Chronic Hepatitis
(Viral & Autoimmune)

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Pathology of Chronic Hepatitis

1. Definition and general histological features
2. Role of liver biopsy in chronic viral & autoimmune hepatitis

Chronic Hepatitis - Definition

1. **Clinical**
   - "Inflammation of the liver continuing without improvement for at least 6 months" (Leevy et al. Fogarty International Center Criteria Committee, US Government Printing Office 1976)
   - **BUT**: Most chronic liver diseases have an inflammatory component that persists for > 6 months
2. **Histological**
   - Inflammation
     - Mainly involves portal tracts (contrasting with predominantly lobular inflammation seen in acute hepatitis)
   - Variable fibrosis

Diseases Associated with Portal Inflammation (Chronic Hepatitis)

1. VIRAL	Hepatitis B, C, D.
2. AUTOIMMUNE	Type 1 (ANA/ SMA positive) Type 2 (LKM/LC-1positive) Type 3 (SLA/LP positive)
3. BILIARY	Primary biliary cirrhosis Primary sclerosing cholangitis
4. METABOLIC	Alpha -1- antitrypsin deficiency Wilson's disease
5. FATTY LIVER DISEASE	Alcoholic Non-alcoholic
6. DRUGS	e.g. methyldopa, isoniazid, nitrofurantoin
7. UNKNOWN	

Portal Inflammation – Histological Assessment

1. **Aetiology Known (e.g. hepatitis B & C)**
   - Assess disease severity
     - inflammatory grade
     - fibrosis stage
   - Identify co-existent disease (e.g. NAFLD)
2. **Aetiology Suspected (e.g. autoimmune hepatitis)**
   - Identify features supporting suspected diagnosis (absence of features suggesting an alternative diagnosis)
3. **Aetiology Uncertain/Unknown**
   - Pattern & composition of inflammatory infiltrate (and other associated features) may provide diagnostic clues

Composition of Inflammatory Cells in Portal Tracts

Lymphocytes (mainly T Cells)	Most conditions

Primary Biliary Cirrhosis - Portal Inflammatory Cells

CD3+ T lymphocytes

Composition of Inflammatory Cells in Portal Tracts

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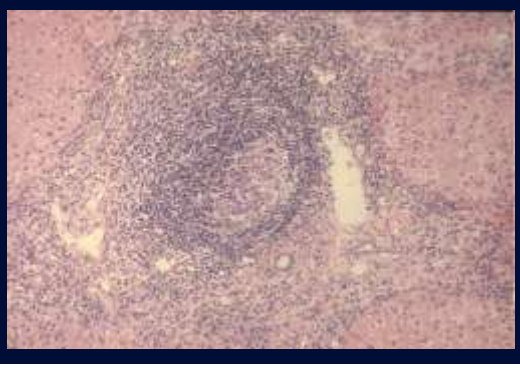
Lymphoid aggregates (B cell rich)	Chronic HCV infection Other chronic inflammatory diseases (e.g. PBC, AIH)

Chronic Hepatitis C Infection - Portal Lymphoid Follicle



Primary Biliary Cirrhosis – Portal Lymphoid Aggregate

(present at site of former bile duct – "tombstone aggregate")

CD20+ B lymphocytes

Composition of Inflammatory Cells in Portal Tracts

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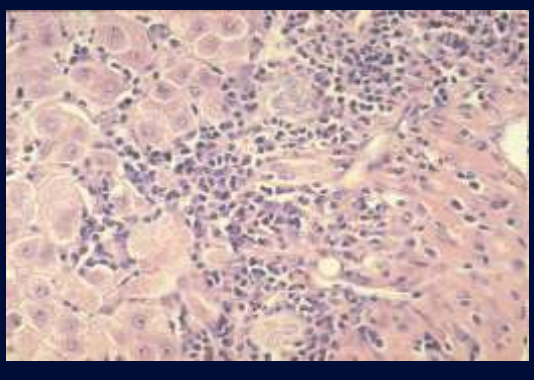
Lymphoid aggregates (B cell rich)	Chronic HCV infection Other chronic inflammatory diseases (e.g. PBC, AIH)
Plasma cells	Autoimmune hepatitis Chronic biliary diseases (PBC > PSC) Other diseases (e.g. HCV, NAFLD) – less common

Autoimmune Hepatitis - Portal/periportal Plasma Cells



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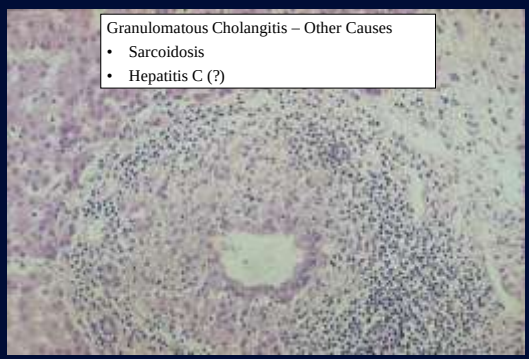
Granulomas	Primary biliary cirrhosis, sarcoidosis PSC (up to 10%), HCV, drug reactions

Primary Biliary Cirrhosis - Granulomatous Bile Duct Lesion



Granulomatous Cholangitis – Other Causes
- Sarcoidosis
- Hepatitis C (?)

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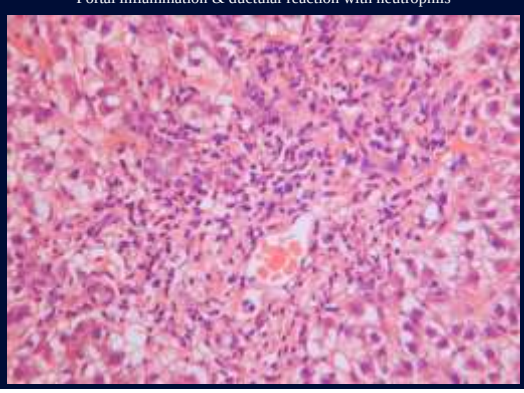
Neutrophils	Ductular reaction • biliary obstruction / ascending cholangitis • chronic biliary disease • acute hepatitis

Acute Hepatitis
Portal inflammation & ductular reaction with neutrophils



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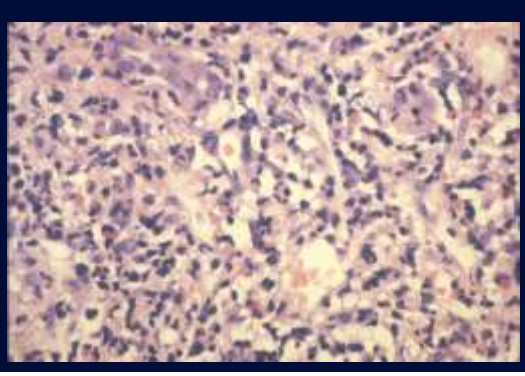
Eosinophils	Drug reaction, biliary obstruction, PBC & PSC, parasitic infestation, acute allograft rejection

Acute Liver Allograft Rejection - Portal Tract Eosinophils

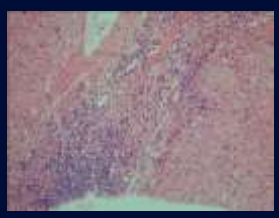


Portal/Periportal Inflammation : Interface Hepatitis ("piecemeal necrosis")

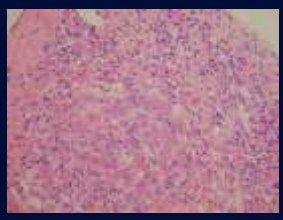
Inflammation at the interface between connective tissue (portal tracts, fibrous septa) and the liver parenchyma

Severity classified according to :

- extent around individual portal tracts/septa (focal vs diffuse)
- proportion of portal tracts involved (e.g.<50% vs > 50%)



Hepatitis C
Chronic hepatitis with mild activity



Autoimmune Hepatitis
Chronic hepatitis with severe activity

Interface Hepatitis ("piecemeal necrosis")

Periportal hepatocyte ballooning & rosetting (Autoimmune Hepatitis)

Periportal fibrosis (HVG)

Severity of interface hepatitis:

- Predicts subsequent development of fibrosis/cirrhosis (HCV, AIH, PBC)
- Guides therapeutic decisions (AIH, ?PBC/PSC – "overlap syndromes")

Pathology of Chronic Hepatitis

1. Definition and general diagnostic features
2. Role of liver biopsy in chronic viral & autoimmune hepatitis

Role of Liver Biopsy in Chronic Hepatitis

1. Establishing a histological diagnosis
2. Identifying or confirming the aetiology
3. Assessing disease severity
   - necro-inflammatory activity (grading)
   - fibrosis (staging)
4. Identifying additional lesions
   - Co-existent disease (e.g. fatty liver disease, siderosis)
   - Neoplastic and pre-neoplastic lesions (large and small cell change)

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Hepatitis B & C– Histological Features
Portal and Periportal Changes

	Hepatitis B	Hepatitis C
Portal inflammation	Yes (mainly lymphocytes)	Yes (mainly lymphocytes)
Lymphoid aggregates	Uncommon (typically smaller)	Common (may include lymphoid follicles)
Bile duct inflammation	Minimal/none	Common • typically mild • often related to lymphoid aggregates • **not** associated with duct loss
Interface hepatitis	Variable (more severe cases can resemble AIH)	Mild

Hepatitis B & C - Portal and Periportal Inflammation

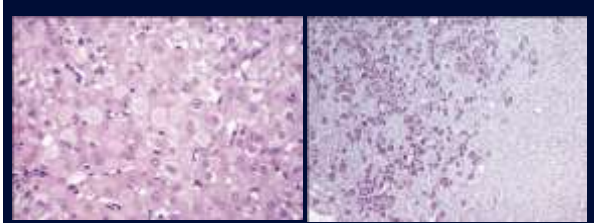
Hepatitis B
Severe interface hepatitis

Hepatitis C
Mild interface hepatitis
Lymphoid follicle

Hepatitis B & C– Histological Features
Lobular Changes

	Hepatitis B	Hepatitis C
Lobular inflammation	**Variable** • prominent inflammation resembling changes seen in acute hepatitis may occur during seroconversion or super-infection	**Mild** • Confluent bridging/necrosis not seen with HCV alone (except in immunocompromised individuals) • When present, consider other causes (e.g. co-existent AIH)
Fatty change	**Typically mild** • Related to other causes (e.g. ALD or NAFLD) • Not related to disease progression	**Common (mainly macrovesicular)** • May be related to viral load (genotype 3) or other factors (e.g. ALD or NAFLD – other genotypes) • Associated with poor response to treatment and disease progression

Hepatitis B – Detecting Viral Antigens in Tissue Sections
Hepatitis B surface antigen (HBsAg) - Orcein

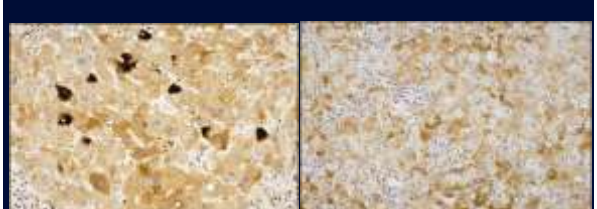


Ground glass hepatocytes

Orcein

Hepatitis B – Detecting Viral Antigens in Tissue Sections
Hepatitis B surface antigen (HBsAg) - Immunohistochemistry

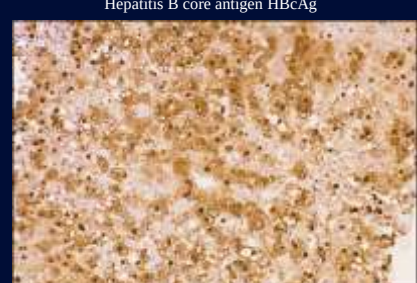
Immunohistochemistry more sensitive (and specific) than Orcein staining



- Dark staining = ground glass inclusions
- Paler stained cells – may not be visible by H & E or Orcein staining

Membranous staining
- Associated with high levels of viral replication

Hepatitis B – Detecting Viral Antigens in Tissue Sections
Hepatitis B core antigen HBcAg



- Staining may be nuclear or cytoplasmic
- Diffuse cytoplasmic staining occurs in states of high viral replication (e.g. post-transplant – may be associated with hepatocyte ballooning)

Hepatitis B – Detecting Viral Antigens in Tissue Sections
Role of Immunohistochemistry

1. Previously used to establish/confirm aetiology, provide information about likely replicative state
2. Now largely replaced by serological investigations, including ability to measure HBV-DNA in serum
3. May still be useful in identifying atypical patterns of HBV infection, especially in immunocompromised individuals (e.g. "fibrosing cholestatic hepatitis")

Hepatitis C – Detecting Viral Antigens in Tissue Sections

- Several antibodies described, reacting with various components of HCV
  - Mainly used for research
- None currently suitable for use in routine clinical practice
  - Some only work on frozen tissues
  - Poor reproducibility in routinely processed tissues
  - Non-specific staining often seen in other chronic liver diseases (e.g. PBC & PSC)

Chronic Hepatitis E in Immunocompromised Individuals

(Kamar 2012, Halac 2012, Behrendt 2014, Kamar 2014)

Mode of infection

- Most cases acquired orally
  - Genotype 3 commonest (contaminated food, especially pork products)
- Occasional cases transmitted via donor organ or blood products

Natural History

- 50-80 % progress to chronic infection in setting of immunosuppression
  - More frequent in recipients of liver than renal allografts (82% vs 58%) (Kamar 2011)

Histological Features

- Early stages characterised by lobular hepatitis
  - Some may have minimal inflammatory changes with few acidophil bodies (Protzer 2015)
- Later develop portal inflammation +/- interface hepatitis (chronic hepatitis)
- 10 -15% progress to cirrhosis
- Occasional cases develop decompensation / graft failure

Chronic Hepatitis E in Liver Allograft
Liver Transplant for Biliary Atresia in 2007 – persistently elevated ALT

Liver biopsy in July 2013 – chronic hepatitis ? cause

HEV detected in November 2013. Treated with Ribavirin
Liver biopsy in March 2015 – resolution of portal inflammation

Autoimmune Hepatitis – Laboratory Investigations
Diagnostic Criteria

Biochemistry	Hepatitic LFTs • Raised AST/ALT
Immunology	Autoantibodies • ANA, SMA (type 1) • LKM , LC-1 (type 2) • SLA/LP (type 3) Immunoglobulins • Raised IgG
Histology	Presence of typical/compatible features Absence of atypical features (e.g. biliary features)

International Autoimmune Hepatitis Group – Scoring Systems for Diagnosis of AIH
(Original –Johnson 1993, Modified – Alvarez 1999, Simplified – Hennes 2008)

- Various combinations of clinical, biochemical, immunological & histological features
- Points allocated for typical features (deducted for atypical features -1993 & 1999 systems)
- Total scores = "definite", "probable" or "not" AIH
- Mainly intended for research purposes – e.g. clinical trials

Role of Liver Biopsy in the Diagnosis of AIH

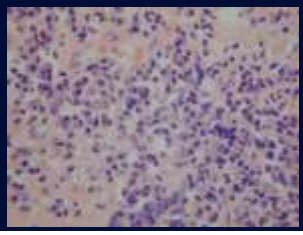
Routine use of liver biopsy still recommended in recent expert reviews and national/international guidelines documents

- International Autoimmune Hepatitis Group (Hennes , Hepatology 2008)
- AASLD Practice Guidelines (Manns , Hepatology 2010)
- Invited Review (Lohse & Mieli-Vergani, J Hepatol 2011)
- British Society of Gastroenterology Guidelines (Gleeson 2012)
- EASL Clinical Practice Guidelines (Lohse 2015)

Others suggest mainly useful in cases where other findings are equivocal or atypical:

- Autoantibodies in low titre or absent ("autoantibody –negative" AIH)
- Features suggesting an alternative diagnosis (e.g. fatty liver disease or biliary disease)

Chronic Autoimmune Hepatitis -Typical Features
Plasma cell rich portal inflammation



BUT:

- Plasma cells not essential to support/confirm diagnosis of AIH
- Plasma cells also seen in other diseases associated with features of chronic hepatitis (e.g. PBC)

Chronic Autoimmune Hepatitis -Typical Features
Interface Hepatitis ("piecemeal necrosis")

Interface Hepatitis

- Often associated with ballooning and rosetting of periportal hepatocytes
- May also be associated with emperipolesis of lymphocytes
- Recent studies suggest that hepatocyte rosettes and emperipolesis more specific than plasma cells and interface hepatitis in diagnosis of AIH (de Boer 2015)

Periportal Fibrosis

Simplified Criteria for the Diagnosis of Autoimmune Hepatitis
(International Autoimmune Hepatitis Group – Hennes , Hepatology 2008)

Assessment of Histological Features	
Typical histology:	All three of (i) interface hepatitis, (ii) emperipolesis and (iii) hepatocyte rosettes are present
Compatible histology:	Chronic hepatitis pattern of injury present, but lacking one or more of the "typical features"
Atypical histology:	Features suggesting another diagnosis (e.g. steatohepatitis) are present

Chronic Autoimmune Hepatitis
Interface Hepatitis - Clinical Significance

Prognosis

- Presence/severity at presentation predicts development of fibrosis
- Persistence after treatment associated with increased risk of fibrosis

Treatment

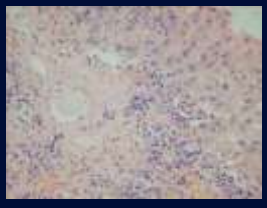
Newly Diagnosed AIH

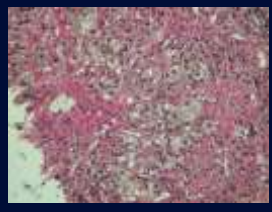
- Indication for commencing immunosuppression
- Mild activity (e.g. Ishak score <4-6) in older person may be grounds for not treating with immunosuppression (Gleeson 2012)

Treated AIH

- Indication for maintaining immunosuppression
  - Histological response typically lags several months behind biochemical response
  - Interface hepatitis present in up to 50% of patients with normal AST and IgG following treatment (Manns 2010) - high relapse rate (>80%)

Autoimmune Hepatitis - Lobular inflammation





Lobular inflammation in AIH

- Typically plasma cell rich
- Often mainly perivenular ("central perivenulitis"), may be diffuse
- More severe cases associated with confluent / bridging necrosis & fibrosis
  - Less responsive to immunosuppression
  - Increased risk of progression to cirrhosis - up to 80% (Cjaza 2007, Manns 2010)
- May present as acute hepatitis / acute liver failure

Autoimmune Hepatitis - Acute Presentation
Incidence & Diagnostic Criteria

30- 40% of cases present as acute hepatitis /acute liver failure
(Czaja & Freese 2002, Manns 2010, Lohse 2011, Gleeson 2012, Lohse 2015)

Increasing prevalence of AIH as a cause for acute liver failure
(Fujiwara 2011)

- ? May reflect improved recognition

Autoantibodies unreliable in the diagnosis of acute AIH

- Autoantibodies and hypergammaglobulinaemia may not be present at the time of presentation with acute AIH (Lohse 2011)
- Autoantibodies present in up to 40% of patients with other causes of acute liver failure - e.g viral or drug-induced (Bernal 2007)

Autoimmune Hepatitis - Acute Presentation
Histological Features

1. Acute presentation of chronic liver disease

- 14-35% have features of chronic hepatitis (Fujiwara 2011, Yasui 2011)
- 10-95% have bridging fibrosis or cirrhosis (Nikias 1994, Burgart 1995, Miyake 2010, Fujiwara 2011)

Autoimmune Hepatitis - Acute Presentation
Histological Features

2. Acute hepatitis (with no signs of chronic liver disease)

(Te 1997, Singh 2002, Hofer 2006, Ichai 2007, Fujiwara 2011, Stravitz 2011, Susuki 2011, Yasui 2011)

- Classical features of acute lobular hepatitis (resembling viral or drugs)
- Mainly centrilobular distribution
- Some cases initially have little or no portal inflammation, before subsequently progressing to more classical features of chronic AIH
- Severe cases with bridging or panacinar necrosis
  - Changes heterogeneous in distribution
  - Typical features of AIH may no longer be apparent
  - Can resemble changes seen in cirrhosis

Autoimmune Hepatitis – Assessment of Fibrosis

25-33% of patients have cirrhosis at presentation (Lohse 2011, Gleeson 2012)
- Includes cases with acute presentation
  (important to distinguish true cirrhosis from post-necrotic collapse)

Patients with cirrhosis at presentation
- Have worse outcome (Feld 2005, Verma 2007, Landeira 2012)
- Less responsive to immunosuppression (Muratori 2009, Efe 2012)
  - But reversal of cirrhosis following treatment can occur (Czaja 2007)
- At risk of developing HCC - approx 0.5 -1%/year
  (Yeoman 2008, Migita 2012, Hino-Arinaga 2012)

Role of Liver Biopsy in Chronic Hepatitis

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3. **Assessing disease severity**
   - **necro-inflammatory activity (grading)**
   - **fibrosis (staging)**
4. Identifying additional lesions
   - Co-existent disease (e.g. Fatty liver disease, siderosis)
   - Neoplastic and pre-neoplastic lesions (large and small cell change)

Chronic Hepatitis
Assessing Disease Severity – Grading and Staging

Grading
- ongoing damage (inflammation and hepatocyte apoptosis/necrosis)
  - Also referred to as "activity"
- potential to progress to chronic (irreversible) damage
- still potentially treatable

Staging
- progressive liver injury (usually fibrosis)
- less likely to be reversible

Semi-quantitative scoring systems
- Mainly used for hepatitis C

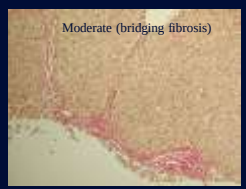
Which System do You use for Scoring Hepatitis C Biopsies?

1. Knodell (1981)
2. Scheuer (1991)
3. Batts & Ludwig (1994)
4. Ishak (1995) ←
5. METAVIR (1996) ←
6. Don't score/see HCV biopsies

Scoring Systems for Hepatitis C
- All incorporate features relating to inflammatory grade and fibrosis stage
- Fibrosis stage more important clinically

System used doesn't matter, so long as:
- Report specifies which system is used
- Scores are used to supplement (not replace) conventional histological reporting
- Clinician reading report understands the scores and uses them appropriately

Fibrosis Staging (Periportal Fibrosis)



Histological Grading and Staging of Chronic Hepatitis
Clinical Applications

- Liver biopsy still recognised as the "gold standard" for assessing inflammatory grade and fibrosis stage
- Use of non-invasive markers of liver fibrosis (e.g. serum markers, transient elastography) is reducing the frequency of liver biopsy to stage fibrosis in chronic liver disease
  - *Mainly useful in identifying patients who have minimal or advanced fibrosis*
  - *Liver biopsy more reliable for assessing intermediate stages of fibrosis*
- Liver biopsy still useful in cases where non-invasive markers have produced indeterminate or unexpected findings.
- Assessing disease severity still important in clinical trials
  - *e.g. pre- and post-treatment biopsies*

Histological Grading and Staging of Chronic Hepatitis
Implications for Treatment

Hepatitis B

- Current algorithms for treatment decisions are based on age, sex, ALT levels, HBeAg status, HBV-DNA levels and disease severity (FibroScan score, liver biopsy)
  - For some individuals treatment decisions can be made without the use of liver biopsy
  - For other patients treatment should be considered if liver biopsy shows **moderate to severe active necroinflammation and/or at least moderate fibrosis , using a standardised scoring system** (EASL Clinical Practice Guidelines, J Hepatol 2012)
    - Presence of normal ALT doesn't exclude significant histological activity

Histological Grading and Staging of Chronic Hepatitis
Implications for treatment

Hepatitis C

(AASLD/IDSA Guidelines, Hepatology 2015; EASL Guidelines, J Hepatol 2015: Zoulim, Gut 2015)

- Improved understanding of viral biology / more effective anti-viral drugs means that treatment decisions based largely on viral genotype
  - *Sustained viral responses rates > 90% with new direct-acting antiviral agents*
  - *Response rates less good in patients with advanced liver disease (especially genotype 3)*
  - *For cost reasons, treatment currently restricted to patients at greatest risk of developing complications (e.g. METAVIR F3/F4)*
  - *Non-invasive methods (e.g. FibroScan) have largely replaced liver biopsy is assessing disease severity*
  - *Liver biopsy still used in cases where non-invasive markers have produced inconclusive findings or a dual pathology is suspected*

Problems With Histological Scoring

1. Numerical scores are categorical assessments not measurements of a continuous variable
   - Panacinar necrosis (Ishak grade 6) versus mild spotty necrosis (grade 1)
   - Scores for different features should not be added (e.g. interface hepatitis and lobular inflammation)
   - Non-parametric techniques required for statistical analysis

Problems With Histological Scoring

2. Observer variation
   - Observer agreement (HCV)
     - good for fibrosis
     - moderate for inflammation
   - Reproducibility improves with experience and paired observations

Problems With Histological Scoring

3. Sampling variability

- Intrinsic to all liver diseases
  - Varies according to histological feature and disease process
  - Overall approximately 20-40% of paired biopsies in HCV vary by at least one grade or stage (Regev 2002, Siddique 2003)
- Sampling variability influenced by biopsy length and diameter
  - Short or narrow biopsies tend to underestimate both disease grade and stage
- What is an "adequate biopsy"?
  - At least 20 - 25 mm long
  - At least 1.4 mm diameter
  - At least 11 complete portal tracts

Problems With Histological Scoring

4. Other considerations

- Scoring should not be used as a replacement for conventional histological reporting
  - Important co-existent liver disease may be overlooked (e.g. NAFLD or features suggesting AIH in HCV positive patients)
- Scoring should only be applied to cases where there is a single disease process
  - i.e. .don't attempt to score biopsies where there appears to be a dual pathology (e.g. HCV & NAFLD)
- Scoring should be done using a system that is appropriate for the disease in question
  - e.g. Ishak/METAVIR systems for HCV versus other causes of chronic hepatitis

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   - Neoplastic and pre-neoplastic lesions (large and small cell change)

Siderosis in Chronic Hepatitis C

- Minor degrees commonly present in HCV
  - may be secondary to necro-inflammatory activity
  - typically have a mixed distribution (hepatocytes & Kupffer cells)
- More severe siderosis with pure hepatocellular distribution raises possibility of genetic haemochromatosis
- Presence of siderosis has adverse influence on response to antiviral therapy

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Malignancy-associated and Premalignant Lesions - WHO Classification 2010
(See also Park 2011, Chan & Burt 2011)

Microscopic foci (< 1mm diameter)

- Large cell change (formerly "dysplasia")
- Small cell change (formerly "dysplasia")

Discrete nodular lesions (>5-10 mm diameter)

- Dysplastic nodule (low grade)
- Dysplastic nodule (high grade)

Large Cell Change (Large Cell Dysplasia)

(from Libbrecht et al. Histopathology. 2001;39:66-73)

Histological Features

- Nuclear and cytoplasmic enlargement
- Nuclear pleomorphism and hyperchromasia
- Multinucleation

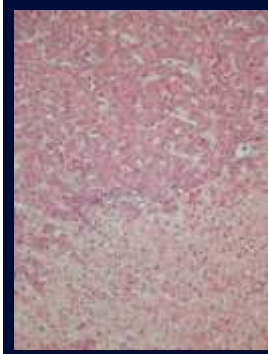
Functional Significance

- Most cases represent senescence changes
  (low mitotic activity, no genetic alterations)
- Some have telomere shortening, DNA damage and other changes associated with malignancy

Clinical Significance

- Associated with increased risk of developing HCC
  - ➢ screening for HCC should be carried out

Small Cell Change (Small Cell Dysplasia)



Histological Features

- Cells smaller than normal
- Increased N/C ratio – "nuclear crowding"
- Mild nuclear pleomorphism
- Cytoplasmic basophilia

Functional Significance

- Most cases represent premalignant change
  (higher proliferative activity, genetic alterations, morphologic continuum with HCC)
- Some may reflect regenerative changes

Clinical Significance

- Associated with increased risk of developing HCC
  - ➢ screening for HCC should be carried out

Role of Liver Biopsy in Chronic Viral and Autoimmune Hepatitis
Summary & Conclusions

1. Most cases of chronic viral hepatitis (hepatitis B and C) are diagnosed on the basis of non-invasive investigations .
2. Liver biopsy remains important in establishing a diagnosis of autoimmune hepatitis
3. Assessment of disease severity (inflammatory grade and fibrosis stage) may have implications for prognosis and treatment
   - But non-invasive methods (e.g. FibroScan) have largely replaced liver biopsy in staging fibrosis in chronic viral hepatitis
4. In cases where a dual pathology is suspected (e.g. HCV and NAFLD), liver biopsy is useful to confirm the diagnosis and may help to identify the predominant cause of liver injury
5. Liver biopsy may identify additional unsuspected lesions that have implications for clinical management (e.g. siderosis, pre-neoplastic lesions)