rounds [immunology | chemistry]

Autoimmune Hepatitis Type 2

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Case Presentation

Patient 1: In November 1999, an 18-year-old Hispanic female sought treatment for non-specific abdominal discomfort, nausea, vomiting, fatigue, and a signifcant unintended weight loss (over the past 6 months) in the Emergency Room. Her physical examination and past medical and family history were unremarkable and she was not taking any medications. The results of liver function and other laboratory tests performed on a serum sample from this patient are shown in [T1]. Autoantibodies were detected using an indirect fluorescence assay (IFA) against rat hepatocytes and renal proximal, but not distal, tubule cells and no staining against stomach cells [I1]. This staining pattern is characteristic of LKM-1 antibodies. A liver biopsy demonstrated mild to moderate piecemeal necrosis, lobular inflammation, and some evidence of cirrhosis.

Principal Laboratory Findings, Patient 1 — T1

Test	Result	Normal Reference Range
AST	307	13 to 40 U/L
ALT	312	10 to 40 U/L
ALP	681	58 to 126 U/L
Anti-HAV IgM	Neg	Neg
Anti-HBs	Neg	Neg
Anti-HCV	Neg	Neg
HCV RNA by PCR	Neg	Neg
ANCA	Neg	Neg
AMA	Neg	Neg
SMA	Neg	Neg
PCA	Neg	Neg
LKM-1	Pos @ 1:2048	Neg

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Anti-HAV IgM, hepatitis A virus immunoglobulin type M antibody; Anti-HBs, hepatitis B surface antibody; HCV, hepatitis C virus; RNA, ribonucleic acid; PCR, polymerase chain reaction; ANCA, anti-neutrophil cytoplasmic antibodies; AMA, anti-mitochondrial antibodies; SMA, smooth muscle antibodies; PCA, parietal cell antibodies; LKM-1 antibodies, liver/kidney microsome type 1 antibodies

Patient 2: In December 2000, a 32-year-old Caucasian female from South America sought treatment in a clinic for the sudden onset of itching that had started on her palms and the soles of her feet and progressed over a 1-week period to her entire body. In August 1996, she had been diagnosed with non-specific liver problems, but further details were not available. At the time of her 1996 diagnosis, she was prescribed prednisone, which she was on until March 1997. Since that time, no other medications have been prescribed. Her past medical history included vitiligo and a basal cell carcinoma of the skin that had been excised from her face in 1999. She reported allergies (development of a rash) only to penicillin. The patient's mother had a history of hypothyroidism, diabetes mellitus, hypertension, and hypercholesterolemia. Her father had hypercholesterolemia and hypertension, and her sister had hypothyroidism. The results of liver function and other laboratory tests from this patient are shown in [T2]. The IFA cellular staining pattern [I1] of this patient's autoantibodies was identical to that observed for Patient 1.

The clinical and laboratory findings, especially the lack of viral hepatitis antibodies and the presence of the LKM-1 antibodies by IFA testing, are characteristic of autoimmune hepatitis type 2 (AIH2) in both patients.

Principal Laboratory Findings, Patient 2 T2

Test	Result	Normal Reference Range
AST	18	13 to 40 U/L
ALT	14	10 to 40 U/L
ALP	54	58 to 126 U/L
GGT	14	8 to 78 U/L
AFP	Undetectable	0 to 44 ng/mL
Total Bilirubin	0.7	0.2 to 1.3 mg/dL
Total Protein	7.6	6.3 to 8.2 g/dL
Anti-HAV, Total	Neg	Neg
Anti-HAV IgM	Neg	Neg
ANCA	Neg	Neg
AMA	Neg	Neg
SMA	Neg	Neg
PCA	Neg	Neg
LKM-1	Pos @ 1:160	Neg
Endomysial IgA	Neg	Neg
Gliadin IgA and IgG	Neg	Neg

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AFP, alpha-fetoprotein; Anti-HAV IgM, hepatitis A virus immunoglobulin type M antibody; ANCA, anti-neutrophil cytoplasmic antibodies; AMA, anti-mitochondrial antibodies; SMA, smooth muscle antibodies; PCA, parietal cell antibodies; LKM-1 antibodies, liver/kidney microsome type 1 antibodies

Clinical Background

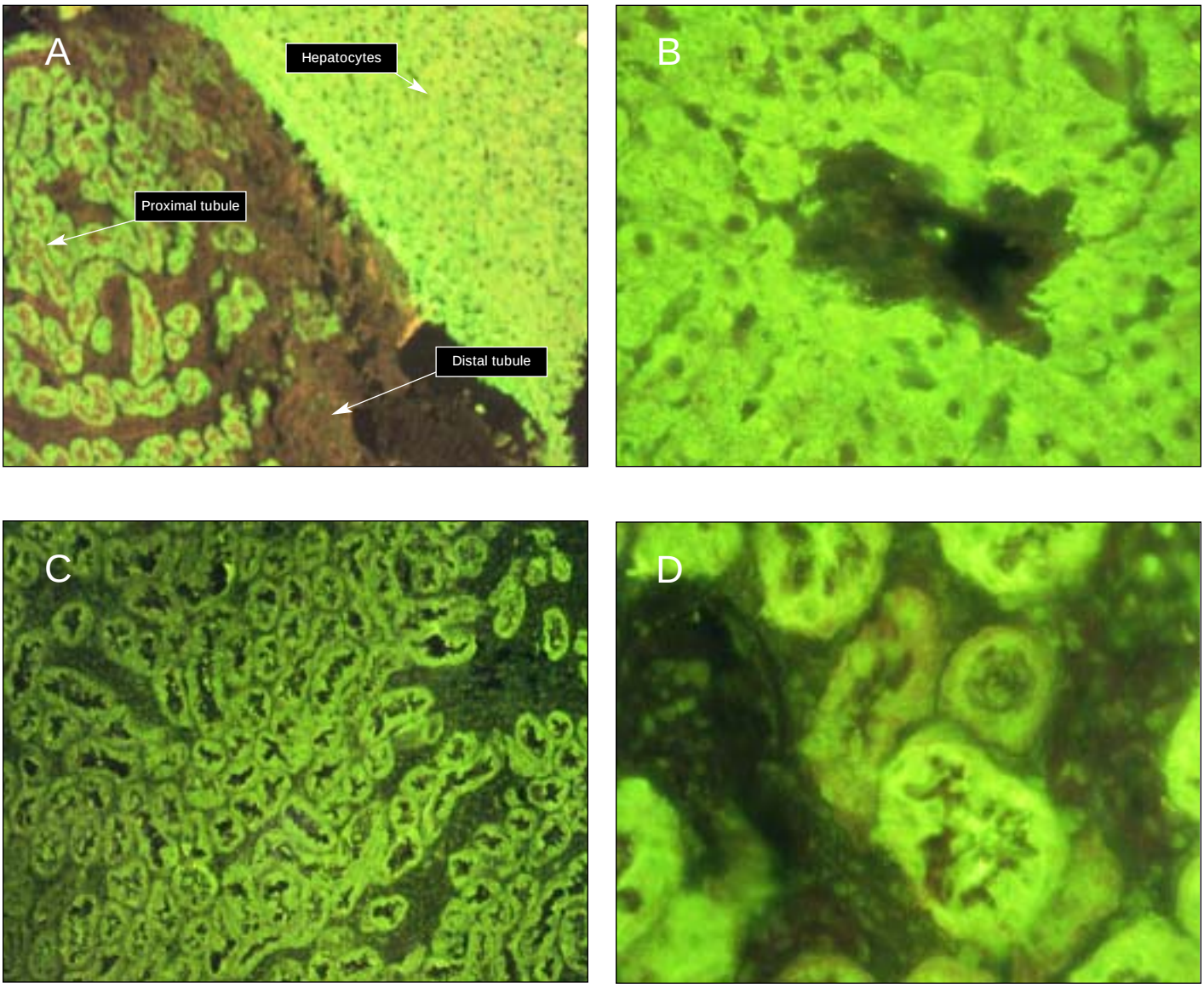
The clinical findings of AIH are similar to those found in chronic viral hepatitis and include vague symptoms such as fatigue, jaundice with mild pruritis, upper abdominal discomfort, polymyalgias, and diarrhea.[1] On physical exam, a wide variety of findings may be seen including hepatomegaly, splenomegaly, spider nevi, ascites, encephalopathy, as well as other concurrent autoimmune diseases.[1] Autoimmune diseases are common in AIH involving many organ systems, but the thyroid gland is the most frequently involved organ. In Western Europe, the incidence of AIH is 0.69 cases per 100,000 and this estimate has been shown to apply to ethnically similar populations.[1] Autoimmune hepatitis has a significant prevalence in North America, accounting for 11% to 23% of all cases of chronic liver disease.[2]

Pathophysiology of AIH

Although the exact mechanism for the development of AIH is not known, it has been proposed that disturbances in T-lymphocyte regulatory function leading to the enhancement of antigen-induced antibody production by B-cells may play a role.[3-5] An abnormal T-cell response to the asialoglycoprotein receptor (ASGPR), which is found on hepatocytes, has been reported.[6] Longitudinal studies of AIH patients suggest that the disease may occur after viral infections with hepatitis A virus (HAV) or Epstein-Barr virus (EBV) in patients with abnormal T-cell responses to ASGPRs.[7,8] Patients without ASGPR-specific T-cell responses did not develop AIH after these viral infections, thus implicating them in disease induction.[7,8] There is also some evidence that AIH may be a late consequence of rubella infection[9] and that treatment of viral hepatitis with interferon may antagonize latent AIH.[10,11] One model of the immunogenesis of AIH suggests that in genetically predisposed individuals, viral infections of hepatocytes elicit a T-cell response that results in hepatotoxicity and stimulates antibody responses to the viral mediated antigens.[6,12] In response to these stimuli, natural killer (NK) cells and CD8+ cells recognize and kill liver cells by an antibody-dependent, cell-mediated cytotoxic mechanism (autoantibody coated liver cells) and by hepatocyte apoptosis, respectively. This model is consistent with findings suggesting that a predisposition to AIH is related to the presence of specific MHC Class II (DR) and MHC Class I (HLA-A, B, C) alleles. Additionally, other mechanisms such as molecular mimicry between the B-cell epitopes of the cytochrome P450 isoenzyme 2D6 and an early protein of herpes simplex virus type 1 have been implicated.[13] Molecular mimicry might trigger autoimmune responses directed at these protein epitopes expressed by hepatocytes.[14]

Diagnosis of Autoimmune Hepatitis

The diagnosis of AIH is difficult because there are no particular signs, symptoms, or liver function test abnormalities that are specific enough to be considered diagnostic. In 1993, the International Autoimmune Hepatitis (IAH) group proposed diagnostic criteria for AIH.[15] These criteria have been modified recently after several controlled studies have confirmed their utility and found slight errors in their application.[16] The diagnosis of AIH using the IAH criteria is based on a scoring system that assesses points. Scores on a scale of 0 to +3 are given for positive criteria when an individual is rated for the following: the presence of 1) biopsy findings of periportal hepatitis, 2) hypergammaglobulinemia (>1.5 times the upper limit of the normal reference range), and 3) a positive serum titer for antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and/or liver/kidney microsome, type 1 (LKM-1) antibodies. Scores on a scale of -5 to 0 are given for negative criteria: the



[I1]. Typical IFA staining pattern for LKM-1 antibodies using serum from patients 1 or 2 on liver/kidney/stomach substrate. (Scimedx M, Denville, NJ) **A**. Staining of renal proximal tubule cells (left) and uniform staining pattern of hepatocytes (right) (100x). **B**. Staining of hepatocytes (400x). **C**. Staining of renal proximal tubule cells but not distal tubule cells (100x). **D**. Staining of renal proximal but not distal tubule cells (400x). Proximal renal tubules contain granule-filled epithelial cells with a prominent brush border that almost completely fill the lumen, whereas distal renal tubules lack a brush border and contain smaller epithelial cells, resulting in a larger, more clearly defined lumen. Distal renal tubule cells appear much less numerous because they are shorter in length.

absence of 1) positive viral markers, 2) excessive alcohol consumption, 3) exposure to blood products, 4) use of hepatotoxic medications, 5) biliary lesions or copper deposits, and 6) increased alkaline phosphatase (ALP), aspartate aminotransferase (AST), or alanine aminotransferase (ALT) ratios. Optional criteria include the presence of specific HLA types and response to therapy. Scoring based on these criteria can indicate 1 of 3 possible diagnoses: definite AIH, probable AIH, or no AIH present. Recent modifications to these guidelines included a change in the magnitude of the ALP:ALT ratio to exclude primary biliary diseases (primary biliary cirrhosis and primary sclerosing cholangitis) as the cause of an increased ALP:ALT ratio, because the presence of these diseases may be confused with AIH.[17,18] It is important to rule out hepatitis B (HBV) and hepatitis C (HCV) virus infection in the diagnosis of AIH because immunosuppressive treatment of AIH can cause these infections to get worse. Serologic hepatitis C testing can be falsely negative in up to 5% of patients, so HCV RNA testing by the polymerase chain reaction (PCR) methodology is needed to rule out HCV infection, especially in patients with HCV risk factors.[2]

Histological Findings in AIH

In patients with AIH, the classic liver tissue histology findings include

interface hepatitis (piecemeal necrosis) with portal infiltrates of plasma cells.[18] Inspection of the tissue sections for hepatocyte inclusions, lymphoid follicles, iron particles, parenchymal inflammation, bile duct injury, onion-skin fibrosis, and sclerosing hyaline, as well as central vein abnormalities will help exclude other common causes of acute and chronic liver injury.[18] Both CD4+ and CD8+ lymphocyte infiltrations are prominent in AIH; however, they are also often seen in tissue sections from patients with chronic hepatitis.[17] The lymphocytes contained in these infiltrates in AIH are characteristic of an antigen-driven response that may be mediated by dysregulation of the Fas/FasL pathways.[17] Since histological findings are not specific and can be mimicked by other causes of hepatitis, they cannot be used exclusively to diagnose AIH.

Autoantibody Pattern in Patients with AIH

Different autoantibodies are found in the serum from patients with AIH [T3]. The serum from approximately 70% of patients with AIH are ANA positive, 74% are SMA positive, 14% are AMA positive, and 3% to 4% are LKM-1 antibody positive.[19,20] Other studies have found that perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is found in the serum from 60% to 90% of patients with AIH type 1 and in 13% of patients with AIH type 2.[21,22] Among patients with type 1 AIH, 60% are ANA positive, 70% are SMA positive, and 60% are AMA positive, while 90% of patients with type 2 AIH are LKM-1 antibody positive and 50% of AIH type 2 patients can have liver cytosolic antigen type 1 antibodies (anti-LC1); however, testing for LC1 antibodies is currently investigational only.[18] Although autoantibody titers are helpful in the diagnosis of AIH, the serum of 20% of patients with AIH is negative for ANA, SMA, and LKM-1 antibodies. Nevertheless, the diagnosis of AIH is based on a scoring system that includes the presence of (ANA, SMA) or absence of (AMA) serum autoantibodies.

Typical Autoantibody Pattern in AIH

T3

Autoantibody	% Positive in Various Types of AIH		
	All AIH	Type 1 AIH	Type 2 AIH
ANA	70%	60%	—
SMA	74%	70%	—
AMA	14%	60%	—
LKM-1	3% to 4%	—	90%

ANA, antinuclear antibodies; SMA, smooth muscle antibodies; AMA, anti-mitochondrial antibodies; LKM-1, liver/kidney microsome, type 1 antibodies.

Liver/Kidney Microsome, Type 1 Autoantibody

The discovery of the liver/kidney microsome type 1 (LKM-1) antibody, directed against cytochrome P4502D6, led to the establishment of subtypes of AIH. The percentage of type 1 AIH patients whose serum contains ANA, SMA, or AMA is 60%, 70%, and 60%, respectively, while the percentage of Type 2 AIH patients whose serum contains only LKM-1 antibodies is 90%. The presence of LKM-1 autoantibodies has also been described in patients with hepatitis C amd hepatitis D infections and can be induced by drugs such as phenytoin, hydralazine, and tienilic acid.[18] The reason for clinical subclassification of AIH is the more severe liver disease that can rapidly progress to liver failure and the poorer responses to standard therapy that are found in patients with Type 2 AIH.[18] Although Type 2 AIH is found predominantly in Europeans, serum testing for the presence of LKM-1 antibodies in North American patients without classic serological findings for AIH may be warranted in those with progressive disease who may benefit from immunosuppressive therapy.[18]

Treatment of AIH

The primary therapy for AIH is administration of corticosteroids (prednisone or prednisolone). In general, therapy should be initiated as soon as possible after diagnosis to decrease the amount of bridging inflammation and subsequent liver complications, such as extraportal fibrosis.[18] An important adjunct to treatment may be the use of other immunosuppressive drugs such as azathioprine, which may allow the discontinuation of steroids in some cases.[18] Steroid treatment should lead to a rapid reduction in AST and ALT levels. Liver transplantation is the standard of care in patients with end-stage liver disease due to AIH and in patients who demonstrate evidence of portal hypertension and decompensated liver disease.[18] However, AIH patients who undergo liver transplantation generally do not respond well to immunosuppression and recurrence of AIH is >20% in these patients which is difficult to differentiate from rejection.[18]

Randomized controlled trials have been performed that indicate decreased mortality due to AIH after treatment. One series of studies found that treatment of AIH with prednisolone led to a 5-year reduction in mortality from 60% in untreated cases to 20% in treated cases.[23,24] Another study found that treatment with prednisone decreased the 2-year mortality rate from 43% in untreated cases to 5% in treated cases.[23] The percentage of patients that undergo remission following corticosteroid therapy is 74% after 2 years, 89% after 3 years, and 95% after 4 years.[25] Progression to cirrhosis (end-stage liver disease) occurs in 45% of patients with Type 1 AIH and in 82% of patients with Type 2 AIH.[2] The majority of patients with AIH demonstrate a waxing and waning chronic hepatitis that continues for years.

Treatment and Course of Patients 1 and 2

Patient 1 was placed on prednisone therapy; however, her symptoms were not controlled by this therapy and her liver function tests remain elevated. This pa-

tient's severe disease has prompted consideration of using azathioprine.

Patient 2 was started on azathioprine (50 mg/day for 6 weeks), followed by an 18 week tapering off period, after which the medication was discontinued. Her symptoms (eg, itching) subsided within 1 week after the initiation of therapy and her liver function tests returned to baseline values after 6 weeks of treatment.

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