with arteries; unremarkable hepatocytic cytology.
FNH and HCA

- Usually young patient, noncirrhotic liver
- Key features:
  - Abnormal vessels, small or large
  - Intact reticulin framework
- Problem features:
  - Architectural irregularities with thicker plates or acinar change
  - Cytologic atypia (more common in FNH)
  - Sampling problems – don’t get diagnostic areas
  - Both FNH and HCA, inflammatory type with ductular reaction
Adenomatosis

- Large numbers of adenomas (>10)
- May be most common in:
  - HNF1α, type 1 variant
  - Inflammatory variant, type 3
Helpful immunostains
- Glutamine synthetase (GS)
- Amyloid A (SAA)
- C-reactive protein (CRP)
- Optional: CK7
Immunostains: FNH vs. HCA

- Glutamine synthetase (GS)
  - Enzyme typically in centrizonal hepatocytes in normal liver
  - More extensive “map-like” pattern in FNH
  - Variable pattern in other settings but typically located around veins in HCA
Glutamine synthetase, 10x:
Normal pattern: perivenous staining, normal liver and HCA
FNH, Glutamine synthetase, 4x, map-like pattern
Immunostains: FNH vs. HCA

- Amyloid A (SAA) and C-reactive protein (CRP):
  - SAA = Reactive/inflammatory form of amyloid
    - Stains as granular deposits in hepatocytes
  - CRP has similar diffuse staining pattern, but not granular
  - Both have prominent staining in Inflammatory HCA
  - Can be seen in background liver, especially around central vein in patients with metabolic syndrome/fatty liver
  - Limited staining in FNH
Amyloid A (SAA), 20x: diffuse cytoplasmic, granular staining of hepatocytes in inflammatory adenoma
K7, 40x: Focal ductular reaction in arterialized zones, consistent with inflammatory HCA

*Note: staining may be intermediate in intensity*
Well-differentiated Hepatocellular Neoplasm
Immunostains: Benign Vs. Malignant

- Glutamine synthetase
  - Present in centrizonal hepatocytes in normal liver, adenoma, and map-like staining in FNH
  - Variable intensity and pattern in HCC

- Amyloid A (SAA)
  - Granular deposits in hepatocytes in inflammatory HCA
  - Variable staining in HCC

- K7
  - Highlights ductular reaction in FNH, HCA
  - CK7 may stay acini, cholestatic areas, patchy staining
CD 34

- Does not stain normal sinusoidal endothelium
- Stains endothelial lining of trabeculae of HCC and other lesions with increased arterial blood flow
- Indicates “capillarization” of sinusoids
CD-34: Pattern most often seen in cirrhosis
CD34 in well differentiated HCC
Immunostains: CD 34

Problem:
Also positive in:
Many adenomas,
FNH, and high grade
dysplastic nodules
as well as some cases
of cirrhosis

Hepatocellular adenoma, CD-34, 20x
Immunostains: CD34

May help confirm presence of neoplasm
Often + in HCC; can help in determining cell plate width
Not commonly seen in nonhepatocellular tumors

**NOT very useful to differentiate benign hepatocellular tumors from very well differentiated HCC**
Well-differentiated Hepatocellular Neoplasms

Immunostains

Benign vs. Malignant (HCA, FNH, HCC)

Glypican-3

Negative in FNH and HCA

**PROBLEM:** no staining of most very well-differentiated HCCs, so not very helpful in distinguishing from FNH and HCA from WDHCC
Well-differentiated Hepatocellular Neoplasms
Immunostains

Benign vs. Malignant (HCA, FNH, WDHCC)

CD34: not too helpful
Glypican-3: not too helpful for WDHCC

Reticulin stain abnormalities remain an accepted criteria but beware of overlapping features