Autoimmune Hepatitis/
Autoimmune Pancreatitis

Edmund Krasinski, Jr., D.O.
F.A.C.G.
Assessment of Liver Function

Which of the following is not a good biochemical assessor of hepatic function?

- A) Serum bilirubin
- B) Serum lactate dehydrogenase
- C) Serum aspartate aminotransferase (AST)
- D) Serum alanine aminotransferase (ALT)
- E) Serum alkaline phosphatase
Assessment of Liver Function

- Correct answer: B
- Measurement of LDH and even more specific LDH-5 adds little to evaluation of suspected hepatic dysfunction
- High levels of LDH seen in:
  - Hepatocellular necrosis, Ischemic hepatopathy “shock liver”, Cancer, Hemolysis
Case Presentation

A 35 yr. Old female presents for evaluation. She has noted jaundice manifest by scleral icterus, acholic stools, choluria. She also complains of undue fatigue. She took a recent trip to New Orleans where she ate raw oysters.
Case Presentation

Meds: Macrodantin

Physical examination: Generalized icterus, Scleral icterus, Tender hepatomegaly, No stigmata of chronic liver disease
Case presentation

Labs: Serum bilirubin 15.0
Serum AST 1500
Serum ALT 1700
Serum Alk phos 120
Case Presentation

Which of the following diseases are consistent with this clinical presentation?

A) Autoimmune hepatitis
B) Viral hepatitis
C) Wilson’s Disease
D) Drug-induced liver disease
E) All of the above
Case Presentation

Correct answer: E) All of the above.
All of the diseases in the differential diagnosis can present as such. All can present with acute decompensation with primarily hepatocellular dysfunction.
Case Presentation

- Autoimmune hepatitis - To be discussed at length.
- Viral hepatitis: HBsAg, Anti-HBC, IgM anti-HAV, Anti-HCV.
- Wilson’s Disease: Serum ceruloplasmin, 24 hr urinary copper, Optho eval for Kayser-Fleisher rings
- Drug induced liver dz. - history of drug PO
Autoimmune Hepatitis

Definition: A self-perpetuating hepatic inflammation of unknown cause, characterized by interface hepatitis, hypergammaglobulinemia, and liver associated antibodies.
Exclusion of other conditions

- Wilson’s disease
- Chronic viral hepatitis
- Alpha 1 antitrypsin deficiency
- Hereditary hemochromatosis
- Drug induced liver disease
- Non-alcoholic steatohepatitis
- Immune cholangiopathies: PBC/PSC
Autoimmune Hepatitis

Nomenclature: AIH replaces terms of lupoid hepatitis, autoimmune liver disease, and autoimmune chronic active hepatitis.
Autoimmune Hepatitis

- No subtypes formally recognized, but descriptive terms:
  - Type 1
  - Type 2
  - Type 3
Basic Diagnostic Tests

- AST, ALT, Bilirubin, alk phos, gamma globulin levels (Assess severity of liver injury and characterize the pattern of injury)
- Serum albumin, PT/INR (Estimate level of impairment of hepatic synthetic function)
- ANA (Antinuclear antibody)
- ASMA (Anti-smooth muscle antibody)
- Anti-LKM 1 (Anti-liver kidney microsomal antibody)
- SLA (Soluble liver antigen)
Autoimmune Hepatitis

- Liver tissue examination
- Histologic changes confirm diagnosis
- Interface hepatitis
- Lobular panacinar hepatitis with interface hepatitis
Autoimmune Hepatitis

- Viral hepatitis exclusion: HBsAg/ Anti-HBc/IgM Anti-HAV/ Anti-HCV
- Wilson’s disease exclusion: Serum ceruloplasmin
- HHC exclusion: Serum Fe, TIBC/ % sat/ Ferritin/ HFE analysis(if needed)
International Criteria for Diagnosis

- Diagnostic Features
  - Exclusion of risk factors for other diseases

- Definitive Diagnosis
  - Daily ETOH < 25 gm/d
  - No hepatotoxic drugs
  - N Alpha 1 AT phenotype
  - Normal ceruloplasmin
  - Normal Fe/ ferritin
  - No HAV/HBV/HCV
International Criteria for Diagnosis

- Diagnostic Features
- Exclusion of risk factors for other diseases

- Probable Diagnosis
- Daily ETOH < 50 gm/ d
- No Hepatotoxic drugs
- Partial A1 AT deficiency
- Abnormal cu/ ceruloplasmin but Wilson’s excluded
- Non-specific Fe/ Ferritin abnls
- No HAV/HBV/HCV
# International Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Diagnostic Features</th>
<th>Definitive Diagnosis</th>
<th>Probable Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory Indices</strong></td>
<td>Serum AST/ALT elev Min chol. chng</td>
<td>Serum AST/ALT elev Min Chol. Chng</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>ANA/ASMA/ALKM $\geq 1: 80$ (adults) $\geq 1: 20$ (peds)</td>
<td>ANA/ASMA/ALKM $\geq 1: 40$</td>
</tr>
<tr>
<td><strong>Immunoglobulins</strong></td>
<td>Glob, IgG $\geq 1.5$ N</td>
<td>Inc. IgG any degree</td>
</tr>
<tr>
<td><strong>Histologic features</strong></td>
<td>Interface hep. Mod-severe, no bile lesions, gran., other dz $\Delta$</td>
<td>Same</td>
</tr>
</tbody>
</table>
International Scoring System for Diagnosis

- Factor
- + AMA
- Viral Markers
  - +
  - -
- Hepatotoxic drugs
- Yes
- No
- Pretreatment score
- Definite diagnosis
- Probable Diagnosis

- Score
  - -4
  - -3
  - +3
  - -4
  - +1
  - > 15
  - 10-15
International Scoring System for Diagnosis

- Factors
- ETOH < 25 gm: +2
- ETOH > 60 gm: -2
- HLA DR3 or DR4: +1
- Concurrent AI Dz: +2
- Other liver Ab: +2
- Interface Hepatitis: +3
- Plasmacytic infiltrate: +1
- Rosettes: +1
- No Charact. Features: -5
- Biliary changes: -3
- Fat/ granulomas: -3
International Scoring System for Diagnosis

- Factors
- Treatment response complete
- Relapse
- Post treatment score
- Definite Diagnosis
  - Probable diagnosis

Score
- +2
- +3
- >17
- 12-17
Pathogenesis

- Principal Hypothesis
- Autoantigen Driven cell-mediated
- Autoantibody Dependent cell-mediated cytotoxicity
Subclassifications

- Type 1- + ANA/ASMA
- Most common USA
- Female gender 78%
- Concurrent autoimmune diseases 38%
- Autoimmune thyroiditis 12%
- Graves disease 6%
- Ulcerative colitis 6%
- Rheumatoid arthritis 1%
- Pernicious anemia 1%
- PSS 1%
Subclassifications

- Type 1
- Coomb’s positive hemolytic anemia 1%
- ITP 1%
- Leucocytoclastic vasculitis 1%
- Nephritis 1%
- Erythema nodosum 1%
- Pyoderma gangrenosum (I have seen one case)
- Fibrosing alveolitis 1%
Subclassifications

- Type 1
- HLA DR3 and DR4 are independent risk factors for susceptibility and suggests a polygenic disorder.
Subclassifications

- Type 2
- + Anti LKM antibody
- Affects mainly children (2-14 yrs)
- Affects 20% European adults
- Affects 4 % USA patients
- Commonly associated with:
  - Vitiligo
  - DM-1
  - Autoimmune thyroiditis
Subclassifications

- Type 3
- + Soluble liver antigen (SLA)
- Newest, Least established
- Maybe a variant of type 1
Variants

- Overlap with PBC
- + AMA
- + bile duct injury on histology
- + response to steroids if alk phos ≤ 2 X
  Normal
Variants

- Overlap with PSC
- +IBD
- + Cholestatic changes
- + injury pattern: Cholestasis, Ductopenia, portal fibrosis, portal edema
- Abnormal Cholangiogram
- Refractory to corticosteroids
Variants

- Autoimmune Cholangitis
- + ANA or ASMA
- - AMA
- + Cholestatic changes
- Ductopenia/ Cholangitis on histology
- - IBD
- Normal cholangiogram
Variants

- Concurrent HCV
- + HCVRNA serum
- ANA or ASMA ≥ 1: 320
- Histology
- Interface Hepatitis
- Absence of viral features
Variants

- Cryptogenic/ Autoantibody negative hepatitis
- Classic features of AIH without autoantibodies
- + Response to conventional corticosteroid regimens
Prevalence

- Type 1 - 1.9 cases/ 100,000 per year
- Type 2 - 3 cases/ 1,000,000 per year (rare)
- 11-23% of chronic hepatitis in USA
- 5.9% OLT in USA
Indications

Basis on the severity of hepatic inflammation rather than the degree of hepatic dysfunction

Regimens:

Prednisone alone

Prednisone/ Azathioprine (AZA) combination
Treatment

- Prednisone alone
- Weaning schedule
- Relative contraindications: Obesity, Osteopenia, Emotional lability, Brittle Diabetes, Labile hypertension, Post-menopausal state, Acne
Treatment

- Prednisone/ AZA
- Weaning schedule for Prednisone
  - AZA 50 mg or (1.5-2.5 mg/kg/d) if needed
- Relative contraindications: Severe cytopenias, Thiopurine methyltransferase deficiency, Pregnancy, Active Neoplasm
Treatment Results

- Remission
  - 65% within 2 years
- Failure
  - 9%
- Incomplete remission
  - 13%
- Drug toxicity
  - 13%
Promising Alternative Drugs

- CyA - Cyclosporine
- Tacrolimus
- Mycophenolate Mofetil
- 6-Mercaptopurine
- Budesonide
- Deflazacort
- Ursodeoxycholic acid
Conclusions

- Criteria for diagnosis have been quantified and a quantitative scoring system exists.
- Subtypes are based on distinctive serologic markers, but their validity not yet established.
- Genetic factors influence susceptibility, clinical expression, and treatment outcomes.
Conclusions

- Evolving antibody discoveries may have diagnostic and prognostic value in future
- Variant forms are common and treatment is directed at the predominant features
- Novel drugs are emerging
Autoimmune Pancreatitis

- **History**

- **1961**: Sarles, et al., described a case of pancreatitis associated with hypergammaglobulinemia.

- **1982-84**: Pancreatitis with other AID described: Sjogren’s syndrome, PSC, PBC.
Autoimmune Pancreatitis

- 1992: Toki, et al., Reported four cases with unusual narrowing of pancreatic duct with diffuse enlargement of the pancreas with lymphocytic infiltration
- 1995: Japanese first report the concept of Autoimmune Pancreatitis (AIP)
Autoimmune Pancreatitis

- 1995: Terms used: Diffusely enlarged pancreas, narrowed pancreatogram, presence of autoantibodies (ANA), fibrotic changes with lymphocytic infiltration, steroidal efficacy
- 2003-2007: Accepted as new clinical entity
Clinicopathologic Features of AIP

- **Age/sex:** More commonly elderly males
- **Clinical Symptoms:**
  - Mild abdominal symptoms, usually without acute attacks of pancreatitis
  - Occasional presence of obstructive jaundice
Laboratory Data

- Increased levels of IgG, IgG4
- Presence of autoantibodies
- Increased hepatobiliary/pancreatic enzymes
- Impaired exocrine/endocrine function
Clinicopathologic Features

- Imaging of the pancreaticobiliary system
- Enlargement of the pancreas
- Irregular narrowing of PD
- Stenosis of intrapancreatic bile duct
- Sclerosing cholangitis similar to PSC
Histopathologic Findings

- Interlobular fibrosis, occasionally intralobular fibrosis
- Atrophy of acini
- Infiltration of lymphocytes and IgG4 positive plasma cells
- Obliterative phlebitis
Clinicopathologic Features

- Sclerosing cholangitis similar to PSC
- Sclerosing Sialadenitis
- Retroperitoneal fibrosis
- Interstitial nephritis
- Chronic thyroiditis
- Interstitial pneumonia
- Lymphadenopathy (Mediastinal/peritoneal
- Pseudotumor: pancreas/liver/lung
- IBD
Clinicopathologic Features

- Occasional association with other autoimmune diseases
- Effective steroid therapy
- Prognosis: Unclear long term
- Pancreatic stones in some
Epidemiology

- Rare
- Recent review of 521 cases of chronic pancreatitis
- 6% AIP
Mayo Clinic Diagnostic Criteria

- **Histology**
  - Lymphoplasmacytic infiltrate with storiform fibrosis
  - +/- Abundant (>10 cells/HPF) IgG4-positive cells
Mayo Clinic Diagnostic Criteria

- Imaging
  - Typical: Diffusely enlarged pancreas w/ delayed rim enhancement and diffusely irregular, attenuated MPD
  - Other: Focal pancreatic mass/ enlargement, focal PD stricture, Panc Atrophy, Panc Ca++, or pancreatitis
Mayo Clinic Diagnostic Criteria

- Serology
  - Elevated serum IgG4 levels (8-140 mg/dl)

- Other organ involvement
  - Hilar/IHD strictures, distal CBD strictures, parotid/lacrimal ducts involvement, Mediastinal adenopathy, retroperitoneal fibrosis
Mayo Clinic Diagnostic Criteria

- Response to steroid therapy
- Resolution/Marked improvement of pancreatic/extrapancreatic manifestations w/ steroid therapy
Mayo Clinic Criteria/ Define AIP

- **Group A (Pancreatic histology)**
  - 1. Typical LPSP by resection or core biopsy
  - 2. IgG4 + cells > 10 HPF

- 1. And / or 2
  - 1. Typical LPSP by resection or core biopsy
  - 2. IgG4 + cells > 10 HPF
Mayo Clinic Criteria / Define AIP

- Group B
- Typical Imaging
- And Elevated IgG4

1 + 2 + 3
- 1) CT or MRI with diffuse enlargement of pancreas or delayed rim enhancement
- 2) Diffusely irregular MPD on pancreatogram
- 3) Elevated IgG4 levels
Mayo Clinic Criteria/ Define AIP

- Group C
- Response to steroids

- 1 + 2 + 3
- 1) Unexplained pancreatic disease
- 2) Elevated IgG4 or IgG4 in other organs
- 3) Resolution/ Improvement of manifestations w/ steroids
Pathophysiology

- Humoral Immunity and Target Antigens
- Cellular Immunity and Effector Cells
Differential Diagnosis

- Pancreatic carcinoma
- Malignant Lymphoma
- Plasmacytoma
- Metastatic carcinoma
- Diffusely infiltrative pancreatic cancer
- Biliary Carcinoma
- Cholangiocarcinoma
- Metastatic Carcinoma
Treatment

- Jaundice: Biliary Decompression
- Steroid therapy: Extrapancreatic lesions, Bile duct/ Pancreatic lesions
- Spontaneous improvement
- Surgery: May be needed to exclude malignancy
Prognosis

- Long term prognosis unknown
- Clinical/Laboratory findings usually reverse with steroids
- Severity may depend on coexisting autoimmune diseases or DM
Conclusions

- Recent studies suggest concept of AIP as a unique clinical entity
- Future studies are needed to clarify pathogenesis and long term prognosis
Conclusions

- “Don’t always say no to steroids.”