A Systematic Approach to Medical Liver Disease

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Why do people fear medical liver?

- Limited number of responses to an infinite number of insults; i.e., many different processes can look alike
- Morphology is only a single static picture of a dynamic physiologic process
- Integration with clinical and pathologic data is essential for accurate diagnosis

So what are we trying to do, as pathologists?

- Translate morphologic abnormalities into useful clinical/management data
  - Diagnosis vs. description
  - Management/workup suggestions even if there is no definite diagnosis
- Give grading/staging info when appropriate
Understanding the Normal Liver

Liver – The Zones

Zone 1 – Periportal
Zone 2 – Intermediate (midlobular zone)
Zone 3 – Centrilobular zone
Normal Portal Tracts

- Portal vein
- Hepatic artery
- Bile duct (interlobular)
- Lymphatic channels
- Chronic inflammation

Some degree of chronic portal inflammation is normal!

Liver – Portal Tracts

Bile Ducts
- Arterioles accompanied by bile duct 70-93% of time
- Connected to bile canaliculi by bile ductules and canals of Hering

Bile Ductules
- Found at periphery of portal tracts
- Ductular reaction is nonspecific response to various processes
  - Often accompanied by neutrophils, also nonspecific
Hepatic arteriole without duct

Normal hepatocytes

Sinusoids
Kupffer cells

Ito or stellate cells

Normal reticulin framework
**Age Variation**

- **Kids**
  - Hepatic plates two cells thick
  - Glycogenated nuclei common
  - Extramedullary hematopoiesis (infants)
  - Iron and copper present (infants)

- **Elderly people**
  - More striking variation in size of hepatocytes
  - Lipofuscin
  - Larger, more densely fibrotic portal tracts

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**Size variation in older age**

**EMH in infant**

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**Lipofuscin**
- Granular
- Zone 3

**This is not bile.**
A systematic approach to the liver biopsy

My Systematic Approach

- View slides without history or lab data first
- Construct a systematic approach that works for you
  - Zone 1 to 3 or 3 to 1
- Decide if you need additional stains
- Construct a morphologic diagnosis
- Correlate with clinical and lab data
- Advance or retreat

Systematic Approach to Liver Bx

Low power
- Adequacy
- Overall architecture
- Lesions
- Overall inflammatory pattern
- Fibrosis

Higher Power
- Portal Tracts
  - Size, inflammation, fibrosis, interface activity
  - Bile ducts: are they there, damage, inflammation
- Lobule
  - Inflammation, cholestasis, fibrosis
  - Don’t forget the Kupffer cells and Ito cells

Higher power, cont.
- Hepatocytes
  - Necrosis, reactive changes, accumulations, degeneration
- Sinusoids
  - Width, congestion, Ito cells, deposits
- Vessels
  - Inflammation, occlusion, thickening, fibrosis, abnormal morphology
Basic Classification

Liver biopsy
  - Hepatocyte injury predominant
  - Biliary
    - Chronic
    - Not chronic
  - Vascular

Assess Pattern
  - Liver
  - Portal

General patterns of hepatitis and associations

- **Portal/periportal**
  - Chronic Viral
  - Drug
  - Autoimmune
  - Early biliary disease

- **Lobular**
  - Drug
  - Acute viral
  - Autoimmune
  - Nonspecific reactive

- **Cholestatic**
  - Drug
  - LDO

- **Granulomatous**
  - PBC
  - Infection
  - Sarcoid
  - Drug
  - Unknown

- **Steatohepatitis**
  - Alcohol, diabetes, drug, obesity

- **Necrosis predominant**
  - Toxic/drug
  - Infection
  - Ischemia/shock

Other (non-hepatitis) patterns to recognize

- **Pure cholestasis**
  - Drug
  - Systemic illness (sepsis)

- **Storage/metabolic**
  - A1AT
  - Glycogen

- **Pigments**
  - Iron
  - Copper

- **Vascular abnormalities**
  - Outflow obstruction
  - NRH

- **Bile duct injury**
  - PBC
  - PSC
  - LDO
A word about adequacy

- Depends on the goal: tumor vs. inflammatory liver disease
  - “Adequate is however much it takes to make a diagnosis”
- Medical liver: diffuse vs. patchy disease
- Poor histology/biopsy quality are as or more important than size
  - Crush, fragmentation, sponges really hurt
- Pathologist must know limitations and communicate them

1.5cm is considered adequate by some; 2.5cm for medical liver disease by others

At least 4 portal tracts for medical liver (some authorities say 11)

Wedge-make sure it’s more than 1.5cm in depth to avoid subcapsular artifact
Case 1

- 32 year old Caucasian man
- Elevated transaminases on routine physical:
  - AST 56, ALT 102
  - Other liver tests normal
- History of IV drug use, needle sticks in job as LPN
- Fatigue but no other symptoms
Diagnosis

Chronic hepatitis C (antibody/PCR confirmatory)
- Grade 2-3
- Stage 3
Why Grade/Stage?

- Decide whom to treat*
- Prognosis
  - 50-80% of HCV patients develop chronic infection
  - Of those, 5-20% progress to cirrhosis
- Risk factors for progression:
  - Male
  - Older than 40
  - Drink more than 50g alcohol/day
  - High grade or stage on liver biopsy

*Everything has changed with the direct acting antivirals.

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Why Grade/Stage?

- Direct acting anti-virals (e.g., Harvoni)
- Improved rates of SVR and now CURE
  - Effective for all genotypes
  - Minimal toxicity
  - It’s crazy expensive (~$95,000 for 12 week course)
- Histologic criteria for treatment that will be covered by insurance
  - Numerical fibrosis score (Metavir), varies by state

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Grading-hepatitis*

- Hepatocyte injury/inflammation=activity
  - Portal inflammation
  - Interface hepatitis (formerly piecemeal necrosis); inflammation and hepatocyte dropout at the limiting plate
  - Lobular inflammation (or spotty necrosis)
  - Necrosis (confluent or lobular)

*The following discussion pertains to viral hepatitis and autoimmune hepatitis, but not fatty liver disease
Grading-Descriptive

- Mild
  - less than half of portal tracts with limiting plate activity;
    minimal lobular activity
- Moderate
  - more than half of portal tracts with limiting plate activity;
    more significant lobular activity
- Severe
  - bridging necrosis, collapse, really striking inflammatory
    infiltrate everywhere

Batts/Ludwig scoring system

Staging

- Amount of fibrous scarring
  - Portal tract expansion
  - Extension of fibrous tissue beyond usual boundaries of portal tract (periportal)
  - Formation of fibrous septa
  - Formation of nodules
  - Pericentral/perivenular

Staging-Descriptive

Mild
- Enlarged, irregular portal tracts
- Periportal borders get irregular

Moderate
- Fibrous septa and bridging

Severe
- Established cirrhosis

Batts Ludwig Scoring System

Batts Ludwig, Scheuer and METAVIR systems very similar.
Stage 0-1

Stage 2-Periportal

Stage 2-Periportal
Stage 3 - bridging

Stage 4 - established cirrhosis
Histology post-treatment

- Inflammation persists despite SVR
  - Also true in transplanted livers
- Early research using non-invasive methods indicates that fibrosis can regress, even advanced fibrosis


Metavir Scoring System

Activity Grade
0: No activity.
1: Mild activity.
2: Moderate activity.
3: Severe activity.

Fibrosis stage
0: No fibrosis.
1: Portal fibrosis without septa.
2: Portal fibrosis with few septa.
3: Numerous septa but not cirrhosis.
4: Cirrhosis.


Role of Liver Biopsy in Medical Liver Disease

- Confirm clinical diagnosis
- Grade and stage (if appropriate)
- Look for possible concomitant diseases
Common Concomitant Diagnoses

- Fatty liver disease/viral hepatitis
- Iron overload disorders/viral hepatitis/fatty liver disease
- HIV coinfection with viral hepatitis
- HBV coinfection with HCV
- Adverse drug reaction and anything

*Genotype 3 has fat as a direct viral cytopathic effect
Hepatitis C itself is believed to cause insulin resistance (and thus fatty liver disease) in some patients with other genotypes
HCV and Iron

- A lot raises the possibility of iron storage disease, but a little does not exclude it.
- Cirrhosis, alcoholic liver disease, NAFLD also causes of secondary iron overload.
- HFE mutations considered independent risk factors for progression of fibrosis in HCV.
HCV and HIV

- If on HAART:
  - HCV may be more aggressive
  - HAART and DAA may have interactions
  - HAART drugs may also cause steatohepatitis
- Untreated HCV often more severe in context of HIV as well
- Things that happen to immunocompromised patients
  - Fibrosing cholestatic variant of HCV
  - Beware neoplasms, infections, granulomas, etc.
Take-Home Messages

- HCV is an epidemic
- Grading/staging essential for prognosis and treatment in HCV
  - Particularly in the age of direct acting antiviral drugs
- Many patients have more than one coexistent disease process

Case 2

29 year old Caucasian female
Pre-op blood work prior to elective surgery
Ast 58, ALT 111; all else normal
ANA 1:80
- High cholesterol; markedly obese; does not drink; negative viral markers
Diagnosis

NASH
- Extensive bridging fibrosis
- NOTE:
  - Up to 35% of NASH patients have positive ANA
  - 9-10% may have positive SMA

Causes of Fatty Liver Disease

- Alcohol
- Metabolic syndrome (includes DM, dyslipidemia, obesity)
- Gastrointestinal bypass
- Wilson's disease
- Drugs
  - Amiodarone
  - Methotrexate?
Sequelae of Nonalcoholic Steatohepatitis

- Possible risk factor for cardiovascular disease
  - Contributes to atherogenic dyslipidemia through pro-inflammatory mediators that affect endothelia

Cirrhosis
- Increased risk of hepatocellular carcinoma, even in noncirrhotic patients

Steatosis begins in zone 3 and expands outwards

Usually a mix of macro- and microvesicular steatosis
Grading and Staging of Fatty Livers

- Many pathologists do not assign numerical grade or stage for fatty liver
  - Reserved for research purposes
  - Often institution dependent
  - Descriptive phrases may make it easier to communicate

Grading of Steatosis

- **Brunt scheme** (add up points for a score)
  - Lobular inflammation
    - 0: none
    - 1: <2 foci/20X field
    - 2: 2-4 foci
    - 3: >4 foci
  - Ballooning
    - 0: none
    - 1: few
    - 2: many
  - Fat
    - 0: less than 5%
    - 1: 5-33%
    - 2: >33-66%
    - 3: >66%

- **Simple person’s scheme**
  - Lobular inflammation
    - A little or a lot
  - Ballooning
    - It’s there or it’s not
  - Fat
    - Mild limited to zone 3
    - Moderate zones 3 and 2
    - Severe-paritobular
Steatofibrosis

- Begins with central vein sclerosis
- Zone 3 pericellular fibrosis (chicken-wire)
- Central-portal fibrous septa
- Cirrhosis

Caveats:
- Some patients have periportal stellate fibrosis +/- ductular reaction
- Pediatric patients often don't have zone 3 pericellular fibrosis

Steatofibrosis-staging

Brunt scheme
- 1A: Delicate zone 3 perisinusoidal fibrosis
- 1B: Dense zone 3 perisinusoidal fibrosis
- 1C: Portal fibrosis only
- 2: Perisinusoidal and portal fibrosis
- 3: Bridging fibrosis
- 4: Cirrhosis
Portal Inflammation in NASH

- Definitely can be present in NASH
  - Associated with higher BMI, female gender, older age, greater insulin resistance
  - Marker of progression in untreated patients
  - Also common in pediatric patients
  - Rule out other things, however
    - Viral, autoimmune
NAFLD vs. NASH

NAFLD: presence of at least 5% steatosis in the liver
  - Much lower rate of progression, particularly if there is no inflammation

NASH: more than 5% steatosis + other features
  - Progressive
  - May develop fibrosis and then cirrhosis
  - These patients offered drug therapy
ALD vs. NASH

<table>
<thead>
<tr>
<th>Seen in both</th>
<th>Seen almost exclusively in alcoholic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>Sclerosing hyaline necrosis</td>
</tr>
<tr>
<td>Ballooned hepatocytes</td>
<td>Satellitosis of neutrophils</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td>Cholestatic features</td>
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<tr>
<td>Mallory bodies</td>
<td>Phlebosclerosis of terminal hepatic venules</td>
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<tr>
<td>Megamitochondria</td>
<td></td>
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<tr>
<td>Pericellular fibrosis</td>
<td></td>
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</tbody>
</table>

EIOH

Mallory-Denk bodies
Approach to Fatty Liver Biopsies

- Is there fat? How much?
  - Up to 5% is physiologic
- Is there steatohepatitis?
  - Constellation of features
- Is there fibrosis? How much?
- Is there anything else?
  - Iron
  - Other disease processes

Don’t miss Wilson’s disease!
Case 3

A 67 year old African-American female with history of CAD and refractory atrial fibrillation.
Epigastric pain and nausea.
AST of 353, ALT 272, alkaline phosphatase 443, bilirubin 5.3. ANA was 1:640, but other autoimmune serologies were negative. Alpha one antitrypsin was also elevated. Viral serologies were negative. Sent home on phenergan.
The next week her blood work was rechecked, and her enzymes were higher than before.
She ultimately died of liver failure.
Diagnosis

Amiodarone toxicity

Amiodarone

- Effective medical therapy for atrial fibrillation
- Asymptomatic transaminase elevations in 25% of patients on long term therapy
- Symptomatic liver dysfunction reportedly in 1-3%
  - Cirrhosis, fatal liver decompensation do occur

Amiodarone hepatotoxicity

- Strongly tissue-bound, so lingers in the body even after drug is stopped
- Drug withdrawal does not guarantee prompt reversal of toxicity
- Can happen at any time point during therapy

Common drugs that can cause steatosis/steatohepatitis

- Amiodarone
- Steroids
- Tamoxifen
- Methotrexate
- Nitrofurantoin
- Calcium channel blockers
- Sulfasalazine
- Halothane
- Cisplatin
- Acetaminophen
- Ibuprofen
- Tetracycline
- Oxacillin
- Valproic acid

What is phospholipidosis?

- A different form of lipid accumulation due to drug binding phospholipid and inhibiting metabolism
- Enlarged, foamy, or granular hepatocytes
- EM inclusions similar to inborn disorders of phospholipid metabolism
- Often, but not always, co-exists with steatohepatitis
Common drugs that can cause phospholipidosis

- Amiodarone
- Amitriptyline
- Chloroquine
- Gentamycin
- Amiodarone hepatotoxicity-pathology
  - Steatosis
    - May be minimal or absent, however
  - Hepatocyte ballooning, Mallory hyaline, satellitosis of neutrophils (pseudoalcoholic liver injury)
  - Phospholipidosis
  - Rarely, granulomas

- Ketoconazole
- Synthetic estrogens
- TPN
- Bactrim

Take-Home Messages

- NAFLD vs. NASH has implications for progression
- As well as treatment, patient perception
- Numerical staging more important for research than daily practice
- Don’t miss coexistent diseases
- Don’t miss Wilson’s disease
- Don’t forget about amiodarone

Can I have some fatty food? Please?

Case 4

56 year old Caucasian female with nausea and vomiting
ALT 1600, AST 900, Alk phos 300
ANA 1:1280
Multiple medications
- Amitriptyline, lisinopril
Viral serologies negative
Diagnosis

- Autoimmune hepatitis
  - Moderate to marked activity
  - Bridging fibrosis
**Autoimmune Hepatitis**

- Unresolving autoimmune disease directed at hepatocytes
  - Injury may be zonal or panlobular
  - Transaminases usually markedly elevated
  - Usually chronic presentation, but acute or fulminant presentations are recognized
  - Usually women

**Autoimmune Hepatitis**

- Lab findings
  - Hypergammaglobulinemia
  - ANA
  - SMA
  - Anti-LKM
  - Anti-LC1
  - Anti-SLA/LP
  - AMA

Less than 5% of patients with apparent AIH have negative ANA and SMA, but titer vary during the course of illness [Bogdanos et al Semin Liver Dis 2009;29:241-53].

**Autoimmune Hepatitis-histologoy**

- Periportal lymphoplasmacytic inflammation
  - May be multi or panzonal
  - Lobular disarray
  - Hepatocyte swelling/ballooning or feathery degeneration
  - Necrosis
  - Acidophil bodies
  - Bridging necrosis with collapse
  - Other
    - Cholestasis
    - Rosettes
    - Emperipolesis
Primary biliary cholangitis/cirrhosis

- Women 45-55 years old
- Elevated AMA in 90%
- Liver enzymes cholestatic
  - Alk phos elevated out of proportion to transaminases
- Normal ERCP
- Natural history
  - Progresses to biliary cirrhosis
  - Very low risk of malignancy
PBC-histology

- Portal mononuclear infiltrates
  - Lymphs, plasma cells, eosinophils
- Lymphocytic cholangitis
- Granulomas near injured ducts
- Minimal to mild interface and lobular activity
- Cholate stasis
- Duct destruction with ductular reaction
- No necrosis
### PBC vs. AIH

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<thead>
<tr>
<th></th>
<th>PBC</th>
<th>AIH</th>
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<tbody>
<tr>
<td>Plasma cells</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Interface activity</td>
<td>+/-</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant lobular activity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bridging necrosis</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Lymphocytic cholangitis</td>
<td>Yes</td>
<td>Li</td>
</tr>
<tr>
<td>Granulomatous cholangitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mitochondrial damage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Copper cholate state</td>
<td>Yes</td>
<td>No</td>
</tr>
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### Autoimmune Liver Diseases and Overlap Syndromes

- **Overlap**
  - AIH/PSC
  - 7-14% PSC
  - AIH/PBC
  - 2-19% PBC

- **Primary**
  - Biliary Cirrhosis

- **Sclerosing Cholangitis**

~18% of AIH patients have an overlap syndrome

### PBC/AIH Overlap

- Clearly documented in the literature
  - Incidence depends on stringency of criteria
- Criteria
  - Ideally both clinical and histologic evidence of both AIH and PBC
  - Alk Phos and AST/ALT elevated x 5
  - AMA plus ANA/ASMA (usually)
  - Florid duct lesion plus lobular necrosis and interface activity
  - Hypergammaglobulinemia
- Treatment
  - Ursod for the PBC component doesn’t hurt
  - Prednisone, other immunosuppressive for AIH component
PBC: Chronic hepatitis-like
AMA-negative PBC (autoimmune cholangitis)

- Positive ANA, often SMA
- Patients more often male
- Many patients histologically similar to AMA+ PBC
  - Some are more appropriately classified as idiopathic adulthood ductopenia
- Treatment identical; behavior usually identical

Take-Home Messages

AIH is a hepatocyte-centric disease that requires immunosuppression
- Drug almost always in the DDX

PBC is a duct-centric disease
- Alk phos-transaminase elevation

Diagnosis of PBC/AIH overlap requires morphologic, clinical, and laboratory evidence of both
Case 5

34YO Hispanic female presented with weight loss, tachycardia
Found to be hyperthyroid, started on propylthiouracil
Three months later, presented with nausea, vomiting, jaundice
AST 1028, ALT 1039, Bili 6.6, alk phos 586; autoimmune and viral studies negative
No evidence of bile duct obstruction
Diagnosis

Cholestatic hepatitis secondary to adverse drug reaction (propylthiouracil)

Approach to Cholestasis

- Bland cholestasis
  - Hepatocellular and/or canalicular
  - No inflammation or hepatocyte damage
  - Drug, drug, drug, infection/systemic disease, weird stuff
Approach to Cholestasis

- Cholestatic hepatitis
  - Hepatocellular and/or canalicular
  - Portal and/or lobular inflammation
  - Hepatocyte damage
  - Drug, viral, autoimmune, large bile duct obstruction, alcohol
    (if fat is present)
Approach to Cholestasis

- **Ductular Cholestasis**
  - Inspissated bile within ductules
  - Interlobular bile ducts are intact
  - Sepsis (cholangitis lenta; patient is about to die) or rarely drug
Ductular cholestasis

Cholate Stasis

- Late feature of chronic biliary disease
- Due to detergent effects of bile (and copper toxicity)
  - Copper often present
  - Periportal hepatocyte ballooning with variably present Mallory hyaline
  - Periportal "halo" in patients with biliary cirrhosis
  - CK7 positive periportal hepatocytes
Approach to Cholestasis

- Cholangiodestructive
  - Often features cholate stasis
  - Portal inflammation with destruction of bile ducts
  - Can lead to biliary cirrhosis
  - Drug, chronic biliary disease (PBC, PSC, etc.)
Take-Home Messages

- Pattern of cholestasis helps narrow differential diagnosis
- Always consider cholestatic drug reaction in cases of cholestatic hepatitis
- Almost any form of cholestatic liver disease can be due to adverse drug reaction
- Hepatitis E is the new player on this block
Other things to keep in mind…
Hepatic venous outflow obstruction
And now a word about reporting.....
Useless Reporting

Liver, needle bx:
- Triaditis of limited significance. No fibrosis.
  - Pathologist of limited significance
  - Gives no useful information
  - Either call it normal or figure out what it is

Useless Reporting

Liver, needle bx: Chronic inflammation. See comment
- Comment: the differential diagnosis includes viral hepatitis, PBC, drug reaction, autoimmune hepatitis, and Coxiella infection. Clinical correlation required.
- Alternate comment: "I am too lazy to do the work of correlating this biopsy with the clinical and lab information."

Useful Reporting

Liver, needle bx:
- Chronic hepatitis with mild activity and moderate increase in fibrosis, consistent with hepatitis C. See comment
- Marked steatosis.
- Comment: Although nonspecific, these features consistent with chronic hepatitis C; amount of fat suggests possible additional component of fatty liver disease.
Useful Reporting

Liver, needle bx: Lymphocytic cholangitis with ductopenia and copper deposition; see comment
- Comment: suggestive of primary biliary cirrhosis; correlate with AMA

Useful Reporting

Liver, needle bx: Steatohepatitis with bridging fibrosis; see comment
- Comment: Patients with NASH often have positive ANA and/or anti-SMA. Features of autoimmune hepatitis are not seen.

Alys is exhausted by the subject matter.