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 hemochromotosis
- 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

Diagnostic Features	Definitive Diagnosis	Probable Diagnosis
Inflammatory Indices	Serum AST/ALT elev Min chol. chng	Serum AST/ALT elev Min Chol. Chng
Auotantibodies	ANA/ASMA/ALKM ≥ 1: 80 (adults) ≥ 1: 20 (peds)	ANA/ASMA/ALKM ≥ 1: 40
Immunoglobulins	Glob, IgG ≥1.5 N	Inc. IgG any degree
Histologic features	Interface hep. Mod-severe, no bile lesions, gran., other dz Δ	Same

International Scoring System for Diagnosis

Factor	Score
+ AMA	-4
Viral Markers	
+	-3
-	+3
Hepatotoxic drugs	
Yes	-4
No	+1
Pretreatment score	> 15
Definite diagnosis	10-15
Probable Diagnosis	

International Scoring System for Diagnosis

Factors	Score
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 inflitrate	+1
Rosettes	+1
No Charact. Features	-5
Biliary changes	-3
Fat/ granulomas	-3

International Scoring System for Diagnosis

Factors	Score
Treatment response complete	+2
Relapse	+3
Post treatment score	
Definite Diagnosis	>17
Probable diagnosis	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 gangrenosa (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 $\leq$ 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
- Diverse populations: Caucasians, African Americans, Alaskan Natives, Japanese, Hispanics, Subcontinental Indians, Asians, Arabs.

Treatment

- Indications
- Basis on the severity of hepatic inflammation rather than the degree of 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 case 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
- Other organ involvement
- Elevated serum IgG4 levels (8-140 mg/dl)
- 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/ extrapancreatc manifestastions w/ steroid therapy

Mayo Clinic Criteria/ Define AIP

- Group A(Pancreatic histology)
  - 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.”