CASE 1
Plasma Cell Infiltrates:
Significance in post-liver transplantation
and in chronic liver disease

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Case

• A 57 yo man, 7 months post-liver transplantation for hepatitis C cirrhosis, presented with abnormal liver enzymes:
  • ALT = 158 U/L
  • AST = 79 U/L
  • Alk phos = 250 U/L
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Diagnosis:
Acute recurrent hepatitis C
Mild acute cellular rejection
Case cont’d…

- Interferon and ribavirin treatment was started
- Prograf dose increased to maintain levels >5
- HCV-RNA became (-) 3 months after starting treatment with normalization of liver enzymes
- Six months after starting treatment, liver tests:
  - ALT 150 U/L
  - AST 113 U/L
  - Alk Phos 258 U/L
  - T bilirubin 2.9 U/L
  - Prograf level 4.4 ng/mL
- A repeat biopsy was performed.
Plasma Cell Hepatitis

*De novo* autoimmune hepatitis

- **Other terms:**
  - Immune-mediated hepatitis
  - Allo-immune hepatitis
  - Plasma cell-rich hepatitis
  - Late rejection with hepatitis features

- First described in children in 1998
- Adult post-liver transplant PBC patients
- Cause of graft loss

Plasma Cell Hepatitis

• A form of graft dysfunction
  • Patients transplanted for liver disease other than autoimmune conditions.

• Characterized by:
  1. Abnormal liver enzymes
  2. Histology similar to classic autoimmune hepatitis
     *Diagnosis is made based on histology

• Recognition crucial because graft failure is high if left untreated
  • Timely treatment is necessary because can result in cirrhosis or chronic rejection

Plasma Cell Hepatitis

Clinical Presentation

- Raised transaminases (200-1000 u/mL)
- Raised alkaline phosphatase levels (200-700 U/mL)
- High autoantibody titers in 50-70% of cases, sometimes 100%)

Fiel, Schiano. Curr Opin Organ Transplan 2012
Plasma Cell Hepatitis

Prognosis

- PCH patients with worse outcomes → increased mortality
- Negative clinical outcome:
  - Development of cirrhosis
  - Need for re-transplantation (chronic rejection)
  - Death → 50% after mean 2.3y

Cases had reduced survival 3-10 years after LT

Ward et al. Liver Transpl 2009;
Plasma Cell Hepatitis
Pathogenesis

• Considered to be a form of acute or chronic rejection
• Reports in HCV+ post-LT (with or w/o IFN exposure)
  • PEG-IFN may induce immunologic graft dysfunction during treatment of recurrent HCV after LT
• Allo- or autoimmunity (epitope spreading)
  – Cellular- and antibody-mediated pathways
    • Allo-antigens (donor specific antibodies)
    • Self antigens (autoantibodies)
• Molecular mimicry (EBV, CMV, parvovirus)
• IgG4+ -related disease

Plasma Cell Hepatitis

Risk Factors

• Low levels of, or recent decrease in, immunosuppression
• Acute rejection episodes prior to PCH
• In HCV cases: Interferon-Ribavirin therapy
• Predisposition to PCH
  – Explants from patients that developed PCH had plasma cell score >30% vs 18% of control patients
• Antibody-mediated rejection (?)→ C4d +
• High anti-GSTT1 titer and GSTT1 donor/recipient mismatch
• High frequency of HLA-DR15

C4d in PCH

Aguillera et al. Liver Transpl 2011;
Trivedi A, et al. Modern Pathology 27(supplement 2):430A
Plasma Cell Hepatitis
Histology

1. Plasma cell population >30% of the infiltrate
2. Moderate to severe interface hepatitis → plasma cells spilling over into the limiting plate
3. Centrilobular hepatocyte necrosis accompanied by inflammation
4. Absence of typical features of acute cellular rejection

Guido and Burra. Semin Liver Dis 2011;
Demetris et al, Liver Transpl 2008
Plasma Cell Hepatitis

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Plasma Cell Hepatitis

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2. Moderate to severe interface hepatitis → plasma cells spilling over into the limiting plate
3. Centrilobular hepatocyte necrosis accompanied by inflammation
4. Absence or minimal changes of typical acute cellular rejection (ACR)
Where else hath plasma cells?
Recurrent AIH

- Incidence = 11-83%
- Average recurrence rate = 20-30%
- Biochemical changes
- Positive autoantibodies
- Hypergammaglobulinemia
- Histological features:
  - Portal inflammation
  - Numerous plasma cells
  - Interface activity


Recurrent AIH in liver allograft 38 months post-LT
Non-transplant setting
Autoimmune Hepatitis

- Positive autoantibodies: ANA, ASMA, LKM
- Hypergammaglobulinemia
- Interface hepatitis -- Apoptosis
- Plasma cells
- Emperipolesis,
- Hepatocyte rosettes

Overlap syndromes

- Autoimmune hepatitis – Primary biliary cirrhosis (AIH-PBC)
- Autoimmune hepatitis – Primary sclerosing cholangitis (AIH-PSC)
- Autoimmune hepatitis and chronic hepatitis C (AIH-HCV)
Overlap syndromes

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Overlap Syndrome of AIH-PBC

- Co-existence of autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC)
- Difficult diagnosis → no consensus
- Prevalence = 2-20%
- Criteria for both diseases must be present
## Paris Criteria

<table>
<thead>
<tr>
<th>PBC</th>
<th>AIH</th>
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<tbody>
<tr>
<td>1. Alk phos at least 2X ULN or GGT 5X ULN</td>
<td>1. ALT at least 5X ULN</td>
</tr>
<tr>
<td>2. AMA (+)</td>
<td>2. IgG at least 2X ULN, or (+) ASMA</td>
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<tr>
<td>3. Liver biopsy showing a florid-duct lesion</td>
<td>3. Liver biopsy with moderate to severe periportal or periseptal lymphocytic interface necrosis</td>
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</tbody>
</table>

Chazouilleres et al. Hepatology 1998
of note... in PBC

- Florid-duct lesions and granulomas
- Plasma cells may also be present!
Overlap HCV-AIH

• Diagnosis of true HCV-AIH is often challenging.
•Requires concurrent presence of serologic markers typically found in AIH and serologic evidence of HCV infection.

• Best approach is to determine the more predominant and easily treated entity and then employ sequential therapy.

Overlap HCV-AIH
Drug-Induced Liver Injury with Autoimmune Features (DI-AIH)

- Diclofenac
- α-methyl DOPA
- Hydralazine
- Nitrofurantoin
- Minocycline
- Statins
- Anti-TNF-α agents
- Circulating antibodies
- Hypergammaglobulinemia
- Resolves with drug withdrawal
- Response to corticosteroid therapy

DI-AIH

Histology: Interface hepatitis
Prominent plasma cells

DI-AIH

Histology: Interface hepatitis
Prominent plasma cells
IgG4-related liver disease (hepatitis or cholangiopathy)

Diagnostic criteria:
1. Mass-occupying lesion
2. Raised serum IgG4
3. Characteristic histology

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Deshpande V, et al. Modern Pathol 2012
IgG4-related Liver Disorders
Histology

1. Dense lymphoplasmacytic inflammation
2. Fibrosis (storiform pattern)
3. Vascular inflammation with phlebitis

>10 IgG4+ cells
Summary

Plasma cells post-transplant

• Plasma cell hepatitis (*de novo* autoimmune hepatitis)
  – Immunologic dysfunction similar to rejection.
  – In patients with HCV, it may be a sequela of IFN treatment.
  – Patients may have an immunologic susceptibility to plasma cell hepatitis.
  – Early recognition and prevention are essential.
  – Should be part of the differential diagnosis of abnormal liver enzyme tests post-transplant

• Recurrent autoimmune hepatitis
Summary

Plasma cells non-Transplant

- Autoimmune hepatitis (AIH)
- Overlap syndromes
- Primary biliary cirrhosis
- Drug-induced AIH
- IgG4-related liver disease