Acute Hepatitis (including Acute Liver Failure)

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Role of Liver Biopsy in Acute Hepatitis

Many of the classical morphological studies of acute hepatitis were carried out before the main causes had been discovered.

Most cases of acute hepatitis now diagnosed on the basis of clinical history and other investigations (e.g. drug history, viral serology, autoantibody screen) and liver biopsy is rarely indicated.

Liver biopsy may still be carried out in cases where the clinical presentation is atypical or the cause is uncertain:
- Distinguishing severe acute hepatitis from decompensated chronic liver disease
- Determining disease severity
- Identifying possible aetiological factors (including cases of acute liver injury not related to hepatitis)

Liver Biopsy in Acute Hepatitis – Diagnostic Approach

1. Is this acute or chronic damage?
2. How severe is the damage?
3. What is the cause?

Liver Biopsy in Acute Hepatitis - Histological Findings

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of inflammation</td>
<td>Mixed portal/lobular (mainly lobular)</td>
<td>Mainly portal/peripoportal (but may sometimes involve lobules)</td>
</tr>
<tr>
<td>Cholestatic features (e.g., bilirubinostasis, ductular reaction)</td>
<td>Common</td>
<td>Less common (except in progressive disease – associated with fibrosis)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Mild (collapse, reversible)</td>
<td>Variable (may progress to cirrhosis)</td>
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Acute and Chronic Hepatitis - Definition

1. Duration of disease
   - Acute < 6 months
   - Chronic > 6 months

2. Histological Findings
   - pattern of inflammation
   - presence of cholestatic features
   - presence of fibrosis

Areas of overlap exist for duration and histology
Distinction between acute and chronic hepatitis may be difficult
Acute Lobular Hepatitis
Histological Findings in Liver Parenchyma

1. Inflammatory Infiltration
   • mainly lymphocytes (T cells >> B cells)
   • plasma cells (esp in AIH)
   • neutrophils (esp in alcoholic hepatitis)
   • eosinophils (esp in drug reactions)

2. Hepatocellular Damage
   • ballooning
   • bile pigment accumulation (bilirubinostasis)
   • lobular disarray (may persist after inflammation subsides)
   • cell death (apoptosis and/or necrosis)

Changes tend to be most marked in perivenular regions (zone 3)

Acute Hepatitis - Spotty Inflammation & Lobular Disarray

Acute Hepatitis - Ballooning & Bilirubinostasis

Acute Hepatitis - Acidophil body

Acute Hepatitis - Haemosiderin-laden Kupffer Cells (Perls)

What else is the Perls’ stain useful for demonstrating?
Acute Hepatitis - Cereoid-laden Kupffer cells (PAS-diatase)

Acute versus Chronic Hepatitis - Portal and Periportal Changes

<table>
<thead>
<tr>
<th>HISTOLOGICAL FEATURE</th>
<th>ACUTE HEPATITIS</th>
<th>CHRONIC HEPATITIS</th>
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<tr>
<td><strong>Inflammation</strong></td>
<td>Mixed (lymphocytes, macrophages, plasma cells, neutrophils, eosinophils)</td>
<td>Mainly mononuclear (may include lymphoid follicles – e.g. HCV, AIH)</td>
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<tr>
<td><strong>Ductular reaction</strong></td>
<td>Common (associated with severity of cholestasis and with neutrophils – “cholangiolitis”)</td>
<td>Less common (associated with severity of fibrosis)</td>
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<td><strong>Fibrosis</strong></td>
<td>Mild (reversible) portal expansion</td>
<td>Progressive periportal fibrosis, may lead to cirrhosis</td>
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* Changes resemble those seen in chronic hepatitis
* May be seen in hepatitis A, also autoimmune hepatitis
### Acute Hepatitis

- **Periportal & Bridging Fibrosis (Reticulin Collapse)**

### Liver Biopsy in Acute Hepatitis – Diagnostic Approach

1. Is this acute or chronic damage?
2. How severe is the damage?
3. What is the cause?

### Liver Cell Death in Lobular Hepatitis (acute or chronic)

#### Pattern of Cell Death

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<th>Histological Features</th>
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<td>Spotty necrosis</td>
<td>Apoptosis of individual hepatocytes (acidophil bodies)</td>
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<td>Confluent necrosis</td>
<td>Loss of groups of adjacent liver cells (zone 3)</td>
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<td>Bridging necrosis</td>
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<td>Loss of hepatocytes in an entire acinus</td>
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<td>Panacinar necrosis involving several adjacent acini</td>
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- Assessing disease severity based on extent of liver cell death
- Apoptosis > necrosis (in mild forms)

### Acute Hepatitis – Acidophil Body
Acute Hepatitis – Confluent Necrosis (Zone 3)

Liver Cell Death in Lobular Hepatitis (acute or chronic)

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Severe Acute Hepatitis – Panacinar Necrosis

Ductular reaction: may suggest a biliary problem

Other Changes Seen in Areas of (Severe) Parenchymal Necrosis

Ceroid-Laden Macrophages

PAS - diastase
Other Changes Seen in Areas of (Severe) Parenchymal Necrosis

Ceroid-Laden Macrophages

CD 68

Orcein

Orcein

Resemble changes seen in liver allograft rejection

Other Changes Seen in Areas of (Severe) Parenchymal Necrosis

Congestion

May suggest a vascular problem – e.g. venous outflow obstruction

Liver Cell Death in Lobular Hepatitis (acute or chronic)

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Assessing Liver Cell Death in Lobular Hepatitis (acute or chronic)

Diagnostic Considerations

1. Prognostic significance.

Severity of liver cell necrosis correlates with:

- Progression to liver failure (acute hepatitis)
- Progression to fibrosis (acute and chronic hepatitis)
- Response to therapy
  - In AIH bridging necrosis associated with poor response to immunosuppression

Severe Acute Hepatitis – Submassive Hepatic Necrosis

Which areas contain residual hepatocytes – green or brown?
Assessing Liver Cell Death in Lobular Hepatitis (acute or chronic)
Diagnostic Considerations

2. Sampling Variability

More severe lesions (bridging necrosis and panacinar necrosis) often unevenly distributed
- Limits utility of liver biopsy in assessing disease severity

3. Acute versus Chronic Damage

Areas of bridging necrosis and nodular regeneration can resemble cirrhosis
Areas of post-necrotic collapse and ductular reaction can resemble cirrhotic septa
- Use of connective tissue stains to determine age of collapse/fibrosis

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Female, age 39. Live transplantation for subacute liver failure, cause unknown

Could this be cirrhotic?

Is this liver cirrhotic?

1. Yes
2. Probably
3. Unsure – more histological stains required
4. Probably not
5. No

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Recent Post-Necrotic Collapse versus Longstanding Fibrosis
Use Of Connective Tissue Stains

<table>
<thead>
<tr>
<th>Stain</th>
<th>Material Demonstrated</th>
<th>Distribution In Normal Liver</th>
<th>Changes In Liver Disease</th>
</tr>
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<tr>
<td>Reticulin</td>
<td>Type III collagen fibres</td>
<td>Portal tracts, hepatic sinusoids</td>
<td>Collapse of reticulin framework in areas of recent liver cell necrosis. (few days)</td>
</tr>
<tr>
<td>Masson's Van Gieson</td>
<td>Type I collagen fibres</td>
<td>Portal tracts, walls of hepatic veins</td>
<td>Increased in hepatic fibrosis (weeks/months)</td>
</tr>
<tr>
<td>Orcein</td>
<td>Elastic fibres</td>
<td>Portal tracts, walls of hepatic veins</td>
<td>Found in long-standing fibrosis/cirrhosis (months/years)</td>
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Severe Acute Hepatitis – Problem with Liver Biopsy Interpretation

Acute versus Chronic Damage - Helpful Pointers
- Clinical context
- Identification of normal vascular relationships
- Use of connective tissue stains to determine age of lesions

Liver Biopsy in Acute Hepatitis – Diagnostic Approach

1. Is this acute or chronic damage?
2. How severe is the damage?
3. What is the cause?
Acute Hepatitis - Common Causes

1. Viral
   - Hepatitis viruses – A, B, C, D, E
   - Other viruses – e.g. CMV, EBV, HSV

2. Drugs

3. Autoimmune

4. Unknown
   - Seronegative hepatitis (“non-A, non-B, non-C hepatitis”)
   - Accounts for 40% of patients in the UK presenting with severe acute hepatitis leading to acute liver failure (Ichai 2008, Bernal 2010)

Histological Findings
- Viral hepatitis (A-E), drugs and ARH have overlapping histological features
- Other viruses rare, but have distinctive features

Acute Liver Failure due to Fulminant HSV Hepatitis

Female, age 38. Liver transplant for acute liver failure. Presumed accidental paracetamol overdose.
Severe IBD, treated with steroids & azathioprine. Taking paracetamol for abdominal pain.
Died 12 hours post transplant.

Zonal Necrosis due to Toxic Liver Injury

- Severe cases associated with:
  - rapidly progressive liver failure  (usually unsuitable for liver biopsy)
  - massively elevated transaminase levels (100-1000x normal)

- Most hepatotoxic agents mainly involve perivenular (zone 3) regions

Acute Hepatitis - Aetiological Considerations

Liver biopsy may identify a cause of acute liver injury not due to acute hepatitis
- Decompensated chronic liver disease (e.g. Wilson’s disease)
- Another cause of acute liver damage (e.g. ischaemic hepatitis, severe alcoholic hepatitis, paracetamol toxicity)
- Hepatic infiltration (usually lymphoma, rarely carcinoma)
  - Liver usually enlarged

Acute Liver Failure due to Fulminant HSV Hepatitis

Histological Findings
- Apparent zonal necrosis and haemorrhage: Resembles paracetamol toxicity
- Coagulative necrosis (non-zonal)

Nuclear inclusions
(mostly in viable hepatocytes at periphery of necrotic areas)

HSV Immunohistochemistry
Patterns of Zonal Necrosis

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<th>Distribution of Necrosis</th>
<th>Examples</th>
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<tr>
<td>Perivenular (zone 3)</td>
<td>Paracetamol (acetaminophen)</td>
</tr>
<tr>
<td></td>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td></td>
<td>Mushroom poisoning</td>
</tr>
<tr>
<td></td>
<td>Some herbal medicines</td>
</tr>
<tr>
<td>Periportal (zone 1)</td>
<td>Ferrous sulphate</td>
</tr>
<tr>
<td></td>
<td>Phosphorus</td>
</tr>
<tr>
<td>Mid-zonal</td>
<td>Bacillus cereus toxin</td>
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Zonal distribution may reflect:
- heterogeneous distribution of enzymes involved in drug metabolism (e.g. P450 enzymes and paracetamol)
- factors related to blood supply (e.g. highest concentrations of ferrous sulphate in periportal regions)

Toxic injury in acute liver failure

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Toxic versus hepatitic injury in acute liver failure

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**BUT**

1. Some hepatotoxic drug agents may induce a “second wave” of inflammatory/immune mediated liver injury
2. Some hepatitic drug reactions may be associated with disproportionately severe zonal necrosis, suggesting a component of cytopathic injury (e.g. halothane)

Ischaemic (Hypoxic) Hepatitis

**Incidence**
- Common
- Frequently under-diagnosed

**Aetiology (often multifactorial)**
- Hypoperfusion (left heart failure)
- Congestion (right heart failure)
- Hypoxia (chronic respiratory failure)
- Shock

**Severe cases associated with:**
- Massively elevated transaminases
- Coagulative necrosis, zonal (centrilobular) distribution
- High mortality (not necessarily from liver failure)

Ischaemic Necrosis (non-occlusive infarction of liver allograft)

- Uneven distribution of ischaemic changes
- Coagulative pattern
- Zonal distribution less uniform than toxic liver injury

Neoplastic infiltration presenting as fulminant acute liver failure

**Prevalence/Clinical Presentation**
- Uncommon – 16/4020 (0.44%) admissions for acute liver failure KCH London (Rowbotham 1998)
- In some cases acute liver failure may be the presenting feature of otherwise undiagnosed malignancy (usually non-Hodgkin’s lymphoma)

**Aetiology**
- Usually lymphoma (including primary hepatic hepatic lymphoma)
- Less commonly carcinoma/other e.g. breast, lung (small cell carcinoma), melanoma, prostate

**Pathological Features**
- Most cases associated with diffuse hepatic infiltration (and hepatomegaly)
  - may not be detected radiologically
- Occasional cases of lymphoma have extensive hepatic necrosis with only scanty neoplastic lymphoid cells (Blakolmer 2000)

Role of Liver Biopsy in Acute Hepatitis - Summary & Conclusions

1. Most cases of acute hepatitis are diagnosed on the basis of the clinical history and results of non-invasive investigations
2. Liver biopsy may still be carried out in cases where the clinical presentation is atypical or the cause is uncertain
3. Histological assessments are useful in making a distinction between severe acute hepatitis and decompensated chronic liver disease
  - Connective tissue stains helpful in distinguishing recent collapse from longstanding fibrosis
4. Histological assessment of disease severity (extent of hepatocyte necrosis) may be clinically relevant in determining prognosis and treatment options
5. In some cases, liver biopsy may point to a previously unsuspected cause of acute liver injury, including cases unrelated to acute hepatitis (e.g. drug toxicity, ischaemia, neoplastic infiltration)