Acute Hepatitis
Including Acute Liver Failure

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Case 1
Case 1

- 34 year old lady
- South Asian origin but born in the UK
- Presented to her local hospital with a 3 month history of feeling generally unwell at start of April 2015
- Epigastric pain, nausea and vomiting were the initial symptoms.
- Treated for H Pylori gastritis with amoxicillin, clarithromycin and omeprazole
- Started to lose weight
- A month into the illness became jaundiced
- Admitted 3 months into her illness with worsening jaundice
- PMH – LSCS, nil else of note
- No relevant travel history
Investigations on Initial Admission

- INR 4.0
- PT 46 seconds
- Alb 21
- ALT 515
- Bili 273
- ASMA, LKM, AMA negative
- IgG 19.8
- A1-AT – normal
- Ferritin 63
- ANCA not done
- ANA 1 in 100 titre
CT at Local Hospital

- Liver diffusely abnormal
- Demonstrates extensive variable enhancement characteristics with large areas of poor enhancement that are generally ill defined
- No discrete mass lesions
- Overall liver a little large
- Periportal oedema present
- Hepatic veins are difficult to discern
- No biliary dilatation
- No intra-abdominal lymphadenopathy
QE Admission

• Attempt at transjugular biopsy at local hospital – unsuccessful
• Started on course of prednisolone on 19.04.2017
• Due to worsening in clinical status transferred to QE on 22.04.2017
• Had a brief admission to ITU for 48 hours due to transient hypotension requiring significant fluid resuscitation
• Caeruloplasmin noted to be low
• Normal EEG on admission
| Date       | Weight (kg) | BMI | Systolic BP | Diastolic BP | Urea (mmol/L) | Creat (mmol/L) | AKI | Na | K | AST | ALT | BILI | ALP | GGT | ALB | GLUC | Ca | Phosphate | CRP | Hb g/L | WBC | PLATS | INR |
|------------|-------------|-----|-------------|--------------|---------------|---------------|----------------|-----|----|---|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-------|-----|--------|-----|--------|-----|--------|-----|
| 22/04/15   | 57.7        | 24.65 | 97           | 66           | 2.0           | 46             | 140            | 3.6 |    |   |     |     |      |     |     |     |     |     |     | 1.95 | 0.93  | <3  | 101 | 7.9 | 131   | 5.1 |
| 23/04/15   | 63.7        | 28.71 | 96           | 61           | 1.7           | 54             | 142            | 4.1 |    |   |     |     |      |     |     |     |     |     |     | 2.5  | 1.3   | <3  | 82  | 8.5 | 114   | 5.5 |
| 24/04/15   | 67.3        | 30.73 | 108          | 68           | 1.3           | 62             | 136            | 4.1 |    |   |     |     |      |     |     |     |     |     |     | 1.97 | 1.3   | <3  | 105 | 9.9 | 132   | 4.8 |
| 25/04/15   | 67.2        | 30.73 | 112          | 75           | 1.2           | 57             | 138            | 4.1 |    |   |     |     |      |     |     |     |     |     |     | 2.02 | 2.5   | <3  | 98  | 10.6| 129   | 4.7 |
| 26/04/15   | 67.2        | 30.73 | 88           | 75           | 1.4           | 48             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.97 | 1.5   | <3  | 93  | 8.5 | 86    | 3.3 |
| 27/04/15   | 67.2        | 30.73 | 108          | 75           | 1.1           | 47             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 106 | 10.6| 83    | 4.2 |
| 28/04/15   | 70.2        | 32.73 | 109          | 75           | 1.1           | 63             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 100 | 7.8 | 81    | 4.9 |
| 29/04/15   | 70.2        | 32.73 | 107          | 75           | 1.1           | 63             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 104 | 7.9 | 82    | 5.8 |
| 01/05/15   | 70.2        | 32.73 | 109          | 75           | 1.1           | 63             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 100 | 7.9 | 82    | 5.8 |
| 02/05/15   | 67.2        | 30.73 | 107          | 75           | 1.1           | 63             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 104 | 7.9 | 82    | 5.8 |
| 03/05/15   | 67.2        | 30.73 | 109          | 75           | 1.1           | 63             | 141            | 3.7 |    |   |     |     |      |     |     |     |     |     |     | 1.94 | 1.2   | <3  | 104 | 7.9 | 82    | 5.8 |

**Event:** Acute p...
Our Assessment

• USS on admission
  – Normal liver echotexture. Good portal vein flow. Good flow seen within the hepatic veins and hepatic artery. No evidence of Budd-Chiari syndrome.
  – The spleen measures 9.9 cm with good blood flow.
  – Normal appearances of the kidneys bilaterally.
  – There is a small amount of free fluid seen deep within the pelvis just anterior to the bladder.

• Acute Liver Failure
  – ? Seronegative hepatitis
  – ? Drug induced liver injury from HP eradication therapy
  – ? Wilson’s disease
  – ? Granulomatous disease
  – ? Infiltrative disease given severity of the weight loss

• Biopsy performed on 27th of April 2015
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?
Case 1 – Liver Biopsy
Histological Findings

• Widespread recent hepatocyte necrosis
  – Bridging necrosis and nodule formation
  – Panacinar necrosis

• Bile ductular reaction ++

• Surviving hepatocyte nodules show spotty inflammation
Case 1 – Liver Biopsy
Diagnosis

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

- Acute/subacute hepatitis
- Bridging and panacinar necrosis
- No strong aetiologial pointers
  - Consider viral agents, drugs and autoimmune hepatitis in differential diagnosis
  - No evidence of underlying chronic liver disease or malignancy
Clinical Progress

• Remained stable for first 9-10 days
• No clinical signs of hepatic encephalopathy
• No biochemical improvement at all
• EEG on day 10 showed slowing of brain waves consistent with hepatic encephalopathy
• MDT discussion on day 10 with decision to list for super-urgent liver transplant
• Day 11 – more drowsy and requiring 20% dextrose to maintain sugars.
• Transferred back to ITU day 11
• Transplant done day 13 of admission with us
Explant
Case 1 – Hepatectomy Specimen
Macroscopic Findings

• Shrunken liver, weight 475g
• Capsular surface knobbly and wrinkled
• Cut surface shows brown areas alternating with yellow areas
  – Brown areas most extensive in left lobe

Liver Biopsy in the Assessment of Medical Liver Disease

• Hepatectomy specimens obtained at liver transplantation provide valuable insights into diseases, which have a heterogeneous distribution within the liver
Another Similar Case
Another Similar Case - Right Lobe
Another Similar Case - Left Lobe
Case 1 – Hepatectomy Specimen

Histological Findings
Panacinar Necrosis
Little/No Necrosis
Nodules with Bridging

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>
</tr>
</thead>
<tbody>
<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>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>
</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>
</tr>
</tbody>
</table>
Ceroid Pigment Laden Macrophages

PAS-diastase

CD 68
Ductular Reaction – Keratin 7
Hepatectomy Specimen – Case 1
Histological Findings

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

• Surviving areas of liver parenchyma
  – Spotty inflammation
  – Patchy bilirubinostasis
  – Nodular regeneration
Hepatectomy Specimen – Case 1
Diagnosis

- Severe acute/subacute hepatitis with multiacinlar necrosis (submassive hepatic necrosis)
- No strong aetiological pointers - “seronegative hepatitis”

(but note subsequent clinical course)
Post Transplant Course

- Complicated by sepsis due to an infected intra-abdominal haematoma
- Eventually discharged day 38 after transplant
- Made a slow but steady physical improvement
- Has been left with significant anxiety problems and restless legs
- Repeat immunology testing revealed that she was in fact SLA positive
Final Diagnosis –

SLA Positive Fulminant Autoimmune Hepatitis
Seronegative vs Autoimmune Hepatitis
Acute Liver Failure Admissions
Birmingham Liver Unit 1987-2007

POD
Seronegative
Other drug/toxin
Viral
AFLP/HELLP
Budd Chiari
AVOD
Wilson's
Miscellaneous
Is it an autoimmune condition?

- In support
  - Female preponderance
  - Responsiveness to steroids in some cases
  - Autoantibody studies

<table>
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<tr>
<th></th>
<th>NANB FHF</th>
<th>Other Causes FHF</th>
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<tbody>
<tr>
<td>Origin of study</td>
<td></td>
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<tr>
<td>England*</td>
<td>M/F</td>
<td>M/F</td>
</tr>
<tr>
<td>Feray et al^6</td>
<td>5/18</td>
<td>10/7</td>
</tr>
<tr>
<td>Bismuth et al^28</td>
<td>1/6</td>
<td>4/7</td>
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<tr>
<td>America</td>
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<tr>
<td>Current study</td>
<td>0/14</td>
<td>3/7</td>
</tr>
<tr>
<td>Mayo Clinic^7,29,30</td>
<td>3/6</td>
<td>3/5</td>
</tr>
<tr>
<td>Liang et al^8</td>
<td>9/8</td>
<td>NA</td>
</tr>
<tr>
<td>Japan^15</td>
<td>4/6</td>
<td>13/7</td>
</tr>
<tr>
<td>Australia^31</td>
<td>3/5</td>
<td>10/9</td>
</tr>
<tr>
<td>Total</td>
<td>57/115</td>
<td>50/67</td>
</tr>
</tbody>
</table>

*Values for NANB FHF from reference 32; values for other causes FHF from reference 33.

Ferraz et al 1996
## Autoantibodies and Igs in Seronegative ALF

**Birmingham 1997-2007**

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<thead>
<tr>
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<th>ANA-positive</th>
<th>ANA-negative</th>
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<tbody>
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<tr>
<td><strong>male:female</strong></td>
<td>3:12</td>
<td>8:16</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>22.1 (5.8-36.6)</td>
<td>12.6 (5.8-24.4)*</td>
</tr>
</tbody>
</table>

* *p<0.001

<table>
<thead>
<tr>
<th></th>
<th>ASMA-positive</th>
<th>ASMA-negative</th>
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<td><strong>number</strong></td>
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<tr>
<td><strong>male:female</strong></td>
<td>0:8</td>
<td>10:24</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>14.7 (9.3-22.4)</td>
<td>14.7 (5.8-36.6)</td>
</tr>
</tbody>
</table>
Autoantibodies and Immunoglobulins in ALF

- King’s College Hospital Liver Unit 1999-2004
- 73 acute liver failure patients (not consecutive)
  - paracetamol poisoning n=20
  - drug-induced (non-paracetamol) n=16
  - viral n=21 (14 HBV)
  - cryptogenic (seronegative) n=16
- serum immunoglobulins
- non-organ specific autoantibodies
  - ANA, ASM, LKM-1, AMA
- anti-SLA (soluble liver antigen)
- application of “autoimmune diagnostic score”
<table>
<thead>
<tr>
<th></th>
<th>Paracetamol</th>
<th>DILI</th>
<th>Viral</th>
<th>Cryptogenic</th>
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<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>16</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Anti-SLA</td>
<td>0</td>
<td>2 (13%)</td>
<td>9 (43%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>ANA/ASM/LKM</td>
<td>0</td>
<td>4 (25%)</td>
<td>5 (25%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Any Autoantibody</td>
<td>0</td>
<td>5 (31%)</td>
<td>11 (53%)</td>
<td>7 (44%)</td>
</tr>
</tbody>
</table>

Bernal et al 2007
Case 2
Case 2

• 45 year old lady
• Admitted to QE on 7\textsuperscript{th} September 2016
• Transfer from her local hospital – concern about PT prolongation (44 at the time of transfer)
• 2 week history of jaundice, pruritis 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
Case 2 – Liver Biopsy
Histological Findings

- Portal inflammation (plasma cell rich) with interface hepatitis
- Spotty lobular inflammation with lobular disarray
- Small foci of confluent necrosis
- 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?

- Acute/subacute hepatitis. Some features suggest possible transition to chronicity
- Moderately severe inflammatory activity, including foci of confluent necrosis
- Overall appearances in keeping with autoimmune hepatitis
Treatment Started

[Graph showing test results with an arrow indicating "Prednisolone 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

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)

- Classical features of acute lobular hepatitis (resembling viral or drugs)
- Some have predominant/pure centrilobular distribution
- A few 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 (e.g. Case 1)
  - Changes heterogeneous in distribution
  - Typical features of AIH may no longer be apparent
  - Can resemble changes seen in cirrhosis
Acute Hepatitis

Histological Features Favouring a Diagnosis of AIH

- Plasma cell rich infiltrate
- Prominent portal/periportal inflammation (interface hepatitis)
- Prominent centrilobular inflammation (“central perivenulitis”)
- Lymphoid aggregates
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 17th 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

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is this acute or chronic damage?</td>
<td>Acute injury with centrilobular inflammation (“central perivenulitis”)</td>
</tr>
<tr>
<td>2. How severe is the damage?</td>
<td>Confluent zone 3 necrosis</td>
</tr>
<tr>
<td>3. What is the cause?</td>
<td>In keeping with drug-induced liver injury (DILI)</td>
</tr>
</tbody>
</table>

- Acute injury with centrilobular inflammation (“central perivenulitis”)
- Confluent zone 3 necrosis
- 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 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, pneumonitis, neuropathy, 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...
REVIEW

The histopathological evaluation of drug-induced liver injury

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

<table>
<thead>
<tr>
<th>Nivolumab in advanced melanoma: a summary</th>
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</thead>
<tbody>
<tr>
<td>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</td>
</tr>
<tr>
<td>As monotherapy, improves objective response rates (ORR) compared with the investigator’s choice of chemotherapy in treatment-experienced patients</td>
</tr>
<tr>
<td>As first-line monotherapy, significantly improves ORR, median progression-free survival (PFS) and 1-year overall survival compared with dacarbazine</td>
</tr>
<tr>
<td>In combination with ipilimumab, significantly improves ORR and median PFS compared with ipilimumab monotherapy</td>
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<tr>
<td>Manageable tolerability and safety profile</td>
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</table>

Scott LJ, Drugs 2015
Evidence for Efficacy

B Patients with PD-L1–Positive Tumors

Progression-free Survival (%)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Nivolumab plus ipilimumab</th>
<th>Ipilimumab</th>
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<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>68</td>
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</table>

Larkin et al NEJM 2015
## Incidence of SAEs to Nivolumab

<table>
<thead>
<tr>
<th>Organ system</th>
<th>CheckMate 037 [22]</th>
<th>CheckMate 066 [23]</th>
<th>CheckMate 069 [36]</th>
<th>CheckMate 067 [37]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NIV (n = 268)</td>
<td>ICC (n = 102)</td>
<td>NIV + IPI (n = 94)</td>
<td>NIV + IPI (n = 313)</td>
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<tr>
<td>Skin</td>
<td>0.4</td>
<td>0</td>
<td>1.5</td>
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<tr>
<td>Gastrointestinal</td>
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<td>2.0</td>
<td>1.5</td>
<td>21.3</td>
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<td>Endocrine</td>
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<td>1.0</td>
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<td>Hepatic</td>
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<td>0</td>
<td>1.5</td>
<td>14.9</td>
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<td>Pulmonary</td>
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<td>0</td>
<td>0</td>
<td>2.1</td>
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<tr>
<td>Renal</td>
<td>0.4</td>
<td>0</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reactions</td>
<td>0.4</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

DAC dacarbazine, ICC investigator’s choice of chemotherapy (dacarbazine or paclitaxel plus carboplatin), IPI ipilimumab, NIV nivolumab, NR none reported.

Scott LJ, Drugs 2015
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 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 multiacininar 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
  - Sampling variability in liver biopsies
  - Extent of hepatocyte necrosis predictive of poor outcome in some studies (Katoonizadeh 2006, Miraglia 2006, Rastogi 2011, Singhal 2012)
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’s 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