Histological Assessments in Acute Hepatitis

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Changing 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, biochemical and serological findings 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:
  - Confirm diagnosis of acute hepatitis
  - Determine disease severity
  - Identify possible aetiological factors
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
Liver Biopsy in Acute Hepatitis
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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 fibrosis

- Areas of overlap exist for duration and histology
- Most of the common causes of acute hepatitis can progress to chronic hepatitis
  - e.g. Viral agents, drugs, autoimmune hepatitis
- Distinction between acute and chronic hepatitis may be difficult – clinically and histologically
Patterns of Inflammation in the Liver

• **Portal Inflammation (Chronic Hepatitis)**
  – Most chronic inflammatory liver diseases (e.g. viral, autoimmune)
  – Also typically seen in acute hepatitis

• **Lobular Inflammation (Acute Hepatitis)**
  – Main pattern in acute hepatitis
  – May be present in some cases of chronic viral and autoimmune hepatitis

• **Mixed portal and lobular inflammation**
Drug-Induced Acute Hepatitis
Female, age 53. Metastatic malignant melanoma
Developed abnormal LFTS after treatment with Nivolumab and Ipilimumab

Diffuse spotty lobular inflammation
Lobular disarray

Portal Inflammation
Interface Hepatitis
Patterns of Inflammation in the Liver

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  – Also typically seen in acute hepatitis

• Lobular Inflammation (Acute Hepatitis)
  – Main pattern in acute hepatitis
  – May be present in some cases of chronic viral and autoimmune hepatitis

• Mixed portal and lobular inflammation

Pattern of inflammation alone cannot reliably distinguish chronic from acute hepatitis

• Clinical context
• Assessment of fibrosis:
  ➢ progressive fibrosis defines chronicity (distinguish from post-necrotic collapse)
Acute Hepatitis
Histological Findings in Liver Lobules

1. Inflammatory Infiltration
   - mainly lymphocytes (T cells >> B cells)
   - plasma cells (esp in AIH)
   - eosinophils (esp in drug reactions)

2. Hepatocellular Damage
   - ballooning
   - bile pigment accumulation (bilirubinostasis)
   - lobular disarray (may predominate and 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.
Hepatocyte Ballooning & Bilirubinostasis
Acute Hepatitis
Hepatocyte Ballooning & Rosetting
Hepatocyte Rosettes

- Clusters of hepatocytes embedded in connective tissue
- May be a manifestation of regenerative activity with hyperplastic hepatocytes trapped in areas of inflamed/collapsed liver parenchyma
- Present in cases of moderate/severe interface hepatitis in cases of chronic (portal) hepatitis – e.g. autoimmune hepatitis
- Also frequently present in cases of acute (lobular) hepatitis
Cholestatic Rosettes

- Clusters of hepatocytes surrounding dilated biliary canaliculi
- Present in cases of severe/prolonged cholestasis (including cholestatic hepatitis)
Acute Hepatitis – Acidophil body
Acute Hepatitis
Hepatocyte Proliferation (Ki 67 immunostaining)
Acute Hepatitis
Ceroid-laden Kupffer cells (PAS-diastase)
Acute Hepatitis - Haemosiderin-laden Kupffer Cells (Perls)
(also useful for highlighting bile plugs)
# Acute versus Chronic Hepatitis - Portal and Periportal Changes

<table>
<thead>
<tr>
<th>Histological Feature</th>
<th>Acute hepatitis</th>
<th>Chronic hepatitis</th>
</tr>
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<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td>Mixed</td>
<td>Mainly mononuclear</td>
</tr>
<tr>
<td></td>
<td>• Lymphocytes, macrophages, plasma cells, neutrophils, eosinophils</td>
<td>• May include lymphoid aggregates/follicles – e.g. HCV, AIH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be associated with periportal extension (“interface hepatitis”)</td>
</tr>
<tr>
<td><strong>Ductular reaction</strong></td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td></td>
<td>• Related to severity of lobular inflammation and cholestasis</td>
<td>• Associated with severity of fibrosis</td>
</tr>
<tr>
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<td>• May be associated with neutrophils – “cholangiolitis”</td>
<td></td>
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<tr>
<td><strong>Fibrosis</strong></td>
<td>Mild (reversible) portal expansion</td>
<td>Progressive periportal fibrosis, may lead to cirrhosis</td>
</tr>
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Acute Hepatitis
Portal Inflammation & Ductular Reaction (with neutrophils)
(may resemble biliary obstruction)
Acute Hepatitis
Ductular Reaction (Keratin 7 Immunohistochemistry)
Acute Hepatitis - Portal Inflammation & Interface Hepatitis
(“acute hepatitis with periportal necrosis”)

- Changes resemble those seen in chronic hepatitis
- May be seen in hepatitis A, also autoimmune hepatitis
# Acute versus Chronic Hepatitis

**Distinguishing Recent Injury from Evolving/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>
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| Reticulin         | Type III collagen fibres | Portal tracts, hepatic sinusoids | Portal expansion due to portal inflammation  
|                   |                       |                              | Collapse of reticulin framework in areas of recent liver cell necrosis. (few days) |
| Haematoxylin      | Type I collagen fibres | Portal tracts, walls of hepatic veins | Increased in hepatic fibrosis  
| Van Gieson (or Trichrome) |                    |                              | (weeks/months) |
| Orcein            | Elastic fibres         | Portal tracts, walls of hepatic veins | Found in long-standing fibrosis/cirrhosis  
|                   |                       |                              | (months/years) |
Acute Hepatitis – Mild Periportal Fibrosis (Reticulin)
Female, age 39. Presented with acute liver failure. Viral and autoantibody screens negative, no drug history. Ultrasound showed shrunken nodular liver ? Cirrhotic

Underwent urgent liver transplantation. Liver explant weighed 640g
Right Lobe
Could this be cirrhotic?
HVG (similar findings with Trichrome)
HVG (similar findings with Trichrome)
Female, age 39. Presented with acute liver failure. Viral and autoantibody screens negative, no drug history. Ultrasound showed shrunken nodular liver ? Cirrhotic

Underwent urgent liver transplantation. Liver explant weighed 640g

Conclusion

• Severe acute hepatitis with bridging and panacinar necrosis
• No evidence of longstanding fibrosis or cirrhosis
• No obvious aetiological pointers (seronegative hepatitis)

(Birmingham Case A/2019 is a similar case)
Cases of Hepatitis Difficult to Classify as Acute or Chronic

1. Acute exacerbation of chronic liver injury (not decompensated cirrhosis)

Examples

- Acute HAV/HEV infection superimposed on cirrhosis
  - Most frequently described in India, associated with high mortality
  - Histological features (other than cirrhosis) not well described

- “Acute” presentation of chronic autoimmune hepatitis
  - 30-40% of patients with AIH present as acute hepatitis / acute liver failure
  - 10-95% have bridging fibrosis or cirrhosis (Nikias 1994, Burgart 1995, Miyake 2010, Fujiwara 2011)

Histological Assessment

- Use of connective tissue stains important to demonstrate longstanding fibrosis/cirrhosis (versus recent post-necrotic collapse)
  - Presence of advanced fibrosis has implications for prognosis and management
Cases of Hepatitis Difficult to Classify as Acute or Chronic

2. Acute hepatitis evolving to chronic liver injury (“acute-on-chronic hepatitis”)

Examples

- Viral hepatitis - HBV, HCV, HEV (in immunocompromised people)
  - Acute phase rarely symptomatic and uncommonly biopsied
- Autoimmune hepatitis
- Drug-induced liver injury

Histological Features

- Transition from lobular to portal inflammation
- Connective tissue stains helpful in identifying evolving fibrosis
Autoimmune Hepatitis - Lobular Dissection by Fibrous Tissue

- Delicate strands of fibrous tissue extending from portal tracts to hepatic veins
- Surround and separate small clusters of hepatocytes forming rosettes
- Normal vascular relationships retained, no elastic fibres
- Distinctive pattern – different to post-necrotic collapse and cirrhotic septa

**Mechanism uncertain**
- May be a consequence of severe interface hepatitis and/or lobular inflammation
- Possibly reflects acute evolving to chronic liver injury
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
## Liver Cell Death in Acute Hepatitis

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Acute Hepatitis – acidophil body
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Acute Hepatitis – Confluent Zone 3 Necrosis
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Severe Acute Hepatitis - Panacinar Necrosis
Ductular reaction, hepatic vein endophlebitis
• Resembles changes seen in biliary disease – e.g. biliary obstruction, PBC/PSC
• Mechanism in severe acute hepatitis with panacinar necrosis is different:
  ➢ Progenitor cell response in cases where hepatocyte regeneration not possible
Hepatic Vein Endophlebitis
Other Changes Seen in Panacinar Necrosis

Ceroid Pigment Laden Macrophages
Other Changes Seen in Panacinar Necrosis

Congestion
May suggest a vascular problem – e.g. venous outflow obstruction
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Severe Acute Hepatitis – Submassive Hepatic Necrosis
Histological Assessment of Liver Cell Death in Acute Hepatitis
Diagnostic Considerations

1. **Severity of necrosis has implications for prognosis and treatment**
   - Extent of necrosis predicts progression to liver failure
   - More severe forms of necrosis less likely to respond to treatment (e.g. immunosuppression in acute autoimmune hepatitis)

2. **More severe forms of necrosis have uneven distribution**
   - Sampling variability in liver biopsy specimens

3. **Some patterns of liver injury can resemble changes seen in cirrhosis**
   - Areas of bridging necrosis & nodular regeneration can resemble changes occurring in cirrhosis
   - Areas of multiacinar necrosis can resemble inflamed fibrous septa in cirrhosis
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     cirrhosis
Liver Transplantation for Subacute Liver Failure (Autoimmune Hepatitis)
Severe Acute Hepatitis with Submassive Hepatic Necrosis

Panacinar Necrosis

Severe Cholestasis.
Little inflammation and no necrosis

Bridging Necrosis
Histological Assessment of Liver Cell Death in Acute Hepatitis
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Severe Acute Hepatitis with Panacinar Necrosis

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
Histological 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 U.K presenting with severe acute hepatitis leading to acute liver failure

**Histological Findings**

- Viral hepatitis (A-E), drugs and AIH have overlapping histological features
  - Viral serology, drug history, auto-antibody serology required to identify the cause
- Other viruses rare, but have distinctive features
Herpes Simplex Virus Hepatitis
(Birmingham Case C/2019)

Female, age 18
- Developed sudden massive rise in transaminases 1 week post-transplant for PSC/AIH. AST rose from 40 on day 7 to 9773 on day 10. Cause uncertain. Hepatic artery patent on imaging.

Coagulative necrosis (non-zonal)

Nuclear Inclusions
(mainly seen in viable hepatocytes adjacent to foci of necrosis)
**Herpes Simplex Virus Hepatitis**
*(Birmingham Case C/2019)*

Immunohistochemistry for HSV antigens
Liver biopsy rarely identifies a previously unsuspected aetiology

- Biopsies mostly obtained from people in whom main recognised causes have been excluded (“seronegative hepatitis”)

- Biopsy sometimes provides aetiological pointers:
  - e.g. features favouring drug or autoimmune aetiology
Acute Hepatitis
Histological Features Favouring a Drug Aetiology

• Predominantly centrilobular (zone 3) inflammation
• Disproportionately severe / well-circumscribed necrosis (relatively little inflammation – lobular and/or portal)
• Unusual patterns of necrosis - e.g periportal (zone 1) necrosis
• Unusually prominent cholestasis
• Eosinophils, granulomas
Immunotherapy Related Hepatitis

66 year old woman with metastatic malignant melanoma, treated with Nivolumab

Inflammation and necrosis confined to centrilobular regions
Acute Lobular Hepatitis - Histological Features Favouring a Diagnosis of AIH

- Portal inflammation / interface hepatitis (resembling chronic AIH)
- Plasma-cell rich inflammatory infiltrate
- Lymphoid follicles
- Centrilobular necrosis / central perivenulitis
- Hepatocyte rosettes
- Emperipolesis

BUT
- None of the above features can be regarded as specific for AIH
1. Portal inflammation occurs in all cases of acute hepatitis (viral, drug & AIH)
   - Plasma cell rich infiltrate favours a diagnosis of AIH

2. Interface inflammation resembles interface hepatitis seen in chronic AIH
   - But interface inflammation difficult to assess in the presence of diffuse lobular inflammation
Centrilobular Necroinflammatory Changes ("Central Perivenulitis") in AIH

- Usually occurs as centrilobular accentuation of diffuse lobular hepatitis - typically associated with portal inflammation

- Some cases may present as isolated central central perivenulitis – without diffuse lobular inflammation or portal inflammation
Centrilobular Necroinflammatory Changes (“Central Perivenulitis”) in AIH

- Similar changes may occur in other forms of acute lobular hepatitis – e.g. viral, drugs
- Plasma cell rich infiltrates may be a pointer
- Hepatocyte rosetting and emperipolesis (typical features of chronic AIH) unhelpful in this setting
  - commonly seen in non-autoimmune acute hepatitis (Balitzer, Modern Pathology 2017)
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 necrosis, severe alcoholic hepatitis, paracetamol toxicity)
- Diffuse hepatic infiltration (usually lymphoma, rarely carcinoma)
  - Liver usually enlarged
Zonal Necrosis due to Toxic Liver Injury

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

Most hepatotoxic agents cause perivenular (zone 3) necrosis
- Cytochrome p450 enzymes converting drug to toxic metabolite present in highest concentration in centrilobular hepatocytes (e.g. paracetamol)

Some hepatotoxic agents cause periportal (zone 1) necrosis
- Periportal hepatocytes exposed to highest concentration of substances absorbed from the gut (e.g. phosphorus)
Toxic Liver Injury – Zonal Necrosis

Centrilobular Necrosis (paracetamol)  Periportal Necrosis (phosphorus)
Toxic versus hepatitis injury in acute liver failure

<table>
<thead>
<tr>
<th>Pattern of necrosis</th>
<th>Toxic (e.g. paracetamol)</th>
<th>Hepatitic (e.g. viral, drugs, autoimmune)</th>
</tr>
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<tbody>
<tr>
<td>Coagulative (may appear lytic later)</td>
<td></td>
<td>Lytic</td>
</tr>
<tr>
<td>Distribution of necrosis</td>
<td>Uniform</td>
<td>Patchy</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+/-</td>
<td>+++/++++</td>
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Role of Liver Biopsy in Acute Hepatitis – Summary and 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 are 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 causes unrelated to acute hepatitis (e.g. toxic liver injury, ischaemia, neoplastic infiltration)