Basic patterns of liver damage – what information can a liver biopsy provide and what clinical information does the pathologist need?

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FATTY LIVER DISEASE

Types of fatty change:
Large droplet
Types of fatty change:
Small droplet
Fatty liver disease:

- Ballooning and inflammation
Recognising ballooning

(B) Normal hepatocytes, ballooning, grade 0. Cytoplasm is pink and granular and liver cells have sharp angles.

(C) Ballooning, grade 1. Hepatocytes have rounded contours with clear reticular cytoplasm. Size is quite similar to that of normal hepatocytes.

(D) Ballooning, grade 2. Cells are rounded with clear cytoplasm and twice as large as normal hepatocytes.

Hepatology. 2012 Nov 1;56(5):1751-9
Nuclear vacuolation
The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9.
(A) Hepatocellular and canalicular bilirubinostasis (arrow).
(B) Ductular bilirubinostasis (arrow).
(C) Megamitochondria (arrows).
# NAFLD Activity Score

<table>
<thead>
<tr>
<th>Steatosis grade</th>
<th>Lobular inflammation</th>
<th>Hepatocellular ballooning</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: &lt;5%</td>
<td>0: None</td>
<td>0: None</td>
</tr>
<tr>
<td>1: 5-33%</td>
<td>1:&lt;2 foci/20x field</td>
<td>1: Mild, few</td>
</tr>
<tr>
<td>2: 34-66%</td>
<td>2: 2-4 foci/20x field</td>
<td>2: Moderate – marked,</td>
</tr>
<tr>
<td>3: &gt;66%</td>
<td>3: &gt;4 foci/20x field</td>
<td>many</td>
</tr>
</tbody>
</table>

**NAFLD activity score (NAS): 0-8**

<table>
<thead>
<tr>
<th>Steatosis (0-3) +</th>
<th>Lobular Inflammation (0-3)</th>
<th>+ Ballooning (0-2)</th>
</tr>
</thead>
</table>

CHRONIC HEPATITIS
• Assess disease severity:
  **Grade** (necro-inflammation)
  **Stage** (fibrosis)
  ? **Score** (using modified Histological Activity Index / METAVIR)

• Assess disease progression or response to treatment

• Exclude co-existing liver diseases
CHRONIC VIRAL HEPATITIS

HBV: Ground glass hepatocytes

Orcein
Liver Biopsy in HBV

- The natural history of hepatitis B is complex, and HBeAg status, ALT level, and HBV DNA level are necessary to discriminate between the various phases, but sometimes these tests are inconclusive.

- Liver biopsy has become more important in the determination of disease activity in patients with hepatitis B with the understanding that patients with normal ALT may have significant inflammation or fibrosis.

- Immunohistochemistry for HBsAg and HBcAg is not recommended for the routine evaluation of patients with chronic hepatitis B, but it can provide information on viral replication and disease phase in selected cases.
HCV:
Lymphoid aggregate/follicle
HCV: Hepatitic bile duct damage
HCV genotype 3: Fatty change
Liver Biopsy in HCV

• Increasingly, the information derived from determining HCV genotype and IL-28B genotype is defining which patients should be treated or not, regardless of the information a liver biopsy might provide, reducing the need to biopsy patients with hepatitis C.

• The introduction of direct-acting antiviral agents and the imminent development of interferon free regimens will probably reduce the need for liver biopsy in hepatitis C, as the high rate of sustained viral response makes the decision to treat less reliant on the stage of disease.
HDV
AUTOIMMUNE HEPATITIS

Autoimmune hepatitis

• Help in making the diagnosis
• Help in assessing the response to treatment
Figure 2 Emperipolesis in primary biliary cholangitis (a, H&E, ×400), and rosettes in non-autoimmune acute hepatitis (b, H&E, ×200).
Simplified histological criteria for the diagnosis of AIH

Table 4 Proposed criteria for the histologic scoring of autoimmune hepatitis

<table>
<thead>
<tr>
<th>Histology score 0</th>
<th>Histologic score 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features not observed in autoimmune hepatitis: florid duct lesion (primary biliary cholangitis), bile duct loss, or copper/CK7 positivity (latter applicable only in cases without any bridging fibrosis)</td>
<td>(1) Hepatitis with mild or moderate necroinflammatory activity with any of the following:</td>
</tr>
<tr>
<td>(a) Ishak A2 (mild/moderate interface activity)</td>
<td></td>
</tr>
<tr>
<td>(b) Ishak B1 (focal confluent necrosis)</td>
<td></td>
</tr>
<tr>
<td>(c) Ishak C2 (2–4 foci of lobular activity per × 10)</td>
<td></td>
</tr>
<tr>
<td>(2) CK7 and copper stains negative (applicable only for cases with Ishak fibrosis score &lt; 3, this feature is not applicable to acute cases)</td>
<td><strong>Histologic score 2</strong></td>
</tr>
<tr>
<td></td>
<td>Hepatitic picture with any of the following:</td>
</tr>
<tr>
<td></td>
<td>(1) Plasma cells: numerous or in clusters</td>
</tr>
<tr>
<td></td>
<td>(2) High necroinflammatory activity featuring at least one of the following:</td>
</tr>
<tr>
<td></td>
<td>(a) Ishak score A3 or higher (at least moderate interface activity)</td>
</tr>
<tr>
<td></td>
<td>(b) Ishak B2 or higher (confluent necrosis in zone 3 or beyond)</td>
</tr>
<tr>
<td></td>
<td>(c) Ishak C3 or higher (5 or more foci of lobular activity per × 10)</td>
</tr>
</tbody>
</table>

*Both (1) and (2) are necessary for histologic score of 1 except in cases with acute presentation when biliary disease is not a consideration and these stains are not relevant.
• “Any kind of liver disease can be caused by a drug”

• **Histological features suggesting a drug reaction:**
  Eosinophils, plasma cells, granulomas, sharply demarcated necrosis, cholestatic hepatitis
Drug reaction
Drug reaction
Drug reaction
Histological predictors of severity in drug-induced liver disease.

• More severe disease associated with:
  1. necrosis
  2. fibrosis stage
  3. microvesicular steatosis
  4. cholangiolar cholestasis
  5. bile duct damage

• Milder disease associated with:
  1. granulomas
  2. increased eosinophils
http://livertox.nih.gov/
HEALTH RISK OF HERBAL PILLS

The night Dr Foster demanded equal pay with male co-stars

The headliners are articles about health risks and celebrity pay disputes.
BILIARY TRACT DISEASE

Causes of Disappearing Bile Ducts

- PBC (and its variants)
- PSC (and its variants)
- Drugs and Toxins
- Chronic transplant rejection
- Graft Vs. Host
- Hodgkin’s Disease, Histiocytosis X
- Sarcoid
- Paucity of interlobular bile ducts
- HIV
- Idiopathic
Biliary tract disease: Orcein stain
Biliary tract disease: Keratin7
Primary Biliary Cholangitis
IgG4 Disease

IgG4+ plasma cells (>10/hpf)
IgG4+/IgG+ cell ratio >40%
Grading and Staging of Biliary Duct Disease

• Grading: hepatitis and cholangitis
• Staging: fibrosis, copper binding accumulation and duct loss

Nodular regenerative hyperplasia
Budd-Chiari Syndrome
Causes of Nodular Regenerative Hyperplasia

• Connective tissue disorders
• Myeloproliferative disorders
• Chronic vascular congestion
• Drugs  e.g. steroids, anticancer drugs, anticonvulsants, immunosuppressive agents
DISCREPANCY RATES IN LIVER BIOPSY REPORTING

• fibrosis staging
• recognising and interpreting bile duct disorders
• misdiagnoses of autoimmune hepatitis
• second diagnoses
Second diagnoses

- fatty liver disease
- hepatocyte iron
- alpha-1 antitrypsin deficiency

Regressed cholangiocarcinoma
Hepatocyte iron
### Normal Liver: Conditions to Exclude

<table>
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<tr>
<th>Diagnoses</th>
<th>Major Findings</th>
</tr>
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<tbody>
<tr>
<td>Alpha 1 anti-trypsin deficiency</td>
<td>Zone 1 hepatocytes have eosinophilic cytoplasmic globules. Globules may not be evident in infants</td>
</tr>
<tr>
<td>Amyloid</td>
<td>Acellular deposits in sinusoids or vessels</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Patchy areas of bile ductular proliferation and fibrosis. The parenchyma can show nodular regenerative hyperplasia</td>
</tr>
<tr>
<td>Ferroportin disease</td>
<td>Mild to moderate iron deposits, Kupffer cells, hepatocytes with elevated ferritin but low transferrin saturation levels</td>
</tr>
<tr>
<td>Glycogenic hepatopathy</td>
<td>Swollen, pale hepatocytes cells in an individual with poorly controlled diabetes</td>
</tr>
<tr>
<td>Glycogen pseudoground glass inclusions</td>
<td>Hepatocytes with large amphiphilic inclusions, associated with immunosuppression from various causes and often with polypharmacy</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Hepatocellular iron accumulation</td>
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<tr>
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<tr>
<td>Hypervitaminosis A</td>
<td>Stellate cell hyperplasia</td>
</tr>
<tr>
<td>Ischemia, low-grade or transient</td>
<td>Scattered apoptotic hepatocytes; no inflammation</td>
</tr>
<tr>
<td>Ischemia, low-grade or transient</td>
<td></td>
</tr>
<tr>
<td>Leukocyte Chemotactic Factor 2 amyloidosis</td>
<td>Amyloid deposited as round inclusions, most commonly in hepatocytes, can be subtle</td>
</tr>
<tr>
<td>Light chain deposition disease</td>
<td>Sinusoids lined with irregularly thickened deposits that mimic pericellular fibrosis</td>
</tr>
<tr>
<td>Mitochondrial injury</td>
<td>Microvesicular steatosis</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>Distinct nodularity to the liver parenchyma but without fibrosis. These changes are best seen on low power magnification</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Mild cholestasis with hyperthyroidism. Fatty change (may be minimal) with hypothyroidism</td>
</tr>
<tr>
<td>Urea cycle defects</td>
<td>Children most common but can affect all ages; changes can range from essentially normal to mild fat and glycogenosis</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Mild fatty change with glycogenated nuclei</td>
</tr>
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</table>
Normal Liver: What happened next

• Seven patients (7.2% patients) eventually developed chronic liver disease:
  autoimmune hepatitis [n=3],
  primary biliary cirrhosis [n=3],
  cryptogenic cirrhosis [n=1]).
WHAT CLINICAL INFORMATION DOES THE PATHOLOGIST NEED?
• A decent clinical history!
Clinicians providing no clinical history!

Pathologist asking clinicians to correlate!!