Viral Hepatitis (I)

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Definition

Hepatitis means **inflammation** of the liver characterized by a variable combination of:

- mononuclear inflammation (lymphocytes and plasma cells)
- hepatocellular necrosis/apoptosis
- hepatocellular regeneration
Viral Hepatitis

Unless otherwise specified, the term "viral hepatitis" is reserved for infection of the liver caused by a group of viruses having a particular affinity for the liver.

Systemic viral infections that can involve the liver include:

1. infectious mononucleosis (Epstein-Barr virus), which may cause a mild hepatitis during the acute phase;

2. cytomegalovirus, particularly in the newborn or immunosuppressed patient;

3. yellow fever, which has been a major and serious cause of hepatitis in tropical countries.

Hepatotropic viruses cause overlapping patterns of disease.
# Viral Hepatitis

## The Hepatitis Viruses

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A Virus</th>
<th>Hepatitis B Virus</th>
<th>Hepatitis C Virus</th>
<th>Hepatitis D Virus</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Icosahedral capsid, ssRNA</td>
<td>Enveloped dsDNA</td>
<td>Enveloped ssRNA</td>
<td>Enveloped ssRNA</td>
<td>Unenveloped ssRNA</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Fecal-oral</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Waterborne</td>
</tr>
<tr>
<td><strong>Incubation Period</strong></td>
<td>2-6 wk</td>
<td>4-26 wk</td>
<td>2-26 wk</td>
<td>4-7 wk</td>
<td>2-8 wk</td>
</tr>
<tr>
<td><strong>Carrier state</strong></td>
<td>None</td>
<td>0.1-1.0% of blood donors in U.S. and Western world</td>
<td>0.2-1.0% of blood donors in U.S and Western world</td>
<td>1-10% in drug addicts and hemophiliacs</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Chronic hepatitis</strong></td>
<td>None</td>
<td>5-10% of acute infections</td>
<td>&gt;50%</td>
<td>&lt;5% coinfection, 80% upon superinfection</td>
<td>None / Very rare</td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No increase above HBV</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Types of necrosis

- Spotty (focal) necrosis / apoptosis
- Confluent and bridging necrosis
- Interface hepatitis ("piecemeal necrosis")
THE THREE TYPES OF NECROSIS IN CHRONIC HEPATITIS

SPOTTY
PIECEMEAL
CONFLUENT
Apoptotic bodies („Councilman bodies“)
Interphase Hepatitis („Piecemeal“ necrosis)
(Chronic) Viral Hepatitis

Interface hepatitis (Piecemeal necrosis)
Liver cell apoptosis and inflammation of the region where the hepatic parenchyma comes into contact with the mesenchymal stroma of the portal tract (interface region)
Confluent necrosis
Viral Hepatitis

Confluent necrosis

Necrosis of large areas of contiguous liver cells

Bridging hepatic necrosis

Central-Central

Central-Portal
Central-to-portal bridging necrosis disrupt the microcirculatory integrity of the acinus scaffold upon which fibrous septa form with subsequent porto-systemic shunting.

**Prognostic significance:**?

• 170 acute hepatitis: 37% incidence of cirrhosis and 19% incidence of mortality (Boyer & Klatskin, 1970)

• Others have not considered BHN as a good predictor of chronicity (Spitz RD, 1978; Nisman RM, 1979)

• BHN is seen in the most severe, coma-producing, and often fatal forms of hepatitis!
Bridging Hepatic Necrosis

Clinical Conditions associated with BHN

• Acute and Chronic viral hepatitis
• Autoimmune hepatitis
• Drug-induced and toxic hepatitis
• Massive or submassive hepatic necrosis of unknown cause
• Acute hepatic allograft failure
• ........................
Acute Viral Hepatitis - Pathology

Clinical evaluation has largely replaced the need for liver biopsy in the diagnosis of most patients with acute viral hepatitis

*< 1% of liver biopsies in many reference centers

**Clinical setting 1:**
Clinical setting or progress of the hepatitis is unusual: ddx with alcoholic hepatitis, drug-induced and ischemic hepatitis

**Clinical setting 2:**
Immunosuppressed population: ddx with opportunistic viral, fungal infections
Acute Viral Hepatitis
Histologic Findings

Regeneration

Diffuse hepato-cellular injury

Inflammatory response

Acute viral hepatitis
Acute Viral Hepatitis
Histologic Findings

- Lobular disarray
- Necrosis
- Lobular inflammation (lymphocytes, plasma cells and macrophages)
- Ballooning degeneration
- Portal tract changes: inflammation and bile duct lesions
- Endotheliitis (up to 69% of cases)
- Cholestasis
Acute hepatitis: Lobular disarray
Apoptotic bodies („Councilman bodies“)
Ballooning degeneration
Classical Causes of Chronic Hepatitis

- Hepatitis B, with or without HDV superinfection
- Hepatitis C
- Autoimmune hepatitis
- Drug-induced hepatitis
- Chronic hepatitis of unknown cause
Chronic Viral Hepatitis

Histologic Findings

- Diffuse hepatocellular injury
- Regeneration
- Inflammatory response
- Fibrosis

Chronic viral hepatitis
Chronic Viral Hepatitis B

Histology

- **Portal inflammation**: CD4+ helper / inducer T-lymphocytes
- **Interface hepatitis** ("piecemeal necrosis")**: CD8+ suppressor / cytotoxic T cells
- **Lobular and Confluent necrosis**
- **HBs-containing ground-glass hepatocytes**
- **HBc-containing „sanded“ nuclei**
- **Portal tracts with maple-leaf configuration**
Morphological Criteria:

• Portal fibrosis (facultative)
• Predominance of portal inflammation
• "Piecemeal," ("interface") Hepatitis
The host’s immune attack against HBV is the cause of the liver injury, mediated by a cellular response to small epitopes of HBV proteins, especially HBcAg, presented on the surface of the hepatocyte.
HBV Infection

„ground-glass“ hepatocytes
HBV chronic infection: Surface antigen (HBsAg)
HBV infection: Core Antigen
Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Bridging necrosis (and fibrosis) is shown only for chronic hepatitis; bridging necrosis may also occur in acute hepatitis (not shown).
Histopathology of Chronic Hepatitis C Characteristic but not specific features!

- Prominent lymphoid aggregates in portal tracts
- Bile duct damage
- Steatosis
Chronic Hepatitis C: Lymphoid follicle
Chronic Viral Hepatitis

The Role of Liver Biopsy

• Grading
• Staging
• Confirming the diagnosis of viral hepatitis
• Confirming or excluding concurrent disorders such as alcoholic steatohepatitis or hemochromatosis
• Assess response to therapy
Chronic Hepatitis

**Grading** = Severity of necroinflammatory changes

(Portal, periportal and lobular activity)

**Staging** = Extent of fibrosis / architectural distortion

V. Desmet, 1994
Fig. 2. Algorithm for the evaluation of histological activity. PMN, piece-meal necrosis; 0, none; 1, mild; 2, moderate; 3, severe; LN, lobular necrosis; 0, no or mild; 1, moderate; 2, severe; A, histological activity; 0, none; 1, mild; 2, moderate; 3, severe.
Metavir Scoring System

A two letter and two number system

**A** = Histological activity

- A0 - no activity
- A1 - mild activity
- A2 - moderate activity
- A3 - severe activity

**F** = Fibrosis

- F0 - no fibrosis
- F1 - portal fibrosis, no septa
- F2 - portal fibrosis, rare septa
- F3 - numerous septa, no cirrhosis
- F4 - cirrhosis

Bedossa P, Poynard T, Hepatology 1996; 24:289
Grade of inflammatory activity in Chronic Hepatitis
HCV - Grade 0 Inflammation in Chronic Hepatitis
HCV - Grade 1 Inflammation in Chronic Hepatitis
HCV - Grade 2 Inflammation in Chronic Hepatitis
HCV - Grade 3 Inflammation in Chronic Hepatitis
HCV - Natural History

Stages of Fibrosis in Chronic Hepatitis

1. Portal
2. Periportal
3. Septal
4. Cirrhosis
HCV - Stage 1 Fibrosis (Portal)
HCV - Stage 2 Fibrosis (Periportal)
HCV - Stage 4 Fibrosis (Cirrhosis)
Chronic Viral Hepatitis (II)

Luigi Terracciano
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Basel, 2016
Each biopsy report should convey

• The cause of the hepatitis when known
• The amount of inflammation
• The amount of fibrosis
• Any other biopsy findings, eg fat
Each biopsy report should convey:
• The cause of the hepatitis when known
• The amount of inflammation
• The amount of fibrosis
• Any other biopsy findings, e.g., fat

Key point 1:
Do this accurately:
Your biopsy report will be perfect in >99% of all cases
Typical reasons for liver biopsy

The primary diagnosis of chronic hepatitis C or hepatitis B is already known in most cases before the liver biopsy is performed.
Typical reasons for liver biopsy

• Determine amount of fibrosis (stage of liver disease)
• Evaluate fibrosis progression
• Evaluate degree of inflammation (grade)
• Evaluate for concomitant liver disease
Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease

**Key point 2:**
This is the main reason for biopsy in most cases of HCV and HBV
Liver Fibrosis Assessment

- Trichrome stain commonly used
- Acceptable but not perfect reproducibility
- Fibrosis variability more likely when:
  - Small biopsy (less than 15 mm)
  - Old inactive cirrhotic livers with large macronodules
  - Biliary tract disease
Liver Fibrosis Assessment

- Reporting fibrosis in a liver biopsy
  - Narrative vs number vs both
    - Mild portal fibrosis
    - MHAI fibrosis stage: 1/6
    - Mild portal fibrosis, MHAI stage 1/6.
Liver Fibrosis Assessment

• Many different staging and grading schemas
  ▪ Most are quite similar
  ▪ None clearly better than the rest
  ▪ Make sure **YOU** know the system well
  ▪ Make sure the clinicians understand the system
    – In the pathology report, it’s helpful to indicate the system you’re using (and the scale), for example:
    – MHAI fibrosis stage = 2/6
Liver Fibrosis Assessment

• Many different staging and grading schemas

  ▪ Most are quite similar
  ▪ None clearly better than the rest
  ▪ Make sure the clinicians understand the system

    In the pathology report, it’s helpful to indicate the system you’re using (and the scale), for example:

    - MHAI fibrosis stage = 2/6

Key point 3: Make sure you don’t get so caught up in filling out numbers that you forget to carefully study the biopsy!
Staging schemas are similar

- Essentially all are fibrosis staging is based on the following conceptual stages and differ only in how they are subdivided:
  - No fibrosis
  - Portal fibrosis
  - Bridging fibrosis
  - Cirrhosis
# General Comparison of the Most Commonly Used Staging Systems

<table>
<thead>
<tr>
<th>MHAI</th>
<th>HAI</th>
<th>META VIR</th>
<th>DESMET</th>
<th>SCHEUER</th>
<th>BATTS</th>
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<tr>
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<td>4</td>
<td>4</td>
<td>4</td>
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</tbody>
</table>
are a NON-LINEAR continuum:

Giving a number doesn’t change that
The numbers in staging and grading systems are not equidistance

A stage 2 liver bx **does not** have twice as much fibrosis as stage 1

A grade 4 bx **does not** have $\frac{1}{2}$ as much inflammation as grade 8.
Staging pitfalls

- Large portal tracts
Staging pitfalls

Marked portal inflammation
Staging pitfalls

Bridging necrosis
Staging pitfalls

• If the biopsy specimen is too small or fragmented, *please* say so in the report.

  “The biopsy is too small to adequately stage but there does appear to be at least mild portal fibrosis”.
Staging pitfalls

“Fibrous caps”
Staging pitfalls

Focal fibrous bridging vs longitudinal section of portal tract
Typical reasons for liver biopsy

• Determine amount of fibrosis (stage of liver disease)
• Evaluate fibrosis progression
• Evaluate degree of inflammation (grade)
• Evaluate for concomitant liver disease
Fibrosis progression

• Fibrosis progression poorly understood

• Overall, 20% of those with HCV are cirrhotic in 20 yrs.

• Determining fibrosis progression is best performed by comparing two trichrome stains directly.
  - Comparing current case to report of old case is less desirable
Findings on Liver Biopsy That May Increase Risk for Fibrosis Progression

- Fibrosis
- Steatosis
- Steatohepatitis
- Coinfection with HBV or HIV
- Iron overload

(not a complete list, but some of the more common findings)
Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease
Inflammation (grade)

• Three “compartments” to inflammation
  ▪ Portal inflammation
  ▪ Interface activity/periportal hepatitis/piecemeal necrosis
  ▪ Lobular hepatitis/spotty necrosis

Most staging systems accompanied by grading systems.
  ▪ For clinical purposes, probably doesn't add much to pathology report over descriptive diagnosis
Inflammation
Inflammation

• In greater than 90% of cases of HCV liver biopsies

• **Portal inflammation is**
  - Either mild or moderate

• **Lobular inflammation is**
  - Either mild or moderate
Inflammation

• In greater than 90% of cases of HCV

• Portal inflammation
  ▪ Either mild or moderate

• Lobular inflammation
  ▪ Either mild or moderate

**Key point 4:** If the inflammation in your biopsy for HCV doesn't look like this, think some more
Inflammation

• If your biopsy shows marked lobular inflammation in particular
  ▪ Start thinking!
  ▪ Check the history
  ▪ Check the liver enzymes
Inflammation

• Chronic HCV does not have enzyme “flares”

• This is in contrast to chronic HBV

• If your biopsy shows marked lobular hepatitis and there has been enzyme flare,
  ▪ Strong possibility of another liver injury superimposed on chronic HCV (could be drug, HBV, etc)
Typical reasons for liver biopsy

• Determine amount of fibrosis (stage of liver disease)
• Evaluate fibrosis progression
• Evaluate degree of inflammation (grade)
• Evaluate for concomitant liver disease
Are liver biopsies helpful in finding Co-existing Diseases?

- Yes
- Yield is much higher when there is clinical suspicious for another disease process.
- The yield is low in patients biopsied solely for staging/grading HCV
  - In a study of 535 Italian patients with HCV or HBV, 3.7% of biopsies yielded additional diagnoses (Dig Dis Sci 2001 Jul;46(7):1409-15)
Steatosis and HCV

Causes

• NAFLD
• HCV Genotype 3
• Drug effect, including some anti retrovirals
• Etoh
HCV - Other findings

Bile duct lymphocytosis and injury

- Up to 1/3 of cases in some studies
- No clear direct clinical relevance
- Not assoc with higher Alk phos

Mod Pathol. 1994 Dec;7(9):937-45
HCV-Other findings

Portal granulomas

• 1.3% of 605 pts.
• No association with TB, IFN therapy
• Often present on repeat bx
• Significance??

HCV-Other findings

- Increased portal plasma cells
- More frequent in those with elevated serum ANA
HCV-Elevated serum ANA

**ANA positive** in 8% of 605 cases of chronic HCV

- 1:40 = 22
- 1:80 = 20
- 1:160 = 8

- ANA positivity associated with
  - Female gender
  - Geographic location
  - Portal plasma cells

J Viral Hepat. 2004 Sep;11(5):459-64
HCV-Elevate serum ANA

No association with:

- Age
- Route of infection
- Genotype
- Fibrosis stage
- Inflammatory grade

J Viral Hepat. 2004 Sep;11(5):459-64
HCV-Other findings

- **Giant cell change** in hepatocytes
- Always limited to zone 3
- Can be focal or involve most lobules
- Approx 1% of bxs in our case material
- Much more common in HCV/HIV coinfection
- Often present on repeat bxs taken several yrs later
- ??clinical correlates

J Clin Pathol. 2008 Sep;61(9):1058-61
HCV-Other findings
HCV - Other findings

“lipid” granulomas

- Actually mineral oil
- No clinical correlate
HCV is a risk factor for intra-hepatic cholangiocarcinoma

Surgical specimens and explants from HCV occasionally show bile duct dysplasia

Am J Surg Pathol. 2007 Sep;31(9):1410-3
Summary
Summary

Each biopsy report should convey

• The cause of the hepatitis when known
• The amount of inflammation
• The amount of fibrosis
• Any other biopsy findings, eg fat
Summary

Each biopsy report should convey:
• The cause of the hepatitis when known
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• Any other biopsy findings, eg fat

Key Pnt 1. Do this accurately:
Your biopsy report will be perfect in >99% of all cases

• (Continue...)

• (Continue...)
2. Fibrosis staging is the main reason for biopsy in most cases of HCV and HBV
   - Take your time; get it right
   - Beware of pitfalls

3. If you want to use a numerical system
   - Take the time to really master it.
   - Don’t get so caught up in filling out the sheet that you miss other histological findings.
Summary

4. The inflammation in chronic HCV biopsies is generally mild to moderate and associated with mild but stable elevations in liver enzymes

• Your biopsy doesn't look like this?
• Has there been a flare in liver enzymes?
• If so, there is a strong probability that there is a second source of liver injury