Acute Hepatitis
Including Acute Liver Failure

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Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham
Case 1
38 year old lady

• Had been unwell with gastroenteritis 2 months prior to admission after holiday in Ireland
• 1 month after that started on fluoxetine
• 2 days later noticed that she was jaundiced
• Was admitted at that stage and then discharged
• Readmitted with worsening jaundice, peripheral oedema and ascites
• PMH of asthma and fibroids
• Alcohol – half a bottle of wine five days a week for last 2 years
Admission Bloods and Liver Screen

- Hb 13.8, WCC 7.6, MCV 91.4, plts 195
- INR 1.8
- ALT 585, Bili 261, ALP 279, GGT 273, Alb 34, Na 135, K 4.1, Ur 2.7, Creat 56
- Hepatitis A, B, C and E negative
- Autoimmune profile and immunoglobulins negative
- Other liver screen all negative
- Leptospirosis negative
CT Performed at Day 1

- Patchy enhancement in the liver but no focal lesions
- Portal vein and hepatic vein patent
- Normal CBD
- Rest of organs normal
- No ascites
Progress Days 1 - 8

• Liaised daily with QE
• Started on prednisolone on day 1
• No significant change in LFTs
• Prednisolone stopped day 8
• Transferred to QE in view of on-going coagulopathy and jaundice
• No suggestion of hepatic encephalopathy
Day 9 Admission to QE

- Bilirubin 236
- ALT 225
- Albumin 25
- INR 2.6
- USS – fatty infiltration of the liver
- Small amount of ascites seen
- No liver flap
Days 10 - 14

- In status quo
- No sign of hepatic encephalopathy – number connection tests all less than 30 seconds
- History reviewed fully on multi-consultant ward round
- Some concerns about alcohol intake although no suggestion of dependency clinically
- Also AST (250) higher than ALT (150 at this stage)
- Caeruloplasmin low – ? Wilson’s
- Transjugular liver biopsy arranged
Biopsy Planned

• Questions –
  1. Is there evidence of acute alcoholic hepatitis?
  2. Is there any suggestion of Wilson disease?
  3. Could this be DILI or seronegative hepatitis?
  4. How severe is the amount of necrosis in the liver?
  5. Is there any suggestion of spontaneous recovery?
Case 1

Liver Biopsy
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?
Panacinar Necrosis (Recent – No Collagen)
Inflammatory Cells – Lymphocytes and Macrophages
Ceroid-laden Macrophages

PAS-D
Liver Biopsy – Case 1

Histological Findings

• Recent panacinar necrosis

• Inflammation (including ceroid laden macrophages ++)

• Periportal ductular reaction

• One small nodule of surviving hepatocytes
Case 1 – Liver Biopsy
Diagnosis

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

1. Acute hepatitis
2. Panacinar necrosis – indicates severe injury
3. No obvious aetiological pointers
   – Consider viral agents, drugs and autoimmune hepatitis in differential diagnosis
   – no features to suggest Wilson disease or alcoholic hepatitis
Days 14 - 20

- Stable
- Biopsy suggests unlikely to recover
- Transplant assessment tests performed
- On day 18 develops liver flap in association with INR of 3.9
- Sodium at the time 119
- Transferred to ITU for CVVH
- Listed for super-urgent liver transplant on day 19 once sodium above 125
- Transplant done on day 20
Case 1

Hepatectomy Specimen

Macroscopy
Case 1. Macroscopic Appearances
Shrunken liver, weight 640 g. Wrinkled/knobbly capsular surface
Case 1 - Macroscopic Appearances
Case 1 - Macroscopic Appearances
Right Lobe
Case 1 - Macroscopic Appearances
Left lobe
Case 1

Hepatectomy Specimen

Microscopy - Brown Areas
Multiacinar Necrosis
Panacinar Necrosis
Hepatic Vein Endophlebitis
Hepatic Vein Endophlebitis
Case 1

Hepatectomy Specimen

Microscopy – Yellow Nodules
Fatty Change (Mediovesicular)
No Inflammation or Necrosis
Confluent Necrosis - Centrilobular
Could this be cirrhotic?
## 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>
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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>
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<td>Haematoxylin Van Gieson (or Trichrome)</td>
<td>Type I collagen fibres</td>
<td>Portal tracts, walls of hepatic veins</td>
<td>Increased in hepatic fibrosis (weeks/months)</td>
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<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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</table>
Ceroid Pigment Laden Macrophages
Hepatectomy Specimen – Case 1

Histological Findings

• Large areas of panacinar necrosis (multi-acinar necrosis)
  – Periportal ductular reaction
  – Inflammation (including ceroid-laden macrophages)
  – Inflammation of hepatic veins

• Surviving nodules of liver parenchyma
  – Fatty change
  – Confluent /bridging necrosis
  – Little inflammation
Hepatectomy Specimen – Case 1

Diagnosis

• Severe acute hepatitis with multiacinar necrosis (submassive hepatic necrosis)
• No strong aetiological pointers ("seronegative hepatitis")
Post Transplant Progress

- Spent 3 days on intensive care
- Spent another 5 days on the ward
- On standard immunosuppression
- No episodes of rejection
- Doing very well
- LFTs all normal
- Renal function normal
Final Diagnosis

Seronegative hepatitis associated with fulminant liver failure requiring transplantation
1237 patients presenting to QEH, Bham with ALF (Jan 1992 – May 2008)

- Paracetamol accounts for 759/843 (90%) of drug–induced ALF cases
- Excluding paracetamol/Budd-Chiari/Wilson’s - seronegative hepatitis accounts for 186/452 (41%) of cases of severe acute hepatitis
What is Seronegative Hepatitis?

- Puritanically it is a syndrome where there are negative tests specifically
  - Hepatitis A, B, C and E
  - Active EBV, CMV, HSV, VZV infection
  - Negative ASMA, AMA, SLA, LKM
  - No clinical or biochemical evidence of Wilson’s
  - No significant drug history – including OTC, herbal and illicit drugs
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<td>4 (25%)</td>
<td>5 (25%)</td>
<td>2 (13%)</td>
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<tr>
<td>Any Autoantibody</td>
<td>0</td>
<td>5 (31%)</td>
<td>11 (53%)</td>
<td>7 (44%)</td>
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</tbody>
</table>

Bernal et al 2007
Case 2
Case 2

• 45 year old lady
• Admitted to QE on 7th September 2016
• Transfer from her local hospital – concern about PT prolongation (44 at the time of transfer)
• 2 week history of jaundice, pruritus and lethargy
• 6 pounds weight loss
• Background HT, OA and previous umbilical hernia repair
• Meds – omeprazole, lisinopril, movicol, naproxen (regular use for 12 months), ondansteron, cyclizine, paracetamol
Investigations at Local Hospital

- ANA 1 in 400
- IgG 28
- dsDNA positive. ASMA, LKM, GPC, ENA negative
- USS – mild intrahepatic biliary dilatation in the left lobe. GB normal.
- MRCP – normal
- ALT 2157
- ALP 177
- Bili 173
- PT 16 seconds. AFP 16.
- Hep A-C negative
- Hep E awaited
QE Admission Investigations

- INR 3.1
- ALT 759
- Bili 241
- Na 131
- Creat 65
- USS - The gallbladder appears to have a thickened, slightly oedematous wall measuring up to 5.4mm, and contains a tiny amount of echogenic debris. No obvious gallstones. No biliary duct dilatation.
- The liver appears normal in size, outline and echogenicity. No obvious focal liver lesions identified.
- The pancreas and spleen demonstrate normal US appearances.
- There is a left sided pleural effusion noted.
Our Assessment

• **ALF**
  – ? Autoimmune
  – ? Infiltrative (weight loss and left pleural effusion)
  – ? Naproxen DILI

• **Plan**
  – CT TAP - No evidence of malignancy. No cause for liver dysfunction is identified. There are some changes suggestive of pulmonary hypertension - a cardiology opinion is recommended, with view to echo.
  – Biopsy
Case 2 – Liver Biopsy
Diffuse Lobular Inflammation and “Lobular Disarray”
Centrilobular Inflammation (Plasma Cells) and Confluent Necrosis
Hepatic Rosettes - Reticulin
Portal Inflammation (+ Interface Hepatitis ?)
Orcein
Case 2 – Liver Biopsy
Histological Findings

• Portal inflammation (plasma cell rich)
• Interface hepatitis (?)
• Spotty lobular inflammation with lobular disarray
• Small foci of confluent necrosis (plasma cell rich)
• Moderate cholestasis
• Periportal and centrilobular fibrosis with early bridging
Case 2 – Liver Biopsy
Diagnosis

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

1. Acute/subacute hepatitis. Some features suggest possible transition to chronicity
2. Moderately severe inflammatory activity, including foci of confluent necrosis
3. Overall appearances in keeping with autoimmune hepatitis
   – plasma cells, interface hepatitis, hepatitic rosettes, emperipolesis
Treatment Started

Graph of ALT, BILI Test Results

Prednisolone Started

[Graph showing a significant drop in ALT levels after Prednisolone was started]
Progress

• Discharged after 14 days on the ward
• LFTs normalised in clinic and IgG fell to 11.49
• SLA came back as weakly positive
• Echo excluded significant PHT
• Azathioprine started 4 weeks after steroids
• Doing well
Final Diagnosis –

Steroid Responsive Acute Autoimmune Hepatitis
Autoimmune Hepatitis - Acute Presentation
Incidence & Diagnostic Criteria

30-40% of cases present as acute hepatitis / acute liver failure

Reported prevalence of acute presentation ranges from 8.7% - 75%
(Nguyen Canh 2017)

Autoantibodies unreliable in the diagnosis of acute AIH

- Autoantibodies and hypergammaglobulinaemia may not be present at the time of presentation with acute AIH (EASL Guidelines 2015, Fujiwara 2016)
- Autoantibodies present in up to 40% of patients with other causes of acute liver failure - e.g. viral or drug-induced (Bernal 2007)
Acute Presentation of Autoimmune Hepatitis - Histological Features

1. Acute presentation of chronic liver disease
   - 14-35% have features of chronic hepatitis (Fujiwara 2011, Yasui 2011, Fujiwara 2016, Dohmen 2017)

2. Acute hepatitis (with no signs of chronic liver disease)
   - Classical features of acute lobular hepatitis (resembling viral or drugs)

Histological Features Favouring Autoimmune Hepatitis As Likely Cause of Hepatitis
   - Published criteria focus mainly on patients presenting with chronic (portal) hepatitis
     - Lymphoplasmacytic portal inflammation
     - Interface hepatitis, hepatitic rosettes, emperiploesis
   - Criteria for diagnosing autoimmune hepatitis less clearly established in patients presenting with acute (lobular) hepatitis
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
- Emperipolosis

BUT:
1. Many of the above features are frequently seen in other causes of acute hepatitis
   - Portal inflammation seen in all types of acute hepatitis
   - Rosettes and emperipolosis also common in non-autoimmune acute hepatitis
     (Balitzer, Modern Pathology 2017)

2. Interface hepatitis difficult to assess in the presence of diffuse lobular hepatitis
Case 3
Case 3

- Complex
- Stage IVc melanoma with metastases in skin, lungs, hila and pleura, adrenal gland.
- Progressed on standard management.
- Bone metastasis repaired left femur Sept 2015.
- Immune related adverse events / complications of treatment
  - Nivolumab suspended twice in 2016 for grade 1-2 diarrhoea treated with high dose steroids with rapid taper
- Evidence secondary immune deficiency.
- Significant weight loss (20kg Sept 2015 – Nov 2016)
- PMH – HT, HC, OA, angioplasties, hypothyroidism
Mid November 2016

• Routine clinic visit
• LFTs normal up to then
• Suddenly
  – ALT  390
  – ALP  37
  – Bili  5
  – INR  1.1
• Autoimmune profile negative, IgG 4.08, Hep B and C negative, EBV negative, low CMV titre of 1069 copies/ml
Differential Diagnosis

- CMV hepatitis
- DILI
- Autoimmune hepatitis triggered by Nivolumab
- Metastatic disease

Liver biopsy performed on the 17\textsuperscript{th} of November 2016
Case 3 – Liver Biopsy
Case 3 – Liver Biopsy
Histological Findings

- Perivenular inflammation and necrosis (“central perivenulitis”)
- Little/no inflammation elsewhere in liver parenchyma or in portal tracts
Case 3 – Liver Biopsy
Diagnosis

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

1. Acute injury with centrilobular inflammation + necrosis (“central perivenulitis”)
2. Confluent zone 3 necrosis
3. In keeping with drug-induced liver injury (DILI)
Drug-induced Acute Hepatitis

- Drugs account for approximately 10% of cases of acute hepatitis and acute liver failure (Ramachandran & Kakar 2009, Reuben 2010)
- Acute hepatitis/cholestatic hepatitis are two commonest pattern of DILI
  - Present in 50% of 249 cases reviewed by DILI Network (Kleiner 2014)
- Many agents implicated – antimicrobial drugs commonest

Histological features

- Frequently indistinguishable from other causes of acute hepatitis (e.g. viral hepatitis, autoimmune hepatitis)
- 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
Search for the LIVERTOX database

Search for a specific medication, herbal or supplement:

nivolumab

Browse by first letter of medication, herbal or supplement:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

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effects as a result of immune enhancement including enterocolitis, dermatitis, endocrinopathy, pneumonia, nephropathy, nephritis and hepatitis. Most of these reactions respond to immunosuppressive therapy, but some have resulted in fatalities and some have required long term therapy. Early recognition and prompt management of these side effects is an integral component of proper use of nivolumab and other check point inhibitors such as ipilimumab and pembrolizumab.

**Hepatotoxicity**
Mild-to-moderate serum aminotransferase elevations are not uncommon (~10%) during nivolumab therapy, but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 0.5% to 1.5% of patients, and a proportion of these individuals develop clinically apparent liver injury that can be severe. The onset of such injury is usually after 2 to 6 cycles, 1 to 3 months after initiation of treatment. The pattern of enzyme elevation is usually hepatocellular but can be mixed particularly at the onset. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. However, autoantibodies are usually not present.

Restarting nivolumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

The effects of PD-1 inhibition on hepatitis B have not been reported as enrollment criteria in the clinical trials of nivolumab have usually excluded patients with chronic viral hepatitis. However, it is possible that anti-PD-1 treatment would exacerbate chronic hepatitis B by enhancing T cell cytotoxicity to viral antigens, and such patients should be monitored during therapy and managed appropriately with antiviral therapy if necessary. In contrast, check point immunotherapy in patients with hepatitis C has not been found to be deleterious and in some cases resulted in a decrease in HCV RNA levels.

Likelihood score: E° (Although no specific cases have been described in the literature, this is a relatively recently approved medication and is likely to be a rare cause of clinically apparent acute liver injury.)

**Mechanism of Injury**
The mechanism of liver injury due to nivolumab is likely to be immunologically mediated and some cases have appeared to respond to corticosteroid or immunosuppressive therapy allowing for continuation or restarting of nivolumab therapy.

**Outcome and Management**
Guidelines for management of patients receiving nivolumab recommend monitoring of liver tests...
Histological Findings in Immune Checkpoint Inhibitor Induced Hepatitis

- 26 cases studied
- Drugs implicated include inhibitors of PD-1/PD-L1 (nivolumab, pembrolizumab) and CTLA4 (ipilimumab) – individually or in combination

Main histological findings:
- Diffuse lobular hepatitis, variable confluent centrilobular necrosis
- Lobular inflammatory cells mainly CD8+ T lymphocytes (esp anti-CTLA-4 cases)
- Mild portal inflammation

Other Findings:
- Bile duct inflammation +/- bile duct loss (Doherty 2017)
- Lobular granulomas/microgranulomas
- Fibrin ring granulomas - anti-CTLA4 cases only (de Martin 2018)
The histopathological evaluation of drug-induced liver injury

David E. Kleiner
Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA

Histopathological challenges in suspected drug-induced liver injury

David E. Kleiner
Progress

• Started on IV methylprednisolone on the day before the biopsy
• Switched to prednisolone on day 3 after the biopsy
• Discharged
• Been in since for symptom control of diarrhoea
• No issues with LFTs
## Nivolumab in advanced melanoma: a summary

Nivolumab is a monoclonal antibody that binds to T-cell PD-1 receptors and inhibits binding of PD-L1 and PD-L2 ligands (i.e. checkpoint blockade) to restore the host’s immune responses to tumours.

**As monotherapy,** improves objective response rates (ORR) compared with the investigator’s choice of chemotherapy in treatment-experienced patients.

**As first-line monotherapy,** significantly improves ORR, median progression-free survival (PFS) and 1-year overall survival compared with dacarbazine.

In combination with ipilimumab, significantly improves ORR and median PFS compared with ipilimumab monotherapy.

Manageable tolerability and safety profile.

Scott LJ, Drugs 2015
Evidence for Efficacy

B Patients with PD-L1-Positive Tumors

Progression-free Survival (%)

Months

No. at Risk

<table>
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Larkin et al NEJM 2015
## Incidence of SAEs to Nivolumab

**Table 3** Select treatment-related adverse events (i.e. those with potential immunological aetiology) of grade 3–4 severity occurring in pivotal CheckMate trials in patients with advanced melanoma

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<th>Organ system</th>
<th>CheckMate 037 [22]</th>
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DAC dacarbazine, ICC investigator’s choice of chemotherapy (dacarbazine or paclitaxel plus carboplatin), IPI ipilimumab, NIV nivolumab, NR none reported.
Liver injury from cancer immunotherapy using monoclonal immune checkpoint inhibitors.

Eleonora De Martin, Jean-Marie Michot, Barbara Papouin, Stéphane Champiat, Christine Mateus, Olivier Lambotte, Bruno Roche, Teresa Maria Antonini, Audrey Coilly, Salim Laghouati, Caroline Robert, Aurélien Marabelle, Catherine Guettier, Didier Samuel

Table 1. Characteristics of overall population with immune-mediated hepatitis induced by immunotherapy for metastatic cancer. Comparison between patients who received anti-CTLA-4 versus anti-PD-1/PDL-1 mAb.

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</tr>
<tr>
<td>Number of doses</td>
<td>2 [1-36]</td>
<td>2 [1-2]</td>
<td>4 [1-36]</td>
<td>0.167</td>
</tr>
<tr>
<td>Previous extra-hepatic</td>
<td>6 (38)</td>
<td>1 (14)</td>
<td>5 (56)</td>
<td>0.145</td>
</tr>
<tr>
<td>IRAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever at the time of</td>
<td>6 (38)</td>
<td>5 (71)</td>
<td>1 (11)</td>
<td>0.034</td>
</tr>
<tr>
<td>hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>437 [147-2289]</td>
<td>450 [147-2289]</td>
<td>424 [180-1387]</td>
<td>0.757</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>460 [266-3137]</td>
<td>491 [266-3137]</td>
<td>429 [305-2671]</td>
<td>1.000</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>18 [6-324]</td>
<td>24 [10-324]</td>
<td>18 [6-135]</td>
<td>0.426</td>
</tr>
<tr>
<td>Alk P</td>
<td>309 [53-768]</td>
<td>184 [71-768]</td>
<td>325 [53-699]</td>
<td>0.918</td>
</tr>
<tr>
<td>ANA ≥ 1:80</td>
<td>8 (50)</td>
<td>3 (43)</td>
<td>5 (55)</td>
<td>1.000</td>
</tr>
<tr>
<td>ASMA 1:80</td>
<td>3 (19)</td>
<td></td>
<td>3 (33)</td>
<td>0.212</td>
</tr>
</tbody>
</table>
Final Diagnosis –

Steroid Responsive Nivolumab induced liver injury
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 are 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 (including cases of acute liver injury not related to hepatitis)
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?
Patterns of Inflammation in the Liver

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

• **Lobular Inflammation**
  – Main pattern in acute hepatitis
  – Varying degrees of lobular inflammation also commonly present in 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 versus post-necrotic collapse)**
Severe Acute Hepatitis (e.g. case 1)
Acute versus Chronic Damage – Diagnostic Problems

Clinical

Severe acute hepatitis versus:

• decompensated chronic liver disease (e.g. Wilson disease)
• acute exacerbation of chronic liver disease (e.g. autoimmune hepatitis, hepatitis A/E superimposed on underlying cirrhosis)

Histological

• Areas of bridging necrosis & nodular regeneration can resemble changes occurring in cirrhosis
• Areas of multiacinar necrosis can resemble inflamed fibrous septa in cirrhosis
Multiacinar Necrosis in Severe Acute Hepatitis (e.g. case 1)

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?
Liver Cell Death in Acute Hepatitis

<table>
<thead>
<tr>
<th>Pattern of Cell Death</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotty necrosis</td>
<td>Apoptosis of individual hepatocytes (acidophil bodies)</td>
</tr>
<tr>
<td>Confluent necrosis (zone 3)</td>
<td>Loss of groups of adjacent liver cells</td>
</tr>
<tr>
<td>Bridging necrosis</td>
<td>Confluent necrosis linking vascular structures (central-central or central-portal bridging)</td>
</tr>
<tr>
<td>Panacinar necrosis</td>
<td>Loss of hepatocytes in an entire acinus</td>
</tr>
<tr>
<td>Multiacinar necrosis</td>
<td>Panacinar necrosis involving several adjacent acini</td>
</tr>
</tbody>
</table>

- Apoptosis > necrosis (in mild forms)
- Severe necro-inflammatory lesions uneven in distribution (e.g. case 1)
  - Sampling variability in liver biopsies
  - Extent of hepatocyte necrosis predictive of poor outcome in some studies (Katoonizadeh 2006, Miraglia 2006, Rastogi 2011)
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 (Ichai 2008, Bernal 2010)

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
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, including cases presenting with acute liver injury not due to acute hepatitis
  - Decompensated chronic liver disease (e.g. Wilson disease)
  - Another cause of acute liver damage (e.g. ischaemic necrosis, severe alcoholic hepatitis, paracetamol toxicity)
  - Hepatic infiltration (usually lymphoma, rarely carcinoma)
- Liver usually enlarged
The End